Clinical Cases in Dermatology
Series Editor: Robert A. Norman

Francesca Satolli
Michael Tirant
Uwe Wollina
Torello M. Lotti *Editors*

Clinical Cases in Pediatric Skin Cancers

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Clinical Cases in Dermatology

Series Editor
Robert A. Norman, Tampa, FL, USA

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Clinical Cases in Pediatric Skin Cancers

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ISSN 2730-6178 ISSN 2730-6186 (electronic)
Clinical Cases in Dermatology

ISBN 978-3-030-93665-5 ISBN 978-3-030-93666-2 (eBook)
https://doi.org/10.1007/978-3-030-93666-2

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Contents

Chapter 1
A Baby with Uniform Papules

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

A four-month male presents with uniform papules on his forehead and back, which had been evident for about 1 month. There was no history of similar lesions in family members. Cutaneous examinations revealed relatively equal papules, 1 mm in diameter with some depressed lesions. Lesions focus on forehead, back and a little bit lesions on abdomen (Figs 1.1 and 1.2). Fungal microscopy is negative.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_1

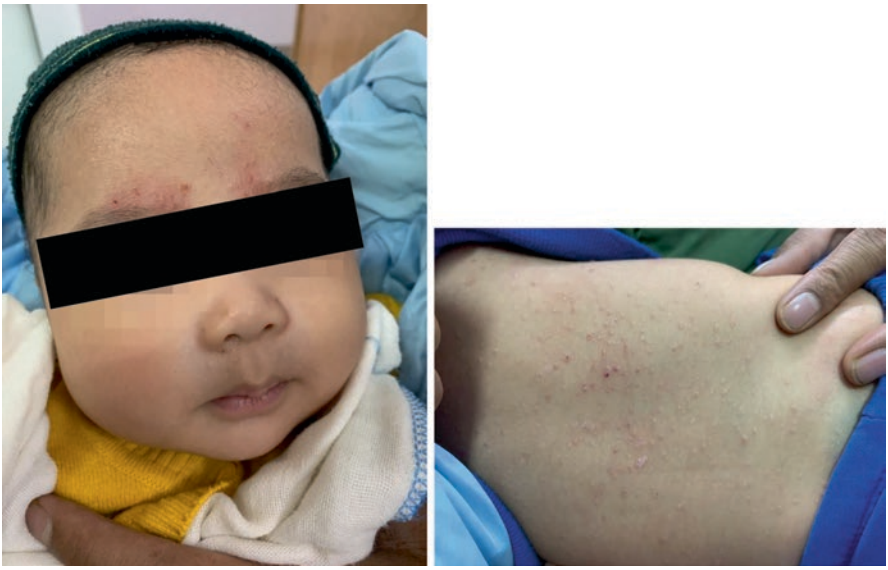

Fig. 1.1 Skin-colored uniform papules 1 mm in diameter. Some depressed lesions

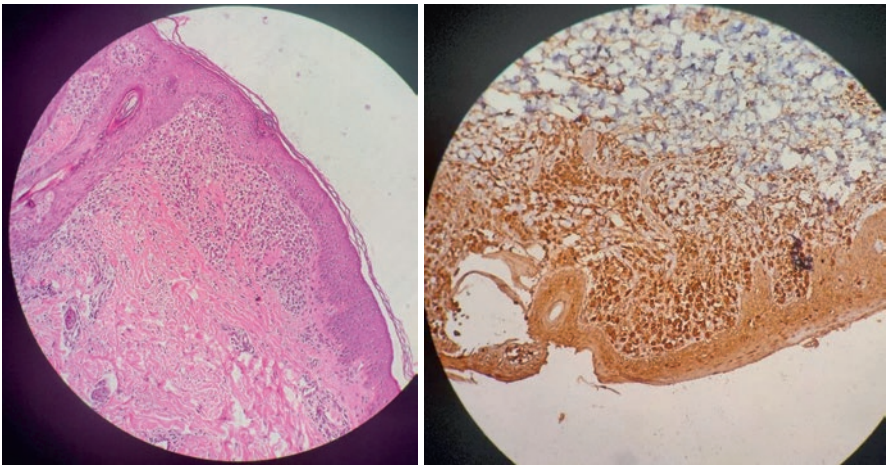

Fig. 1.2 Histopathology showing a dense histiocytes infiltrate of the superficial dermis

Histopathology revealed infiltrated histiocytes with cytoplasmic eosinophils in the superficial dermis, some monocytes and eosinophil in the dermis. Immunohistochemical markers show that S100, CD1a, CD68 are positive.

Based on the case description and photographs, what is your diagnosis?

1. Atopic dermatitis
2. Langerhans cell histiocytosis
3. Benign cephalic histiocytosis
4. Seborrheic dermatitis

Diagnosis

Langerhans cell histiocytosis.

Discussion

Langerhans cell histiocytosis is a rare neoplasm of hematopoietic myeloid precursor cells that most commonly affects white male children, with a peak incidence of 1 to 3 years of age. Characteristically, CD1a/S100B/CD207-positive mononuclear cells with bean- shaped nuclei infiltrate single-organ systems, most commonly the bone, but also the skin, or multiple organ systems. Also, approximately 60% of LCH-cells bear a V600E mutation in the *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) oncogene, and 33% of BRAF wild-type lesions harbor mutations in the *MAP 2K1* (mitogen-activated protein kinase 1) gene leading to universal MEK (mitogen activated protein/extracellular signal-related kinase kinase) and ERK (extracellular signal-regulated kinase) activation.

Significant risk factors for LCH include maternal urinary tract infection during pregnancy, feeding problems or blood transfusions during infancy [1] Hispanic ethnicity, crowding, low education level [2] neonatal infections, solvent exposure, family history of thyroid disease [3] and in vitro fertilization [4].

The most commonly affected organs overall are: bone (80%), skin (33%), pituitary (25%), liver (15%), spleen (15%), hematopoietic system (15%), lungs (15%), lymph nodes (5–10%), and the central nervous system excluding the pituitary (2–4%). Cutaneous involvement is typically representative of multisystem disease, because 87% to 93% of patients also have systemic involvement.

In Li et al's retrospective analysis of 918 cases of LCH in China (newborns to patients 65 years of age), 510 patients (56%) were reported to have skin lesions, of which 106 patients (12%) presented with cutaneous lesions as the initial disease manifestation. Cutaneous involvement typically presented as pinpoint erythematous or skin-colored papules or pustules. The morphology can mimic a seborrheic dermatitis or an eczematous erythematous, skin-colored, or brown petechial rash with or without scale, scabbing, crusting, or purpura [5]. This broad variety of skin and mucosal manifestations frequently leads to a delayed diagnosis as skin lesions are misinterpreted as eczema, miliaria, scabies, varicella, seborrheic dermatitis, folliculitis, or candidiasis.

LCH should be kept in mind as a rare, but important, differential diagnosis when the above-mentioned lesions are seen, especially if they are resistant to therapy and are spreading. In the case we presented, cutaneous lesions are also initial disease manifestation and it is difficult to make a right diagnosis in the first examination without histopathology [6].

Key Points

- LCH is an inflammatory myeloid neoplasia.
- Attributed to activating mutations of the MAPK pathway in all patients.
- The clinical course varies from single-system disease, often with spontaneous resolution, to life-threatening, treatment-refractory multisystem disease.
- When LCH affects the skin, it typically presents as pinpoint erythematous or skin-colored papules or pustules mimicking eczema or seborrheic dermatitis.
- Most patients presenting with cutaneous disease also have systemic involvement.
- Identification of patients with risk organ involvement is essential, because these patients need more aggressive treatment.

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Chapter 2
A Boy with a Slow, Painless Nodule and Blister on the Back of His Neck

Feifei Hu and Lujuan Gao

A 12-year-old boy came to our hospital complaining of a slow, painless nodule and blister on the back of his neck, which the patient had noticed three months ago (Fig. 2.1).

What Is Your Diagnosis Based on the Description and the Photograph?

1. Degenerating fibroxanthoma
2. Foreign body reaction
3. Dermoid cyst
4. Pilomatrixoma
5. Sebaceous cyst

According to the patient's complaint, a nodule on the back of his neck appeared without obvious cause about three months ago. The diameter was about 0.5 cm, which was not taken seriously at that time. The nodules gradually increased since then, and later a blister appeared on the surface one month prior to consultation. The patient started to getting nervous, and told his father about the skin lesion. They referred to the department of dermatology in a nearby community hospital and the diagnose of epidermal cyst was made by ultrasound. However, they doubted the diagnosis.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_2

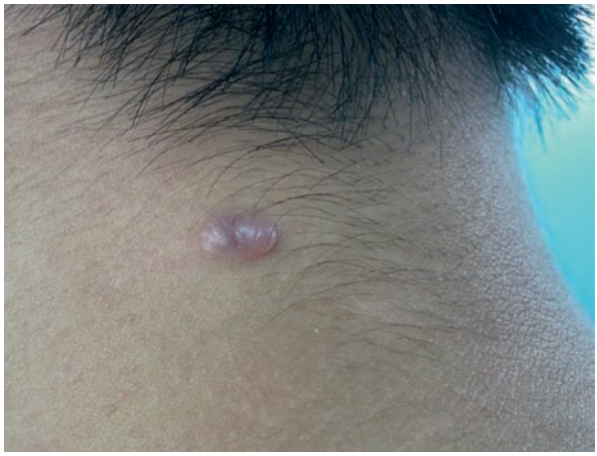

Fig. 2.1 A 12-year-old boy came to our hospital complaining of a slow, painless nodule and blister on the back of his neck, which the patient had noticed three months ago

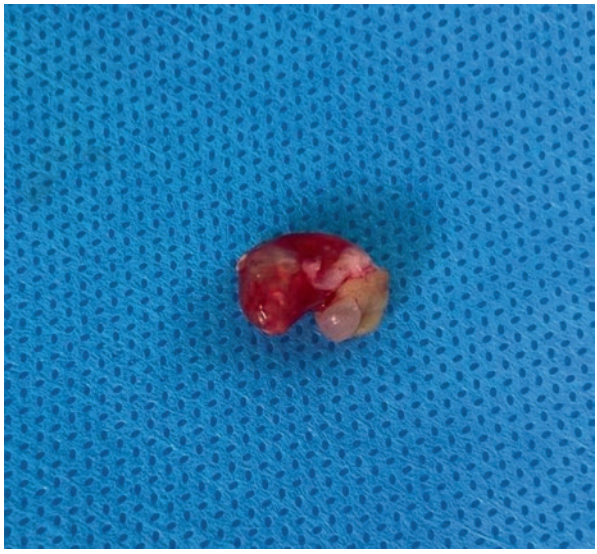

Fig. 2.2 The anatomic sample: well-defined, encapsulated, red-yellow tumor, measuring approximately 1.5 cm in greatest diameter

Upon physical examination, a 1.5-cm fixed, rock-hard and painless nodule with a 0.5-cm blister on the surface was observed on the back of the neck. No other relevant medical information was identified in the patient's clinical history.

We performed surgical resection with clear margins under local anesthesia. The anatomic sample obtained showed well-defined, encapsulated, red-yellow tumor, measuring approximately 1.5 cm in greatest diameter (Fig. 2.2). Histopathological evaluation of the resected tissue reported a benign pilomatrixoma (Fig. 2.3).

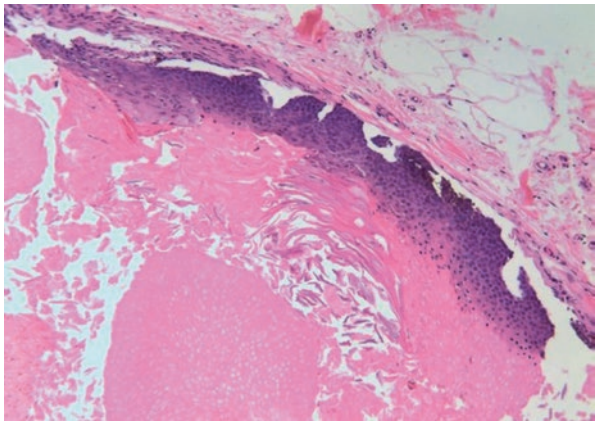

Fig. 2.3 Histopathological: a cyst with central matrical cornification. The cyst wall consists of basaloid matrical cells and shadow cells can be seen in the center. (HE×10)

Diagnosis

Pilomatrixoma (Perforating: Blister type).

Discussion

Pilomatrixoma, also known as pilomatrixoma, is a rare benign tumor arising from the hair follicle [1].

CTNNB1 mutations have been reported in a high percentage of pilomatrixomas. Expression of β-catenin, the protein encoded by CTNNB1, is also frequently observed. It is supposed to be a component of the key signaling pathway that influences cell differentiation and proliferation [1].

Pilomatrixoma is a benign adnexal tumor very common in pediatric age and in young adults that derives from follicular matrix cells. It can be induced by trauma or insect bites. It is most often located in the head and neck, followed by the extremities and upper trunk, while rarely in the lower extremities. So far, no cases of pilomatrixoma have been reported on the palms, soles, or in the genital region [2].

It usually presents as a solitary, slow-growing dermal or subcutaneous nodule without symptoms. The multiple lesions maybe relate to Gardner Syndrome, Turner Syndrome, Rubinstein–Taybi Syndrome, Churg–Strauss syndrome, xeroderma pigmentosum or sarcoidosis. Most masses measure less than 1.6 cm in diameter, while lesions with a diameter of 20 cm were also reported as characterized as “rock-hard” and plate-like on palpation [2].

Several clinical variants of pilomatricomas have been described which include perforating, anetoderma, proliferating, pigmented multiple and familial [3]. The clinical variants increased the difficulty of diagnosis. Perforating pilomatrixoma often displays as a bilster or ulceration appearance. Blister type in the case of our patient is very rare. The “rock-hard” nodule on palpation can assist the diagnosis.

Ultrasound is the most commonest modality used in diagnosis of pilomatrixoma. It is economical and convenient, but only 40–50% of lesions are correctly diagnosed. In our case, it was misdiagnosed as an epidermal cyst by ultrasound. Fine needle aspiration is also an important modality used in diagnosis of pilomatrixoma. The cytological triad of basaloid cells, ghost cells, and giant cells can be diagnosed, but only 44–45% of lesions are correctly diagnosed [2].

Pathology is the gold standard for diagnosis. Pilomatrixomas evolve with time and have been classified into three histopathologic stages: early, fully developed, and regressive.

The early pilomatrixoma frequently presents as a cyst with central matrical cornification. The cyst wall consists of basaloid matrical cells that show an abrupt transition to central eosinophilic cornified matrical cells in which barely discernible nuclear out-lines remain. Sometimes, pink trichohyalin granules, illustrative of matrical cornification, are identifiable at the transition point. The central anucleate cornified cells are commonly referred to as ghost or shadow cells. In fully developed pilomatricomas, a cystic configuration is commonly lost. Solid collections of basaloid matrical cells and matrical corneocytes are present in varying degrees. The cornified matrical cells elicit considerable fibrosis and a secondary granulomatous infiltrate, which can become predominant in longstanding lesions. Matrical cells have a proliferative capacity as high as any human tissue and can display numerous cells in mitosis. The designation proliferative pilomatricoma refers to a pilomatricoma with a high mitotic index. At times, such lesions can be misinterpreted as carcinoma. In late lesions, basaloid matrical cells may be lacking. An involutional pilomatricoma at times can presents with only a few shadow cells buried in a larger fibrosing granulomatous reaction. Calcification and ossification also ensue in late lesions [1].

Complete resection with clear margins is the preferred treatment and serves as diagnostic confirmation. In the case of multiple pilomatrixomas, all lesions should be removed. The pilomatricoma may recur after limited excision. While, in our case, there was no recurrence during a follow-up period of 20 months.

Key Points

- Pilomatrixoma is a rare benign tumor arising from the hair follicle, which is quite common in childhood and adolescence.
- Complete resection is the preferred method.

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Chapter 3
A Boy with Recurrent Erythema and Blisters

Yang-Yang Luo, Jian-Ping Tang, Zhu Wei, Jing Chang, and Bin Zhou

An 1-year old boy was admitted to our ward complaining of recurrent erythema, wheal and blisters for the past seven months. He had pigmented and hypopigmented spots on the trunk at 3 months after birth. Sometimes there were wheals or blisters (Fig. 3.1a) due to scratching, temperature rising or vaccination. Moreover the rash spreaded all over the body and was presented with peau d'orange appearance (Fig. 3.1b). Physical examination did not present alterations in other organs or systems.

Based on the History and the Photography, What Is Your Diagnosis?

1. Bullous pemphigoid
2. Papular urticaria
3. Urticarial pigmentosa
4. Diffuse cutaneous mastocytosis
5. Mycosis fungoides

Following his hospitalization, he received related auxiliary examinations including routine blood tests, abdominal ultrasonography, skin biopsy and bone marrow biopsy. The skin histological appearance showed numerous mast cells arranged diffusely in the dermis stained by Hematoxylin&eosin (Fig. 3.2a). And the CD117

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_3

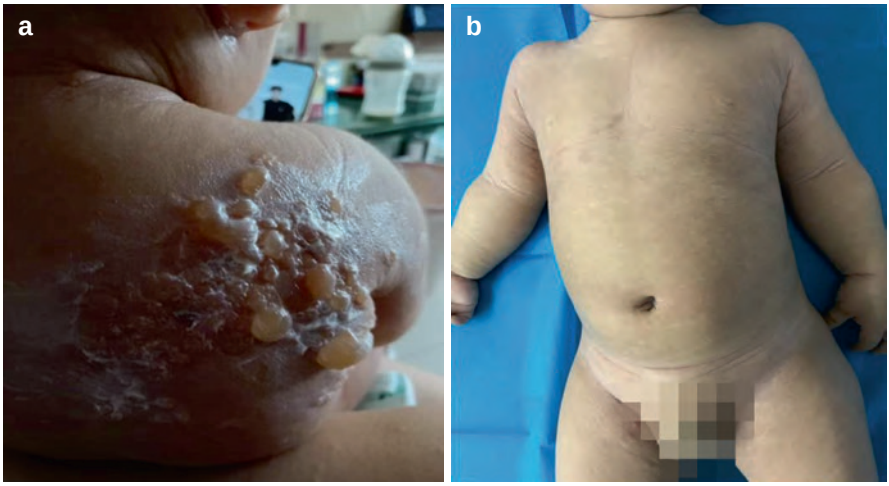

Fig. 3.1 Clinical manifestation of the patient. (**a**) recurrent blisters on erythema; (**b**) peau d'orange appearance

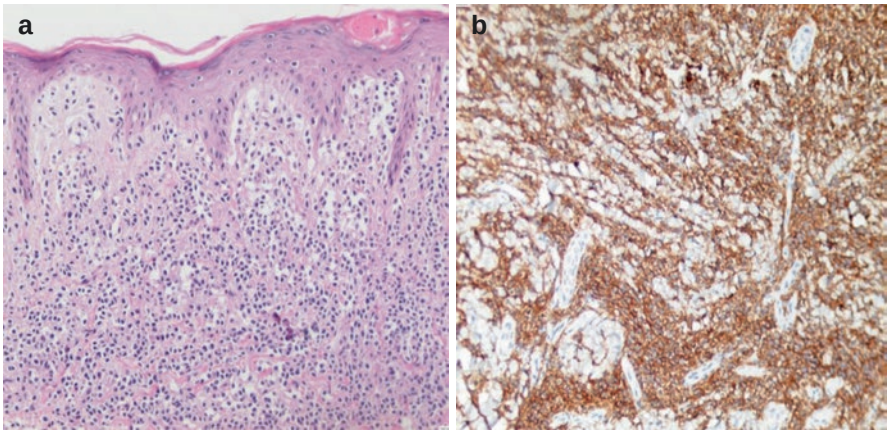

Fig. 3.2 The characteristics of histopathology. (**a**) numerous mast cells arranged diffusely in the dermis stained by Hematoxylin eosin; (**b**) the CD117 (c-kit) immunohistochemical reaction was diffusely positive in mast cells

(c-kit) immunohistochemical reaction was diffusely positive in mast cells (Fig. 3.2b). Other laboratory and imaging investigations did not show any evidence of systemic abnormalities.

Then he received the therapy of intravenous glucocorticoids and antihistamines. The pruritus was relieved and no new blister was discharged. After that, the glucocorticoids was gradually reduced to discontinuation. One year later, there is no pruritus or new rash in the patient.

Diagnosis

Diffuse cutaneous mastocytosis.

Discussion

Mastocytosis is a heterogeneous disorder characterized by the pathological increase and accumulation of mast cells (MCs) in different tissues and organs [1]. It is divided into 3 main forms: cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma depending on the sites of organ involvement. And the CM includes 3 variants: urticarial pigmentosa, diffuse CM (DCM) and mastocytoma of skin [2]. DCM is an extremely rare and severe variant that usually manifests with erythema, dermal thickening and edema with a typical leather or peau d'orange appearance [3]. Cutaneous symptoms consist of widespread spontaneous blisters with erosions, erythroderma or thickening of the skin and positive Darier's sign (rubbing of skin lesions results in the reddening and urticarial swelling). Other MC mediator-related symptoms due to the widespread MC load in the entire skin includes simultaneous occurrence of pruritus, flushing, vomiting, diarrhea, abdominal pain, hypotension and anaphylactic shock [4].

Urticarial pigmentosa is the most common variant of cutaneous mastocytosis characterized by hyperpigmented, brownish macules and patched with positive Darier's sign. Unlike other forms of mastocytosis, there is rarely any internal organ involvement [5].

Bullous pemphigoid is an autoimmune bullous disease classically characterized by tense blisters over urticarial plaques on the body accompanied by intense pruritus. Diagnosis relies on the histopathological results demonstrating eosinophilic spongiosis, the detection of IgG and/or C3 deposition at the basement membrane zone using direct or indirect immunofluorescence assays and the quantification of circulating autoantibodies against BP180 and/or BP230 using ELISA [6].

Papular urticaria is a chronic inflammatory disease characterized by a hypersensitivity reaction to the bite of arthropods and manifested through papule-type skin lesions, wheals, vesicles, blisters or scabs. Occasionally, the patient might develop hypo-or hyperchromic pigmentations in the skin with intense pruritus [7]. While mycosis fungoides is the most common cutaneous T-cell lymphoma, a type of non-Hodgkin T-cell lymphoma presenting with cutaneous patches, plaques, and tumors [8].

The patient was presented with typical peau d'orange appearance and positive Darier's sign. The histopathology showed numerous mast cells in the dermis with positive CD117. Diffuse cutaneous mastocytosis is clearly diagnosed. The mainstay of treatment includes controlling mast cell mediator-related symptoms and avoiding triggers. Treatment options include antihistamines, systemic and topical corticosteroids, mast cell stabilizers and psoralen with UVA [9].

Key Points

- Diffuse cutaneous mastocytosis is rare diease characterized by erythema, dermal thickening and edema with a typical leather or peau d'orange appearance.
- Antihistamines, systemic and topical corticosteroids are the main treatment options for DCM.

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Chapter 4
A Case of Ulcerated Hemangioma

Neslihan Deniz and Ümit Türsen

Introduction

A 1-year-old infantile male patient presented to us with a 60-mm × 40-mm right ear and face superficial protuberant infantile hemangioma that appeared at birth growing steadily over time and then gradually developed 30-mm × 35-mm ulceration of the inferior half over the last 6 weeks. In his medical history, he had systemic steroid, oral propranolol and sirolimus drug medication. With the regression of the lesion that benefited from the treatment, discontinued the treatment and relapsed. Prednizolon 1.5 mg/kg/day and propranolol 3 mg/kg/day were restarted by our pediatric oncology department. Prednizolon was discontinued in outpatient clinic examinations 1 month later and then 2 drops of 0.5% betoxalol solution was applied thrice daily over the entire lesion by our dermatology department. The ulcer complete healing was achieved by 3 month, leaving a whitish scar. At monthly outpatient clinic reviews, the child's recorded vital signs ranged as follows: heart rate, 120–135 beats per minute; blood pressure, 80–96/55–73 mmHg; and random glucose, 5.6–8.2 mmol/l. Propranolol and 0.5% betoxolol solution were continued for 6 months, and there was no ulcer recurrence at 12 months after stopping treatment (Figs. 4.1 and 4.2).

Based on the case description and photograph, what is your diagnosis?

- Capillary malformation
- Congenital hemangiomas and vascular malformations
- Kaposiform hemangioendothelioma and tufted hemangioma
- Subcutaneous tumors
- Pyogenic granuloma

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_4

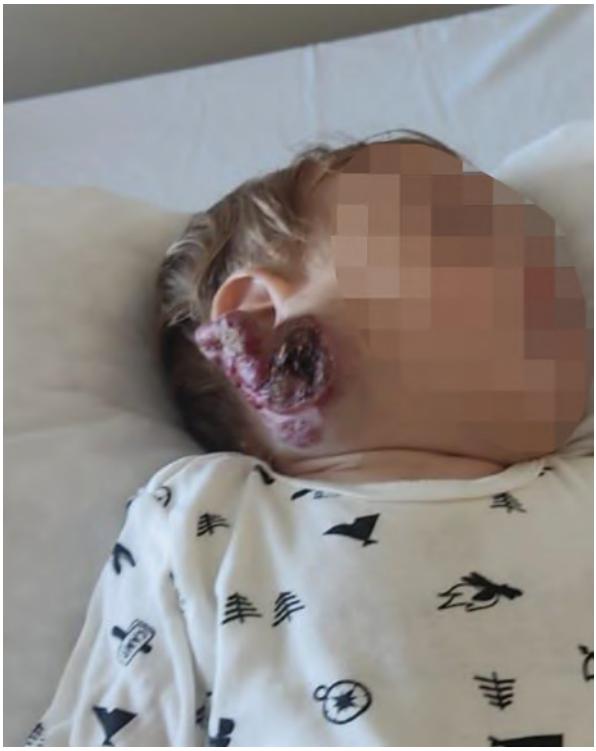

Fig. 4.1 Clinical evolution of an infantile ulcerated hemangioma on upper ear of patient

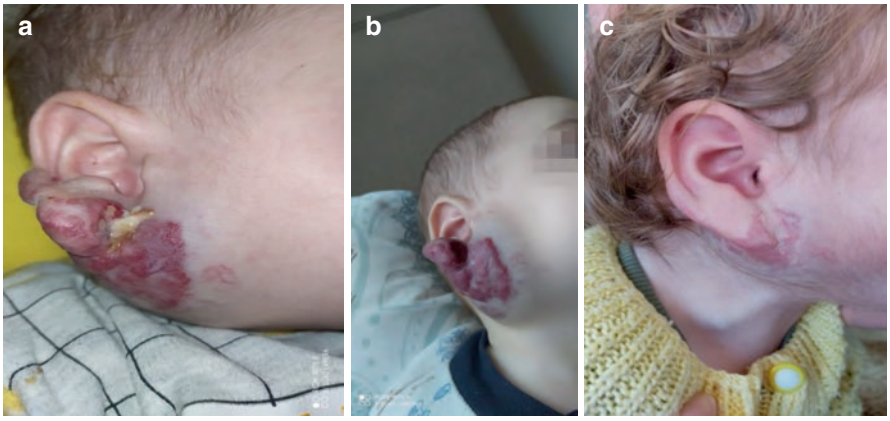

Fig. 4.2 (**a**) Right ear hemangioma (60 mm × 40 mm) with inferior-half ulceration (30 mm × 35 mm) in a 1 year-old child before starting propranolol and prednol. (**b**) 2 months after prednol and propranolol treatment (**c**) After 12 months of follow-up, complete healing after 6 month of propranolol, prednol, %0.5 betaxolol solution, leaving behind a whitish telangiectasic scar

Diagnosis

Ulcereted infantile hemangioma.

Discussion

Infantile hemangiomas are the most common tumors of childhood. Although most are benign and self-limited some hemangiomas can cause complications such as ulceration or life-altering disfigurement. Treatment of hemangiomas should be determined by the size, morphology, location of the lesion (s), the presence or possibility of complications, the potential for scarring or deformity, the age of the patient, and the rate of growth or curl [1] Ulceration is common complication of hemangiomas and is usually in the centrofacial and perineum regions. Propranolol is the first-line agent for hemangiomas with the potential to impair function or cause permanent disfigurement. Potential mechanisms of action for propranolol may include vasoconstriction, decreased expression of vascular endothelial growth factor and, triggering of apoptosis [2, 3]. The randomized controlled trial shows that propranolol is effective in the treatment of infantile hemangioma at a dose of 3 mg per kilogram for 6 months. 10% of patients in whom treatment with propranolol was successful required systemic retreatment during follow-up. Known adverse events associated with propranolol (hypoglycemia, hypotension, bradycardia and bronchospasm) were observed infrequently [4]. Rebound growth was observed in approximately 14–25% of children after propranolol was discontinued [5].

Topical beta blockers can be used to treat mild to moderate relapses. A retrospective study was conducted to evaluate the efficacy of timolol gel solution in the treatment of ulcerated infantile hemangioma. In this study, 30 children with ulcerated infantile hemangioma were identified. The results show that timolol can be well tolerated with oral propranolol [6]. Systemic corticosteroids were compared with propranolol in randomized trial. In this study, 34 children with facial hemangioma were assigned to treatment with propranolol 2 mg /kg/day and prednisolone 2 mg/kg/day for 16 weeks. Response to treatment, generally defined as cessation of progression and volume reduction, was achieved by 96 percent and 92 percent of patients in the propranolol and systemic corticosteroid groups, respectively. This study showed that propranolol is not inferior to steroid in terms of therapeutic effects in IH [7]. Abrupt withdrawal or rapid reduction of glucocorticoids should be discontinued slowly, as rebound proliferation may occur. Pulsed dye laser (PDL) 595 nm can be used as an alternative for medically resistant ulcerated hemangiomas. In summary, in our patient, positive results were obtained in the combined treatment of oral propranolol and low dose prednisolone. In our patient, topical beta blockers were used in the treatment and good results were obtained. No recurrence was experienced.

Key Points

- Oral propranolol and low dose oral prednisolone are very effective in the treatment of ulcerated infantile hemangioma.
- -Topical beta blockers are used as alternatives in the treatment of ulcerated infantile hemangioma.

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Chapter 5
A Case of Unusual Erythematous and Desquamative Skin Disorders in a Child

Gizem Aydın, Mustafa Anıl Yılmaz, Yasemin Yuyucu Karabulut, Ümit Türsen, and Kıymet İnan

A 9-year-old male patient presented with a non-itching red swelling on lower abdomen for two months. There is no medical illness in the medical history of his family and himself. It was initially treated as tinea by family physician then he was sent to our hospital for the persistence of the plaque.

In dermatological examination, there are two 4*2.5 and 4*1.5 cm annular erythema plaques in the suprapubic area, 3*2 cm in the right inguinal region and 4*2 cm in the left lumbar region (Fig. 5.1).

Based on the case description and photograph, what is your diagnosis?

- Lichen scleroatrophicus
- Fixed Drug Eruption
- Morphea
- Mycosis Fungoides

Biopsy was performed and the histomorphological examination of the biopsy specimen, orthokeratosis and follicular plugging were observed in the epidermis. Lymphocytes that fill the papillary dermis also lie transepidermally. These lymphocytes have significant cytological atypia such as nuclear enlargement, nuclear contour irregularity and perinuclear halo. In the immunohistochemical study, strong cytoplasmic staining with CD3, CD4 and CD5 in lymphocytes which filling the dermal papillae, showing alignment at the dermoepidermal junction and spreading transepidermal in patches was observed. Some of these lymphocytes showed strong

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_5

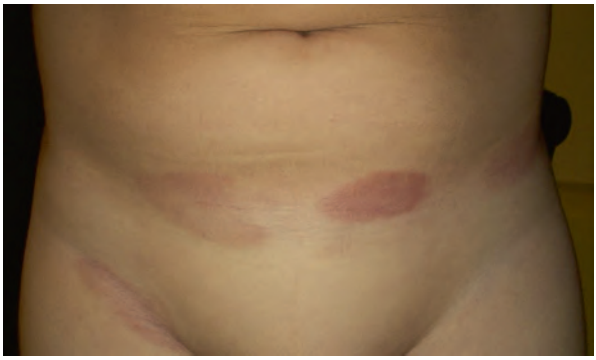

Fig. 5.1 There are annular erythema plaques in the suprapubic area, right inguinal region and left lumbar region

cytoplasmic staining with CD8 and the ratio CD4/CD8 was 4. Most of the lymphocytes that filling the dermal papillae showed loss of expression with CD7 (Fig. 5.2). Moderate cytoplasmic staining was seen in very few lymphocytes in the dermal papillae with CD30 and CD20 positivity was not observed.

Diagnosis

Mycosis Fungoides.

Discussion

Mycosis fungoides, which is characterized by infiltration of the skin with malignant T cells is the most common primary cutaneous lymphoma in adults and children. It comprises approximately %65 of all primary cutaneous lymphomas in pediatric patients. The mean age at diagnosis in pediatric patients is 10, and this condition is rare in infants. The male to female ratio of MF is 1.1: 1 in young patients under 30 years old [1].

Similar to adults, children may have an indolent clinical course that is difficult to distinguish from inflammatory skin conditions [2]. In adults, classic MF presents initially with scaly erythematous patches that may progress into infiltrated plaques and tumors in %35 and %20 of patients. The incidence of classic MF in children is approximately %41. Unlike adults, the majority of children with MF present with nonclassic variants of the disease, which include hypopigmented, hyperpigmented, folliculocentric, and poikilodermatous forms. Multiple variants are often present at the time of diagnosis. Hypopigmented form is >%50 of pediatric cases [1].

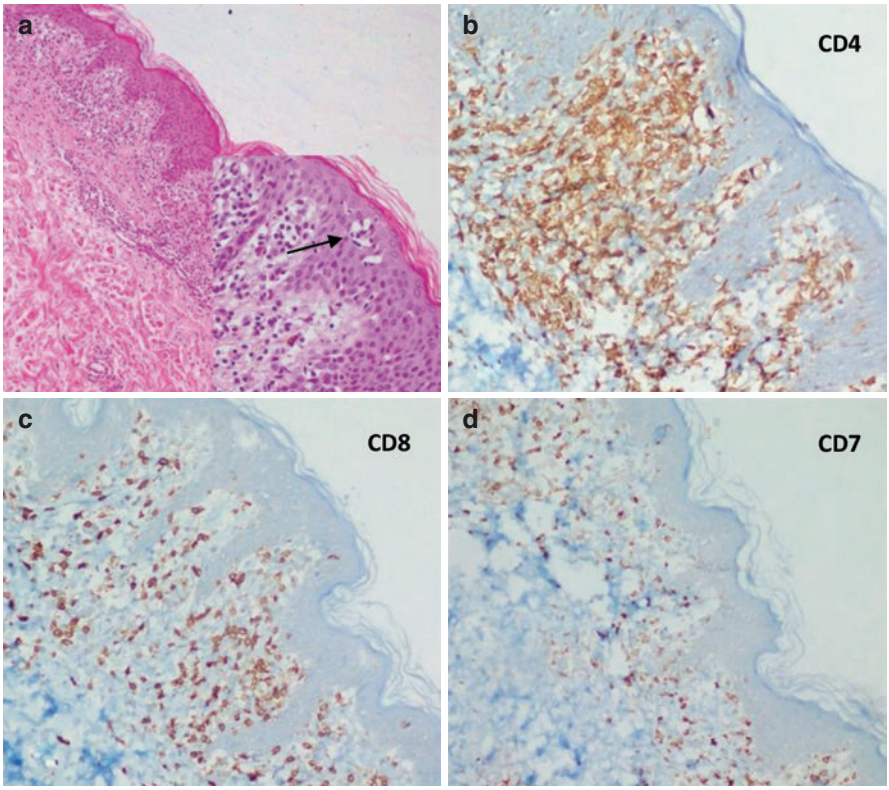

Fig. 5.2 (**a**) Lymphocytes that fill the dermal papillae and progress transepidermally were seen in the fibrotic papillary dermis (H&EX100), arrow; Pautrier's microabscess. (**b**) CD4 expression in a large number of lymphocytes (CD4X200), (**c**) CD8 expression in fewer lymphocytes (CD7X200). (**d**) CD7 expression in fewer lymphocytes (CD8X200)

Clinically, the cutaneous lesions of mycosis fungoides typically progress through three somewhat distinct stages, an inflammatory premycotic phase, a plaque phase and a tumor phase. The patch stage includes superficial lichenoid infiltrate, mainly lymphocytes and histiocytes and a few atypical cells infiltrating the epidermis without significant spongiosis. This stage may mimic other dermatoses such as eczema or lichenoid dermatoses, like our case. In pediatric cases the atypia may be difficult to appreciate and multiple biopsies are required to make the diagnosis and numerous studies may be needed to prove a clonal proliferation of T cells. In plaque stage, mycosis fungoides progresses, there is more obvious epidermotropism and a denser dermal infiltrate. There may be intraepidermal collections of atypical cells. When tumours start to form clinically, histomorphology shows a much denser dermal infiltrate. There may be no exocytosis of lymphocytes in this stage. Transformation to large cells may occur [3]. Sezary syndrome is the leukemic form of the disease in

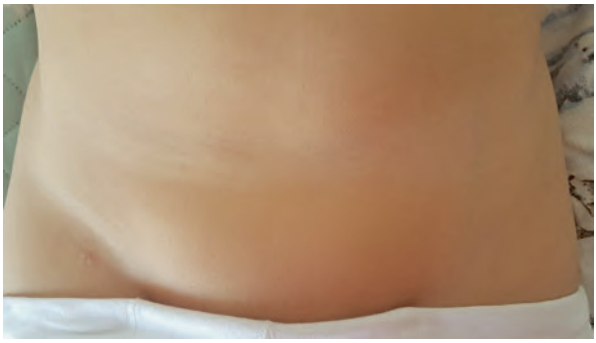

Fig. 5.3 Regression of the lesions after phototherapy

which erythroderma is accompanied by measurable blood involvement by malignant lymphocytes with hyperconvoluted, cerebriform nuclei known as Sezary cells [4].

The neoplastic lymphocytes typically have a T-helper phenotype (CD3+, CD4+, CD8−); less commonly, the neoplastic cells may express cytotoxic T-cell phenotype (CD3+, CD8+, CD4−). Studies have shown the cytotoxic T-cell phenotype is more frequently seen in children than adults and the CD8+ variant may be associated with an indolent course. The loss of CD7 expression can be observed even in the early phases of the disease [1]. Pautrier's microabscesses (lymphocytes with cerebriform nuclei and formation of intraepidermal aggregates) are pathognomonic for MF and are rarely seen in other lymphomas.

According to the studies conducted for the last 10 years, the most common treatment method is phototherapy. Topical corticosteroids were often used in combination with phototherapy and were used as the sole treatment in %9 of patients. Other topical agents such as retinoids (%6) and topical nitrogen mustard (%2) were used less frequently. Local radiation and surgical excision were used in a minority of cases (%1) [1].

The patient was threated with phototherapy (narrow-band UVB two times a week). Significant improvement was observed clinically after the current treatment (Fig. 5.3).

Key Points

1. Mycosis Fungoides is the most common primary cutaneous lymphoma in adults and children.
2. Children with MF often present with nonclassical variants of the disease. The most common of these are hypopigmented, hyperpigmented, folliculocentric and poikilodermic types.
3. Phototherapy is the most commonly used treatment method in pediatric patients.

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Chapter 6
A Complex Skin Disease

Tugba Kevser Uzuncakmak, Ayşe Mine Önenerk, and Zekayi Kutlubay

Case

A 16-year-old male presented to the dermatology department with a 2-month history of rapidly growing crusted and ulcerated lesions on his forehead. Clinical examination revealed several lentiginous proliferations on sun exposed areas on face, extansor surfaces of upper extremity and on pretibial region. He has widespread crusted erosions on scalp, frontal region, perioral region, periorbital edema, a 2 cm ulcerated lesion with oozing and a 4 mm pink nodular lesion beyond this ulcerated lesion. (Fig. 6.1). His lesions were first appeared when he was 2 years old and he was under follow up in the departments of dermatology, plastic surgery and pediatric oncology, routinely. On dermoscopic examination ulceration, telengiectatic vessels on a pink structureless basis and superficial scales were detected (Fig. 6.2). In his laboratory tests including complete blood counting, biochemistry, erythrocyte sedimentation rate and C-reactive protein, an increase in acute phase markers were detected.

He was referred to plastic surgery department for excisional biopsy. Histologically,well differiated infiltrated squamous cell carcinoma and basal cell cell carcinoma were detected (Fig. 6.3). No perivascular or perineural invasion was detected. He was referred to department of oncology for further investigation.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_6

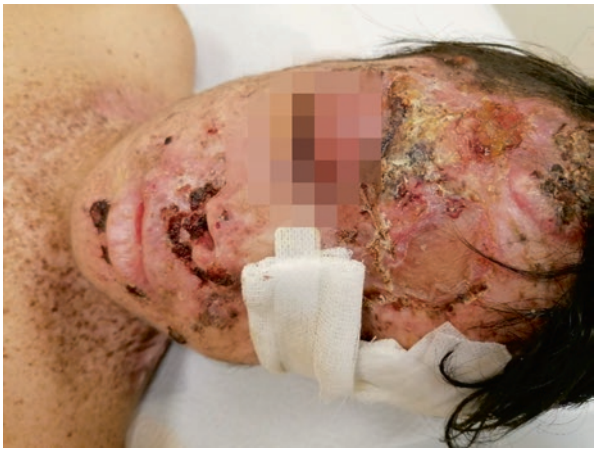

Fig. 6.1 Lentiginous proliferations, widespread crusted erosions on scalp, frontal region, perioral region, periorbital edema, a 2 cm ulcerated lesion with oozing and a 4 mm pink nodular lesion beyond the ulcerated lesion

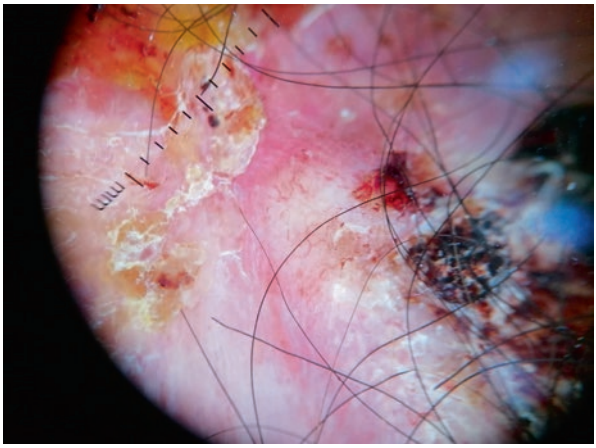

Fig. 6.2 A 4 mm pinkish structurelesss papular lesion with peripheral telengiectasias near crusted erosion on frontal region

Based on the case description and the photograph, what is your diagnosis?

- Hydroa vacciniforme
- LEOPARD syndrome
- Rothmund- Thompson syndrome
- Xeroderma pigmentosum

Diagnosis

Basal cell carcinoma and squamous cell carcinoma in xeroderma pigmentosum.

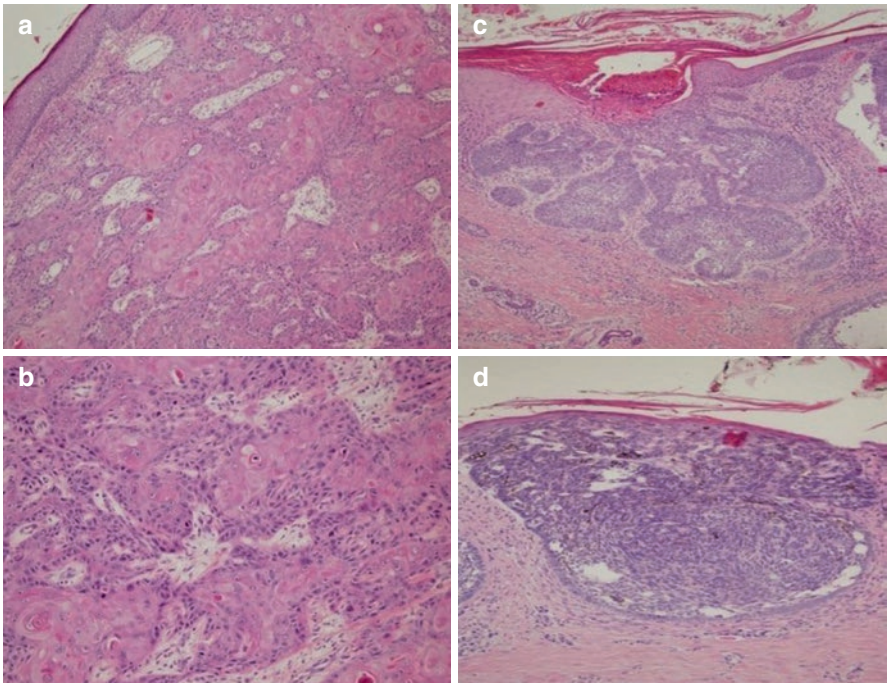

Fig. 6.3 (**a**) Well differentiated squamous cell carcinom (H&E, ×200), (**b**) Well differentiated squamous cell carcinom (H&E, ×400), (**c**) Basal cell carcinoma, nodular type (H&E, ×200), (**d**) Basal cell carcinoma, superficial type (H&E, ×200)

Discussion

Xeroderma pigmentosum (XP) is a rare hereditary disorder characterized by impaired DNA repair function [1]. This rare disorder was first defined by Hebra and Kaposi in 1874, afterwards, in 1882, the term xeroderma pigmentosum was used by Kaposi, referring to its characteristic dry and pigmented skin. It has been reported in all races with an equal prevalence in males and females. Characteristic lesions of XP usually begin at age of 1–2 years. The prevelance of XP is estimated to be approximately 1/250,000 population in United States. This ratio is approximately similar in Europe and reported to be higher (1 case per 40,000 population) in Japan [1, 2]. Similar with the other autosomal recessive disorders, the parents are heterozygotes and they are healthy. Usually there is no family history.

The disease is seen in 3 clinical phases according to clinical findings. Although the skin looks healthy at birth, typically, a diffuse erythema, lentiginous pigmentation and scaling occur after 6 months. These findings are commonly seen on sun-exposed areas, appearing especially on the face. Then these skin changes appear on the other parts of the body usually on lower legs, the neck, and even the trunk in

extreme cases by the time. Although these features may seem to diminish during the winter months due to the decreased sun exposure, they become permanent sooner [1].

In the second stage of the disease, poikiloderma, including mottled hyperpigmentation and hypopigmentation, telangiectasias and skin atrophy, is the main cutaneous finding. Telangiectasias may occur both in the sun-exposed areas and in unexposed skin and even on mucosal surfaces. In the third stage, different malignancies, including squamous cell carcinomas, malignant melanoma, basal cell carcinoma, and fibrosarcoma may occur. These malignancies may occur as early as age 4–5 years and are more prevalent in sun-exposed areas. Nearly half of the patients survive beyond age 20 years. Metastatic melanoma and squamous cell carcinoma are the important causes of mortality in these patients. It was reported that XP patients have an 10,000-fold greater risk of developing cutaneous malignancy when compared to the general population, median onset age of cutaneous cancers was also reported to be <10 years [3]. Actinic damage occurs very early, between ages 1 and 2 years. Education of the patient and the caregivers is the most important topic in the management of xeroderma pigmentosum. The need for adequate solar should be reinforced at every visit. Sunblocks should be used, even in winter months and during evening and early morning hours. The exposed surfaces of the skin should be shielded with protective, double-layered clothing and broad-brimmed hats. The eyes should be shielded with UV-absorbing sunglasses with side shields. Ocular problems may occur in aşmost 80% of individuals with xeroderma pigmentosum. The most common ocular problems are photophobia and conjunctivitis. The propensity for malignancies, such as squamous cell carcinoma, basal cell carcinoma, sebaceous cell carcinoma, and fibrosarcoma, can also involve the eyes of patients with xeroderma pigmentosum.

The main goal in the treatment of patients with XP is to protect the patients from sun exposure. Using waterproof sunscreens including both chemical and physical filters is a must do for these patients. Topical 5 fluorouracil, imiquimod 5%, systemic acitretin may be iniated for actinic keratosis. Using DNA repair enzyme into the skin via specially engineered liposomes is anew treatment modality in patients with XP. T4 endonuclease V has been shown to repair cyclobutane pyrimidine dimers resulting from DNA damage. No significant adverse effects were found among any of the patients. It was shown to lower the rate of development of basal cell carcinoma lesions after 1 year of treatment [4].

Gene therapy for xeroderma pigmentosum is still in experimental stage. Several pathways of correcting the defects in xeroderma pigmentosum have been shown in vitro and in animal studies using viral vectors (adenoviruses and retroviruses) carrying the gene replacement products. Skin grafting with the genetically corrected skin was also noted to be useful in xeroderma pigmentosum patients in the future.

Hydroa vacciniforme (HV) is a rare photodermatosis with an unknown etiology. It usually occurs in childhood accepted within the spectrum of *Epstein-Barr* virus–related lymphoproliferative disorders [5]. Clinically it is characterized by recurrent vesicles on sun-exposed skin that heal with vacciniform or varioliform scarring.

Histopathologically, intraepidermal reticular degeneration and cellular necrosis are commonly detected. Most of the patients heal spontaneously during late adolescence. Commonly, mild burning, itching, or stinging in exposed sites begins a few hours or days after sun exposure. Vesicles heal with varioliform scarring. The lesions often occurs in spring, with recurrences in summer [5].

LEOPARD syndrome is a complex dysmorphogenetic disorder of variable penetrance and expressivity. This syndrome is the acronym LEOPARD of the main features of the disorder, including eentigines (multiple), electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth and deafness [6]. The diagnosis of LEOPARD syndrome may be very difficult in early childhood and can be clinically suspected in patients who have 3 main features: characteristic facial features, hypertrophic cardiomyopathy, and café au lait spots in the first months of life.

Rothmund-Thomson syndrome, or poikiloderma congenitale, is another rare autosomal recessive disorder associated with mutations in the *RECQL4* helicase gene located on 8q24 [7]. It is characterized by early photosensitivity and poikilodermatous skin changes, juvenile cataracts, skeletal dysplasias, and a predisposition to osteosarcoma and skin cancer. Patients usually present with a rash (poikiloderma), small stature, and skeletal dysplasias. The acute phase begins in early infancy as red patches or edematous plaques, sometimes with blistering. Clinically lesions usually firstly begin from the cheeks then later occur on other areas of the face, the extremities, and the buttocks. In chronic stage cutaneous manifestations are characterized by poikiloderma (atrophy, telangiectasias, and pigmentary changes). These changes are typically seen on the face, extensor surfaces of extremities, and buttocks with sparing of the chest, abdomen, and back. Acral hyperkeratotic lesions can be seen on the elbows, knees, hands, and feet during puberty. Photosensitivity is a feature in more than 30% of cases. Gastrointestinal and hematological abnormalities have also been noted to occur.

Key Points

- Xeroderma pigmentosum is an autosomal recessive DNAa repair disorder h dermatological, ocular, and neurological manifestations with skin cancer predisposition.
- Clinically lesions usually appear by 2 years of age with increased number of lentigines (freckle-like pigmentation) in sun-exposed areas and extreme sensitivity to sunlight resulting in acute severe sunburns.
- Cutaneous malignancy risk is almost 10,000 folds higher in XP patients than the general population.
- The median age of cutaneous malignancies is <10 years in XP patients.
- Avoiding from sun exposure is the main therapeutic approach in XP patients.
- Topical 5 fluorouracil cream, imiquimod 5% cream and systemic acitetin can be offered for actinic daamage.

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Chapter 7
A Congenital Lesion of the Scalp with an Unusual Shape

Fabio Arcangeli and Elisa Sama

An 18-month-old male infant presented for evaluation of a well-defined linear and raised lesion on the right posterior parietal scalp (Fig. 7.1). His parents reported its presence from birth. The lesion had increased progressively in size until reaching 3.5 × 1 cm and had changed colour from intense red to yellowish pink.

The patient did not have any related symptoms except for sparse hair at the lesion. The medical history did not reveal any pregnancy or post-pregnancy trauma.

The physical examination showed a yellowish pink lesion, with a smooth and shiny surface, very similar to a scar lesion but with a soft consistency (Fig. 7.2).

A previous ultrasound examination excluded intracranial connection and brain abnormalities. This was subsequently confirmed by a nuclear magnetic resonance examination.

In the absence of a clinical diagnosis a surgical excision was planned.

Based on the history and the photographs which diagnosis would you propose?

1. Encephalocele
2. Lipoma
3. Meningothelial hamartoma
4. Keloid

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_7

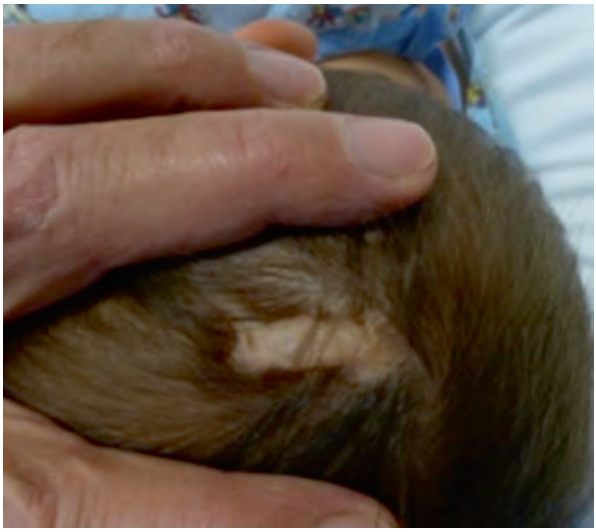

Fig. 7.1 A yellowish pink raised lesion on the posterior scalp

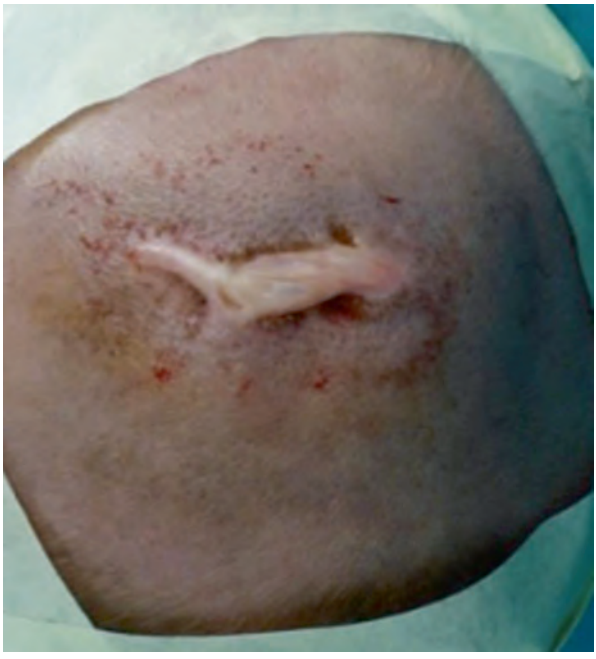

Fig. 7.2 The unusual shape lesion with a smooth and shiny surface

Diagnosis

Meningothelial hamartoma.

Discussion

A total excision was performed. The histological examination showed pseudo-vascular lumens bordered by often spindle shaped elements. They were devoid of significant atypia and sometimes multinucleated, arranged in a disordered way and mixed with connective fibers and adipose tissue (Fig. 7.3). Because the diagnosis was still unclear, to exclude other possible diagnosis such as angiosarcoma or melanoma, immunohistochemistry was performed. It resulted negative for HMB-45, S-100, cytokeratins, factor VIII and positive for epithelial membrane antigen (EMA), vimentine and focally for CD 68 (Fig. 7.4).

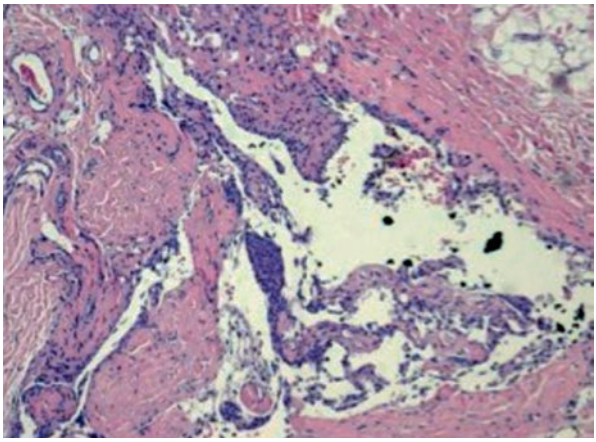

Fig. 7.3 The histologic examination showed a pseudo-vascular pattern, with disseminated epithelioid cells mixed up with connective fibers and adipose tissue, within deep dermis

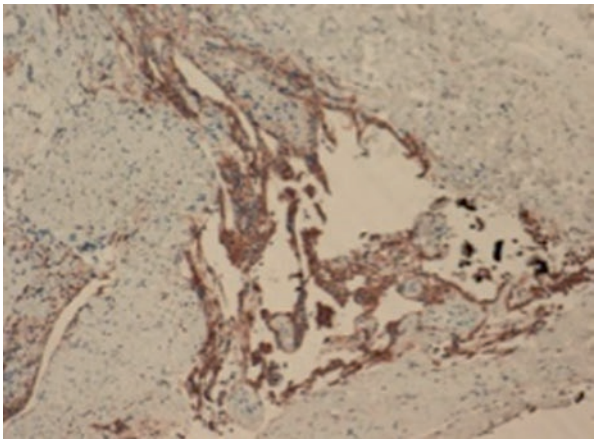

Fig. 7.4 The immunohistochemistry revealed a strong positivity for epithelial membrane antigen (EMA) and focally positivity for CD 68

On the basis of the histological examination and the immunohistochemical study a diagnosis of meningothelial hamartoma was made. One year after surgery no signs of recurrence were present.

Soft tissue masses of the scalp are commonly encountered in clinical practice. Pediatric scalp lesions are fortunately benign in most cases (98%) [1]. Congenital lesions include menigocele or encephalocele, due to a neural tube defect where part of the skull has not formed properly, dermoid cyst, lipoma and others [2]. It is important to consider that the lack of lesional mobility or a midline location should prompt an initial radiographic evaluation to rule out cranial meningo or encephaloceles.

Encephaloceles are usually found immediately after birth but sometimes a small encephalocele can go undetected. Encephalocele is a sac-like protrusion of the brain and the meninges through an opening in the skull. In our case the ultrasound examination excluded any communication with intracranial space.

Lipoma is the most common benign tumor of the scalp. It presents as a soft subcutaneous mass with an elastic or rubber consistency. In our case the shape and consistency did not suggest the diagnosis of lipoma.

Keloid is an abnormal proliferation of fibrous tissue that forms at the site of a cutaneous injury. It grows beyond the original margins of the scar, creating typical crab claw-like shapes. Keloid usually has an erythematous, smooth and shiny surface. Its consistency can range from soft to rubber but in most cases, it is very hard. In our case the shape of the lesion could suggest a diagnosis of keloid but no trauma was reported and the consistency was very soft.

Meningothelial hamartoma, first described by Suster and Rosai in 1990 is a collection of meningothelial elements in an ectopic location. It is characterized by a mixture of various components (among which meningothelial elements) of the connective tissue arranged in a disordered way in the dermis. It was also called "rudimentary meningocele", "sequestered meningocele" and "hamartoma of the scalp with ectopic meningothelial elements" [3]. It may have been associated with rare hair, as in our case, and the most common sites involved are the occipital midline and posterior regions of the scalp. Locations on parieto-occipital area, vertex and forehead regions have been reported too [3]. In general, it does not extend beyond the subcutis. The cause of meningothelial hamartoma is still unknown. Several hypotheses were proposed: some authors think it comes from ectopic meningothelial remains during embryologic development, some others have suggested the abortive migration of cells from the neural crest or that it is a form of meningocele with an obliterated intracranial communication [3].

The treatment of choice is surgical removal.

Key Points

- Soft tissue masses of the scalp are common and they are benign in most cases
- Congenital lesions include menigocele or encephalocele, dermoid cyst, lipoma and others
- The lack of lesional mobility or a midline location should prompt an initial radiographic evaluation to rule out cranial meningo or encephaloceles

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Chapter 8
A Female Patient with Brown Ulcerated Papule

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

A 17-year-old girl presents with a 3-year history of a slow-growing brown papule on the forehead. The patient describes that the lesion had begun as a small 'spot', which had gradually enlarged and recently been ulcerated and intermittently bleeding. She is a high school student. There is no previous history of skin disease excluding acne and no family history of similar problems. She denied any other symptoms (Figs. 8.1 and 8.2).

Based on the case description and photographs, what is your diagnosis?

1. Melanoma
2. Nodular basal cell carcinoma
3. Acquired melanocytic nevus
4. Basal cell nevus syndrome
5. Xeroderma pigmentosum

Histopathology revealed large, round aggregations of basaloid keratinocytes extend from the epidermis into the dermis and central ulceration and necrosis with an associated inflammatory response. Centrally, the nuclei have become crowded with scattered mitotic figures, and necrotic bodies were evident.

Diagnosis

Nodular basal cell carcinoma.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_8

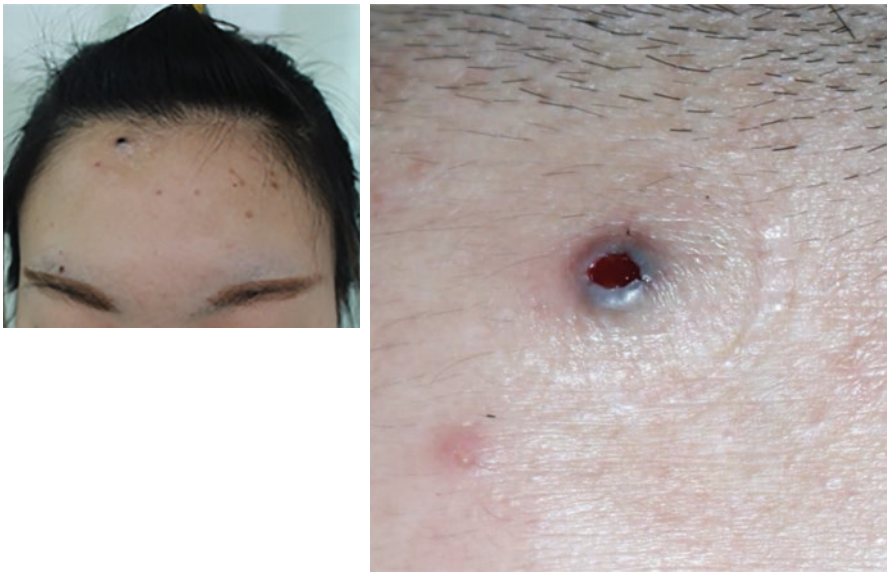

Fig. 8.1 A hyperpigmented papule 7 mm in diameter with an elevated rolled border and central ulceration. Some post inflammatory hyperpigmentation lesions

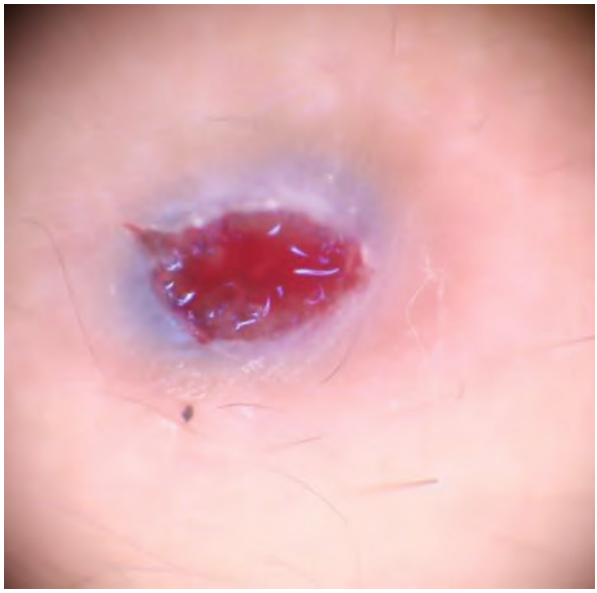

Fig. 8.2 The lesion under dermoscopy

Discussion

Basal cell carcinoma (BCC) is a common, locally invasive, keratinocyte cancer. It is the most common form of skin cancer. BCC is also known as rodent ulcer and basalioma. BCCs are particularly prevalent in elderly males. However, they also affect females and younger adults.

Basal cell carcinoma (BCC) in children younger than 15 years is rare [1] and is usually associated with a predisposing genetic condition such as basal cell nevus syndrome and xeroderma pigmentosum [2]. Reports of pediatric cases unrelated to a genetic syndrome are rare.

In a large study of 36,207 children done by De la Luz Orozco-Covarrubias et al. [3], 53 types of skin tumors were demostrated in which 36 were primary and 17 were metastatic. Among these 36 primary tumors, only 5 cases were BCC (13%). The incidence of BCC was only 1.9 in 10,000 patients. In another wide series of 6264 chilhood cancers, 21 primary malignant skin tumors were diagnosed and only 9.5% of them were reported to be BCC [4]. In an article published in 2007, 107 idiopathic BCC cases were reviewed and the head was (90.4%) the most often site. Most common localization was cheek in the head and neck region. The scalp accounted for 14.5% of the cases. In the same study, nodular, adenocystic, follicular nodulocystic, superficial, and typical nonaggresive variants were reported to constitute 80% of all cases. 18% of recurrence was reported in that study. Any correlation between the histopathologic variant and the prognosis was not mentioned [5]. In the case we presented, localization was the forehead and the histopathologic variant was nodular.

BCC is most commonly seen in patients with light-colored hair and skin. Major risk factors for BCC are increased sun exposure, vitiligo-albinism, immunosuppression (AIDS, drug use due to organ transplantation), and radiation. Genetic factors are important as well [3–5]. Most likely cause in our case was supposed to be sun exposure. Other major risk factors of BCC were not encountered at all.

Gorlin-Goltz syndrome (basal cell nevus syndrome) is an autosomal dominant inherited disorder, which is characterized by multiple basal cell carcinoma, maxillary keratocysts, multiple pits of palms and soles, ectopic calcification of cranial membranes, cysts of jaw, and musculoskeletal malformations [6]. Xeroderma pigmentosum is an autosomal recessive inherited disorder, which is characterized by sun sensitivity, increased freckling, pigmentation, and dryness of sun-exposed skin and increased risk of cutaneous neoplasms (BCC, squamous cell carcinoma, and melanoma) [7]. No family history was observed in our case. In additon, no genodermatosis signs have been seen other than the skin pathologies [8].

The lesion of this patient was diagnosed as an idiopathic form of basal cell carcinoma, both clinically and histopathologically.

Key Points

- Basal cell carcinoma in children younger than 15 years is rare
- It is usually associated with a predisposing genetic condition such as basal cell nevus syndrome and xeroderma pigmentosum.

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Chapter 9
A Firm Lump of the Eyebrow

Maria Beatrice de Felici del Giudice, Roberta Manuguerra, Michele Maria Dominici, and Claudio Feliciani

A 5 year-old female was referred to the dermatologic department for the presence of a nodule in the medial part of the right eyebrow, appeared 1 year earlier. The overlying skin was completely normal and a delimited, subcutaneous, round and firm nodule was detected (Fig. 9.1). No previous trauma was reported.

An ultrasound check revealed a well-circumscribed hyperechoic nodule with internal calcification, completely localized in the subcutaneous tissue.

A surgical excision of the whole lesion was performed without any recurrences in 2 years of follow up. Hystopathologic exam showed a well-defined dermal nodule composed almost exclusively of shadow cells and some calcifications (Fig. 9.2).

What Is Your Diagnosis?

1. Dermoid cyst
2. Trichilemmal cyst
3. Pilomatrixoma
4. Eruptive vellus hair cyst
5. Foreign body granulomatous reaction

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_9

Fig. 9.1 Clinical feature: round hard nodule covered by normal skin localized in the medial third of the eyebrow (black arrow)

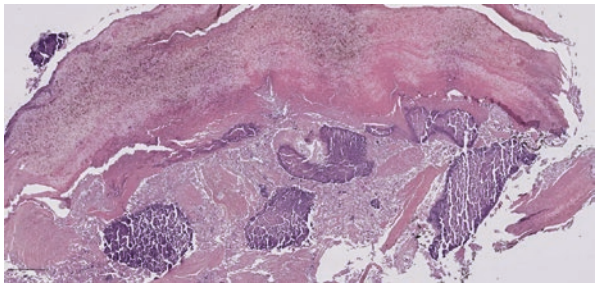

Fig. 9.2 Histopathologic features: well-circumscribed dermal nodule composed almost exclusively of shadow cells and some calcifications (H&E, x10)

Diagnosis

Pilomatrixoma.

Discussion

Pilomatrixoma (also known as trichomaticoma or calcifying epithelioma of Malherbe) is an amartoma of hair matrix cells with an uncertain etiology. In some studies a mutation in CTNNB1 gene of Wnt pathway is described. Mutations would lead to an overexpression of beta-catenin, a pivotal protein that regulates several cellular processes, including hair follicle maturation and differentiation [1].

Pilomatrixoma is a benign skin tumor localized in the deep dermis or subcutaneous fat, appearing more commonly on the head and neck region, followed by upper limbs, trunk and lower limbs [2]. It is rare but the real incidence is not so clear [1]. The childhood and adolescence are the ages of the first peak of incidence, being the V-VI decades the second one [1]. Females seem to be slightly more involved [3]. Clinically, pilomatrixoma appears as a well circumscribed and firm nodule with a normal overhead epidermis; this clinical type, called mass type, is the most common and when multilobated it is characterized by the “tent sign” in which the nodule protrudes from the skin.

When the lesion is more superficial, the epidermis can appeare bluish (pigmentation type). Other clinical types are the keloid-like type and the ulcerated or perforated one, in which calcific material extrudes from the tumor [2]. Generally, pilomatrixoma is asymptomatic but mild pain and pruritus can be reported, especially in bigger lesions. It is more frequently a solitary lesion and, when multiple, it is described as associated with inherited and/or syndromic conditions, such as Turner's, Gardner and Kibuki syndrome, sclerosis tuberosa, myotonic distrophy [1].

Imaging tests, especially ultrasonography, can be helpful in the definition of preoperative diagnosis. Ultrasound examination usually shows a hyperechoic dermic or subcutaneous lesion with inner multiple little calcifications that clarify the typical hardness of the nodule.

Histopathologically, the epidermis is generally normal and the tumor is characterized by a mixture of basaloid and ghost cells. The latter predominate in long-lasting lesions, being ghost cell a maturation of basaloid cells that acquire abundant eosinophilic cytoplasm and develop small hyperchromatic nuclei. Another clue of final maturation is the presence of internal calcifications that are probably remnants of ectodermal pilar keratinocytes [1].

Malignant modification in pilomatrix carcinoma is rare and usually occurs in adulthood [4], nevertheless radical surgical excision is the treatment of choice also in children. Recurrence rate is low after surgery and continuous recurrences of the same lesion need attention and strict follow up.

Key Points

- Pilomatrixoma is a rare benign skin tumor that appears as a solitary, firm and hard nodule
- When multiple it is mandatory to exclude other syndromic or inherited diseases
- Ultrasound examination is important for a better definition and as a preoperative tool
- A complete excision is the gold standard of the treatment also in childhood

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Chapter 10
A Girl with Erythema all Over the Body

Shu-Zhen Yue, Yang-Yang Luo, Jian-Ping Tang, and Bin Zhou

A 1-year-4-month-old girl presented to the office with abdominal red macules for more than 1 month, accompanied by itching. She was once treated with drugs (specifically unknown). No obvious effect was seen. The rash gradually affected the whole body, accompanied by desquamation (Fig. 10.1). At the same time she had repeated fever for half a month.

Based on the Case Description and the Photograph, What Is Your Diagnosis?

1. Drug-induced hypersensitivity syndrome
2. Biotin deficiency
3. Netherton syndrome
4. Omenn syndrome

After admission, according to the medical history, physical examination and auxiliary examination, the possibility of "acetaminophen" drug allergy was considered, and the drug should be stopped, and gamma globulin and other symptomatic treatments were given. After 16 days of treatment, the rash almost disappeared and he was discharged from the hospital. One week after discharge, erythema on the trunk began to appear again, which developed rapidly and affected the whole body, and the whole body was flushed and desquamated, which aggravated into hypertrophic plaques with itching. Therefore, he was admitted to the hospital again and was

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_10

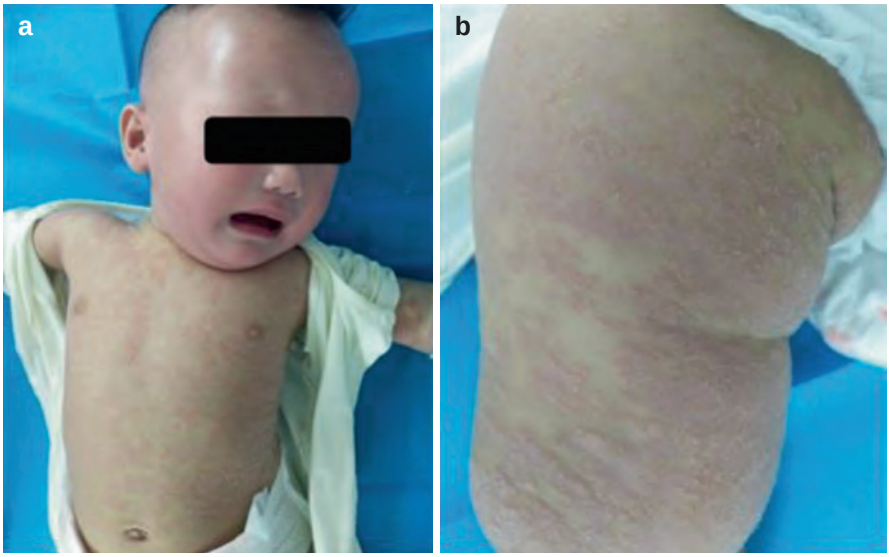

Fig. 10.1 Clinical manifestation of the patient. (**a**) erythema on his face and trunk; (**b**) erythema on the lower limbs

still treated with intravenous immunoglobulin after admission, but the control effect was not good, and the skin lesions did not disappear significantly. Gene sequencing results report RAG1 homozygous mutation. Parental gene sequencing: RAG1 heterozygous variants. The child finally died of severe pneumonia and respiratory failure.

Diagnosis

Omenn syndrome.

Discussion

Omenn syndrome is a rare and severe combined immunodeficiency disease, with an early onset (within 6 months), desquamative erythroderma, hepatosplenic lymphadenopathy, eosinophilia, diarrhea, IgE Increased, loss of B lymphocytes, severe damage to T and B lymphocytes [1].The prognosis of this disease is poor, and death is often caused by organ failure and severe infection. It is currently known to be caused by RAG1 or RAG2 gene defects [2]. Studies have found that gene mutations such as IL7R and DNA ligase can also cause such diseases [3]. Drug hypersensitivity syndrome is a rare and severe drug eruption that is often life-threatening due to

severe organ damage (such as liver failure). Biotinidase deficiency is an autosomal recessive genetic disease in which biotin absorption and utilization disordera are caused by mutations in the biotinidase gene. It often manifests as severe nerve, skin damage and metabolic disorders. The fatality rate and disability rate are high. Netherton syndrome is a rare autosomal recessive genetic disease. The clinical features include ichthyose erythroderma, intussusception fragility (bamboo hair), and atopic constitution.

The disease is generally symptomatic and supportive treatment, including nutritional support, avoiding infection, infusion of albumin, immunoglobulin, etc. The effective treatment is bone marrow transplantation or stem cell transplantation. If no transplantation is performed, the survival period is generally no more than 1 year [4]. Omenn syndrome is young at onset, the disease progresses quickly, and the disease is serious. It is easy to be misdiagnosed and missed. It needs to be carefully differentiated from other diseases. The incidence of Omenn syndrome is low, but the mortality rate is high. Attention should be paid to the unique clinical manifestations of the disease in order to better diagnose and treat early, and improve the survival rate of children.

Key Points

- Omenn syndrome is rare and severe combined immunodeficiency disease.
- Typical characteristics include desqumtive erythroderma, hepatosplenic lymphadenopathy, eosinophilia, diarrhea, edema, IgE Increased, loss of B lymphocytes, severe damage to T and B lymphocytes.

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Chapter 11
A Girl with Prethoracic Subcutaneous Nodule

Wen-Jia Yang, Hao Guo, Xing-Hua Gao, Jiu-Hong Li, and Jing Lan

A 3-year-old young girl presented to the dermatology department. At the time of her birth, her parents found that there was a 1.0 cm × 1.5 cm subcutaneous mass at her sternal corner of anterior chest wall, with the obviously border. The surface of the rash was hairy. The mass persists and gradually increases to 2.0 × 2.4 cm as the child grows older (Fig. 11.1). Palpatory findings on physical examination, the nodule was soft and compressible, with no tenderness and no arterial pulse sense. When the little girl cried and presented with other emotional agitation, subcutaneous nodules were more prominent and darker than normal.

Based on the Case Description and the Photograph, What Is Your Diagnosis?

1. Venous Malformation
2. Hemangioma
3. Verrucous Vascular Malformation
4. Blue Rubber Bleb Nevus Syndrome

Doppler ultrasound showed that the area of hypoechogenicity at the sternal angle of the anterior chest wall was visible in the cutaneous layer to the extent of about 0.98 × 0.31 cm. The boundary was clear and with no obvious envelope. The superficial fascia was hypoechoic locally in the range of about 1.85 × 1.13 cm, with abundant but slow blood flow in the above hypoechoic areas (Fig. 11.2).

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_11

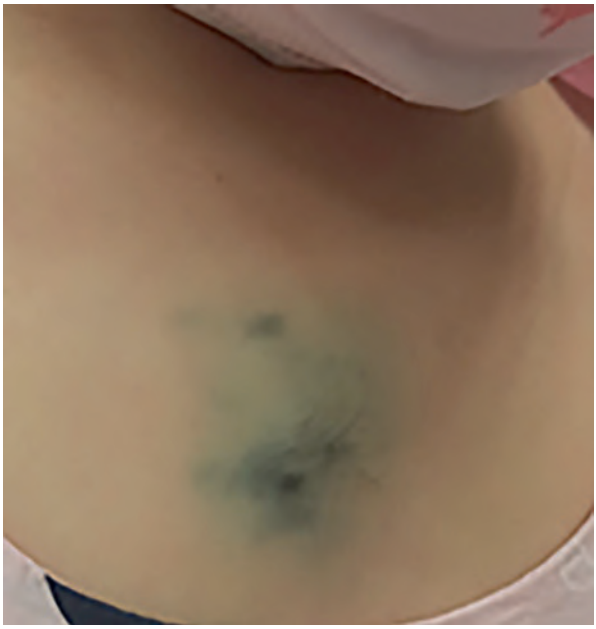

Fig. 11.1 Clinical manifestation of the patient: Dark blue soft nodules with hairy surface, with compressible palpation

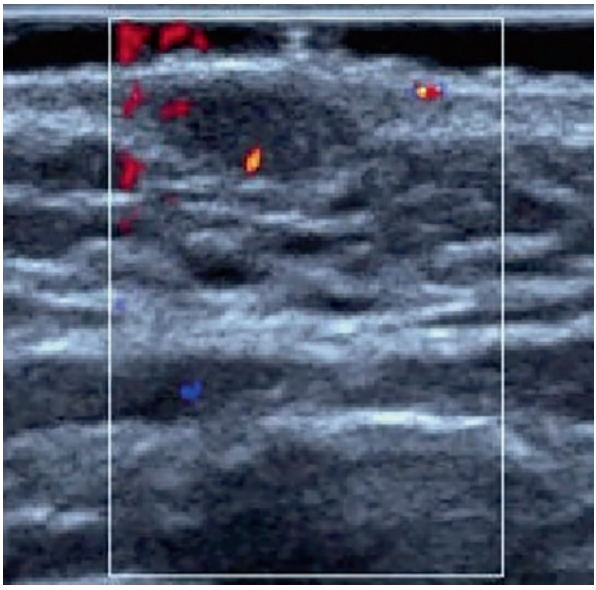

Fig. 11.2 Doppler ultrasound: There is low-velocity blood flow in the hypoechoic area of the subcutaneous and superficial fascia area

Diagnosis

Venous Malformation.

Discussion

Congenital vascular malformations (CVMs) include lymphatic malformation, venous malformations (VM), capillary malformations, arterial malformation and arteriovenous malformation. Among the above type, the first three are slow flow malformations, and the latter two are fast flow malformations [1]. VM is one of the most common form of CVMs. VM is born with a congenital vascular defect and never fade spontaneously for the rest of life [2]. Some deep vascular lesions may not appear until they grow elder. Hormone levels such as puberty and pregnancy can stimulate its growth. It will continue to grow slowly at a rate proportional to the growth of the body. Depending on the amount of mixed fibrous connective tissue, the mass have different densities. The deep inside of the venous malformation is connected to the venous circulation through capillaries or veins. The disease can be complicated with thrombotic veins, phlebolithiasis, local hyperhidrosis and hirsutism. When the condition is severe, the surrounding tissues may be compressed and manifest with symptoms and signs, such as limb pain when the nerve is compressed.

These diseases were classified only based on clinical findings. Some venous malformations showed familial inheritance [1]. Various VM-related syndromes were name-based eponyms, such as: Gorham–Stout Syndrome, Klippel-Trenaunay!, Klippel-trenauney Syndrome, Servelle-Martorell syndrome, Parkes-Webber Syndrome and so on. The above-mentioned syndromes were classified based on their unique characteristics of skin, subcutaneous tissue, bones and blood vessels.

The imaging examination of vascular malformation is very important for the correct diagnosis and treatment of the disease. The understanding of vascular anatomy, hemodynamic characteristics and lesion location needs the help of advanced imaging methods, such as doppler ultrasonography(US) and magnetic resonance imaging (MRI). Doppler ultrasonography (US) has become the best method for initially diagnosing VM because of its low cost, noninvasive, no ionizing radiation and the ability to judge hemodynamic characteristics. However, vascular magnetic resonance imaging MRI is beneficial to determine the scope and type of damage and guide appropriate treatment [3] (Figs. 11.1 and 11.2).

For some syndromes with osteolytic damage, radiotherapy or bisphosphonate can prevent bone destruction. Vein injuries in limbs and other parts can be treated with elastic bandages. Ultrasound-guided sclerotherapy or venous embolization can be performed under angiography. However, before any treatment, a comprehensive and reasonable assessment of the disease should be done by US or MRI, and intraoperative prevention of thrombosis.

Venous malformations need to be differentiated from the following disorders. Hemangioma is not a vascular malformation, but a vascular tumor originating from endothelial cells. It develops after birth, mainly in the infant or neonatal period to grow rapidly and then slowly degenerate, some hemangioma can disappear by itself. Verrucous Vascular Malformation is a microvascular malformation that extends to the subcutaneous tissue, mostly located in the lower limbs, with hyperkeratotic

wart-like changes on the surface in the late stage. Blue Rubber Bleb Nevus Syndrome is a multiple venous malformation involving the skin and gastrointestinal tract, accompanied by gastrointestinal bleeding and iron deficiency anemia [4].

The little girl was fully evaluated and removed all venous malformations under general anesthesia. There was no sign of recurrence during follow-up for half a year.

Key Points

- Venous malformation is a congenital disease.
- Finding venous malformation related syndromes and appropriate imaging tests are important for the treatment of the disease.

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Chapter 12
A Newborn Girl with Blisters

Hong-Hui Xu and Xing-Hua Gao

A 12-day-old full-term girl presented with several blisters and erosions on the extremities at birth. Three days later, disseminated blisters developed on the extremities and lateral trunks. She was hospitalized and disseminated blisters on erythematous base were found on the extremities (Fig. 12.1). The lesions distributed in a linear appearance.

Based on the Case Description and Photography, What Is Your Diagnosis?

1. Bullous pemphigoid
2. Neonatal herpes simplex
3. Linear IgA bullous dermatosis of childhood
4. Incontinentia pigmenti
5. Epidermolysis bullosa simplex

The patient was the first-born child weighing 3.9 kg. Her parents have no consanguinity. There was no known family history of skin, teeth, bone, eye, or neurological problems. Peripheral blood cell count revealed white blood cell 26.6×10^9/L, lymphocyte 7.55×10^9/L, neutrophil 16.2×10^9/L, and eosinophil 2.50×10^9/L. Skin biopsy demontrated eosinophilic spongiosis, and a mild

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_12

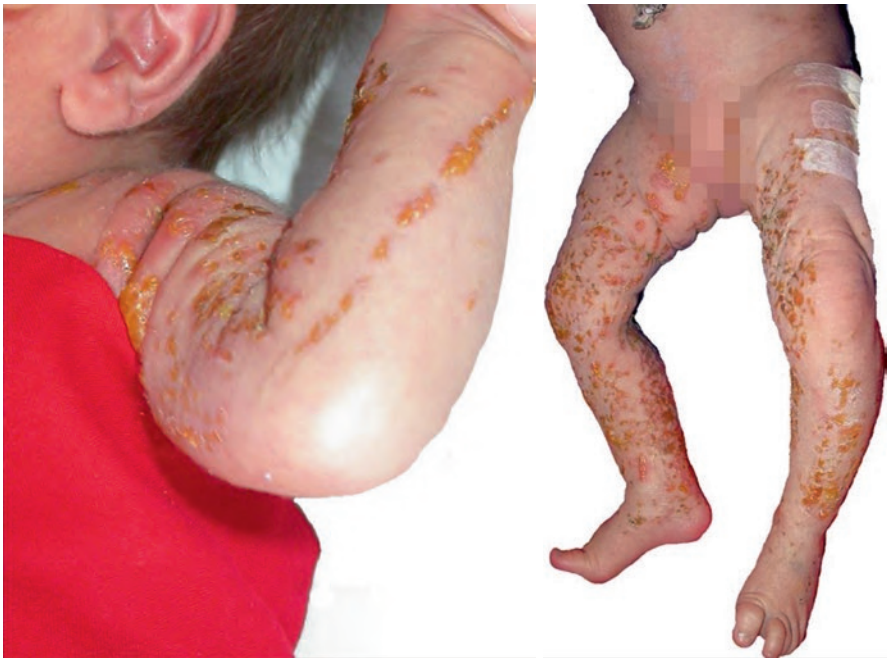

Fig. 12.1 A 12-day-old full-term girl presented with disseminated blisters on the extremities which were found on her birthday

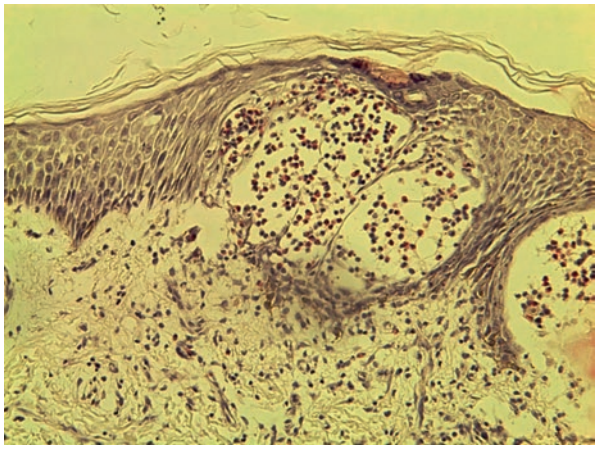

Fig. 12.2 The biopsy from the vesicles on the thigh showed conspicuous eosinophilic spongiosis and vesicles with mild inflammation in the superficial dermis (HE, 200×)

inflammatory infiltration in the superficial dermis (Fig. 12.2). Direct immunofluorescent revealed no deposition of IgG, IgM, IgA, or C3. The blisters resolved spontaneously after 2 weeks leaving hyperpigmentation. The peripheral eosinophilia resolved gradually.

Diagnosis

Incontinentia pigmenti.

Discussion

Incontinentia pigmenti (IP) was first defined by both Bloch in 1926 and Sulzberger in 1928. IP is an uncommon X-linked dominant inheritance neurocutaneous genodermatosis involving skin, teeth, hair or neurologic system. About one third of patients have a family history of IP condition. It is lethal for male fetuses in the uterine, that is why almost all IP patients are female. Very rarely baby boy was born alive with Klinefelter syndrome [1].

About 80% of IP patients carry a mutation in *NEMO*/inhibitor kappa kinase gamma (IKKγ) gene located on chromosome Xq28 [2]. Female mice with a heterozygous deficiency in *IKKγ* gene develop skin symptoms similar to those of IP. IKK is required for NF-κB activation, which TNF-induced apoptosis. NF-κB inactivation results in *IKK*-deficient cells susceptible to apoptosis, which may be the mechanism of the vesicular manifestation of IP. The neighboring cells retaining the IKK activity are resistant to apoptosis and result in the verrucous lesions seen IP.

Most IP patients have cutaneous lesions at birth or in the first two weeks after birth. The skin lesions present predominantly on the extremities, trunk or neck in a linear or whirling distribution following Blaschko lines. The four stages of skin lesions usually occur in sequelae, vesicular stage, verrucous stage, hyperpigmented stage and atrophic stage. The early manifestation of vesicles with or without erythematous bases occur at birth or within first few weeks of life, which usually resolve in a few days to weeks. Verrucous lesions present overlap with vesicles or a few weeks after the resolution of vesicles. The verrucous lesions usually resolve after half a year with secondary hyperpigmentation. Some patients may develop atrophic lesions during adolescence and early adulthood.

Histologic findings depend on the types of lesions biopsied. Biopsy from vesicles demonstrate intra-epidermal eosinophilic spongiosis and dyskeratotic keratinocytes. Verrucous lesion show papillomatous hyperkeratosis, clusters of dyskeratotic cells, eosinophilic infiltration in the epidermis and dermis, and melanophages or melanin in the dermis. The histological changes of hyperpigmented and atrophic lesions including melanin deposition in the dermis and epidermal atrophy are not specific for IP.

Other manifestations of ectodermal dysplasia include hair, nail, and dental abnormalities. Hair features include scarring alopecia, scant eyelashes, and coarse appearance of hair. Nail changes include nail dystrophy!, subungual keratotic tumors and bone deformity of the fingers. Oral abnormalities include delayed dentition, conical or pegged teeth, and cleft palate. The dental findings are diagnostic for IP. Ophthalmologic manifestations Cmay be found within a few weeks after birth,

and blindness is the serious comorbidity. The Central nervous system abnormalities may present as a variety of symptoms including seizures, stroke, metal retardation. The neurologic findings have been reported in 30% of IP patients occurring from the neonatal period through the early infantile period. Ophthalmologic and neurologic complications are the major cause of morbidity and mortality.

The diagnosis of IP is not difficult if the patient presents with typical skin lesions. On the other hand, it might be difficult if the patient with early-onset neurological disorders but without typical skin lesions. In 1993, Landy and Donnai Diagnostic established the diagnostic criteria for IP. The criteria was revised on the basis of advanced recognizing of the manifestations and the analysis of the *IKKγ* gene defect by Minić et al. in 2014 [3].

There is no efficient treatment for IP. The cutaneous lesions generally do not need treatment besides secondary infection control and prevention. Routine assessments of dental and bone development are warranted. Periodic evaluations of the neurologic and ophthalmologic complications are required especially within the first year of life. Gene therapy with an adenovirus vector containing a normal *NEMO* gene was reported able to reduce incidence and delayed onset of seizures in a mouse model of IP [4].

Key Points

- Incontinentia pigmenti is an X-linked dominant neurocutaneous genodermatosis caused by a defect in the *NEMO/IKKγ* gene which is usually lethal for male fetuses.
- The diagnosis of IP is based on the typical skin lesions, other systemic abnormalities and the gene mutation analysis.

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Chapter 13
A Nodular Lesion with Blue Hue on the Lower Leg

Nooshin Bagherani, Akbar Hassan Pour, and Bruce R. Smoller

A 15-year-old girl referred with appearance of a painless, progressively enlarging, blue-hued nodular lesion on the lower part of the left leg for 6 months. The lesion was firm and nontender to palpation. The patient mentioned the appearance of a similar lesion at the same site in 3 years ago which had been excised by a surgeon, but the resection resulted in an oozing discharge for 2.5 years, just before the appearance of the current lesion (Fig. 13.1).

Based Upon the Above-Mentioned History and Clinical Feature, What Is Your Diagnosis?

- Nodular hidradenoma
- Kaposi sarcoma
- Lymphangioma
- Hidradenocarcinoma
- Metastatic lesion

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_13

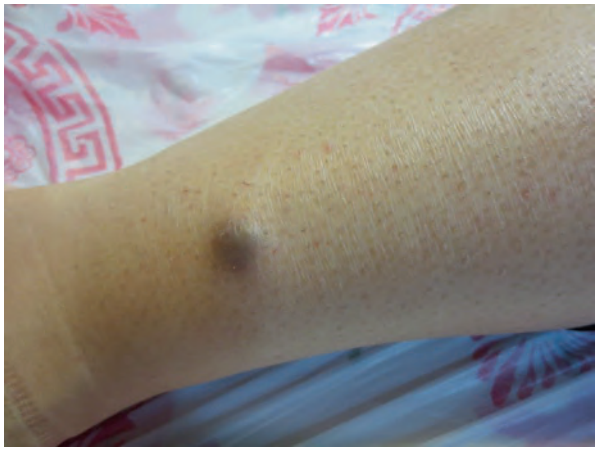

Fig. 13.1 A painless, progressively enlarging, blue-hued nodule on the lower part of the left leg in a 15-year-old girl

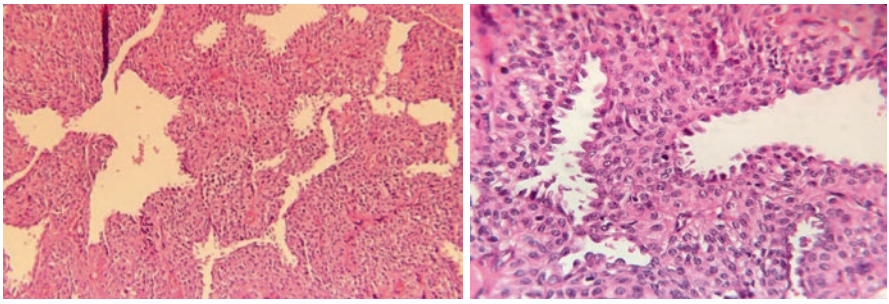

Fig. 13.2 Pathological views of the lesion seen in the Fig. 13.1 (H&E staining)

Diagnosis

Nodular hidradenoma

On pathologic examination, a well-circumscribed tumor was seen which was composed of a solid sheet of polyhedral clear cells configuring cystic spaces and ductal structures (Fig. 13.2).

Discussion

Nodular hidradenoma is a benign adnexal tumor derived from either eccrine or apocrine sweat glands [1]. This tumor frequently involves the head, neck, and anterior trunk. The lower extremities are an atypical site for involvement [1, 2]. It shows a preponderance in females (female to male ratio 1.7:1) with a mean age of 37.2 years [2, 3].

The lesions of nodular hidradenoma are characterized by a single, small, slow-growing, well-defined nodule with varied hue. Their surfaces can be smooth, atrophic, thickened or ulcerated. Its size ranges between 5 and 30 mm [2]. Histologically, they appear with different morphologic variants including solid, cystic, and clear cell subtypes [3].

On pathologic examination, they are composed of lobulated masses in the dermis with extension into the subcutaneous fat. There are two cell types including the polygonal cells with clear appearance containing glycogen, and smaller, elongated, and darker cells at the periphery [3].

Wide surgical excision is the treatment of choice for nodular hidradenoma. Its recurrence has been reported after surgical excision. It can rarely transform to a malignant lesion [3], with lowest frequency of malignant transformation occurring in those located on the lower extremities [1].

Key Points

- Nodular hidradenoma is a benign adnexal tumor derived from either eccrine or apocrine sweat glands.
- The lower extremities are an atypical site for involvement by nodular hidradenoma.

  Nodular hidradenoma can rarely transform into a malignant lesion.

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Chapter 14
A Pediatric Case Presenting with Poikiloderma

Zdravka Demerdjieva, Bisera Kotevska Trifunova, and Stefana Damevska

A 4-year-old boy presented with a history of mottled hypo- and hyperpigmentation at sun-exposed areas developed gradually over the last two years. During the past months, the skin changes became more widespread, involving the palms and soles. The mother was healthy (gravida 4, para 4), with no history of exposure to drugs or infectious diseases during pregnancy. Antenatal ultrasonography a month before the birth showed an intrauterine fetal hypotrophy. There were no complications during delivery, with no obvious skin abnormality at birth. Parents were nonconsanguineous and denied any history of genetic anomalies in the elder children or any inherited skin disorder. The patient's developmental delay was noticed at one year of age.

Physical examination revealed poikilodermatous changes with acral distribution affecting the face (Figs. 14.1 and 14.2) and limbs (Figs. 14.3 and 14.4), with marked palmoplantar hyperkeratosis (Fig. 14.5). On close clinical examination, a firm, horny growth of 0.5 cm in length and 0.3 cm in width at the base was seen on the dorsal aspect of the right hand (Fig. 14.6). Intraoral examination revealed a diversity of malformations including abnormal crown formations, microdontia, and hypoplastic teeth (Fig. 14.7).

The child had been seen previously by a pediatric gastroenterologist who made a provisional diagnosis of pyloric stenosis. Ophthalmologic consultation revealed an incipient cataract of right eye.

Skin biopsy showed an atrophic epidermis and flattening, dermal melanophages together with pigmentary incontinence (Fig. 14.8). No significant inflammatory infiltrate of the papillary dermis was evident.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_14

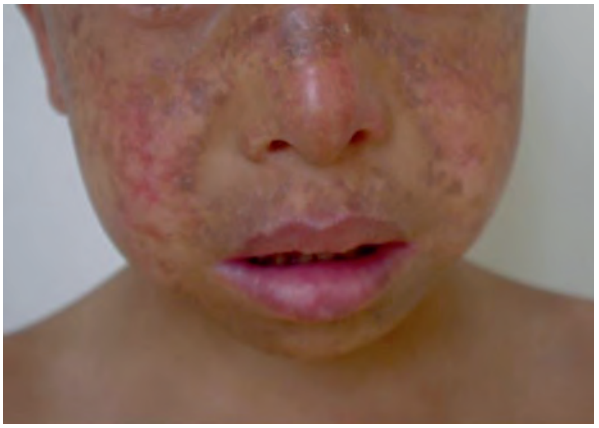

Fig. 14.1 Poikilodermatous changes affecting face

Fig. 14.2 Close up view of poikilodermatous skin on the left side of the face

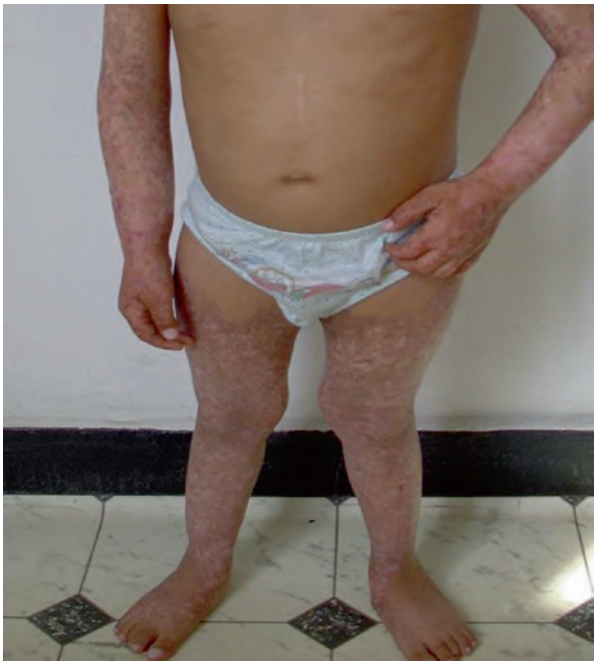

Fig. 14.3 Reticulated erythematous patches on the extremities, sparing the trunk

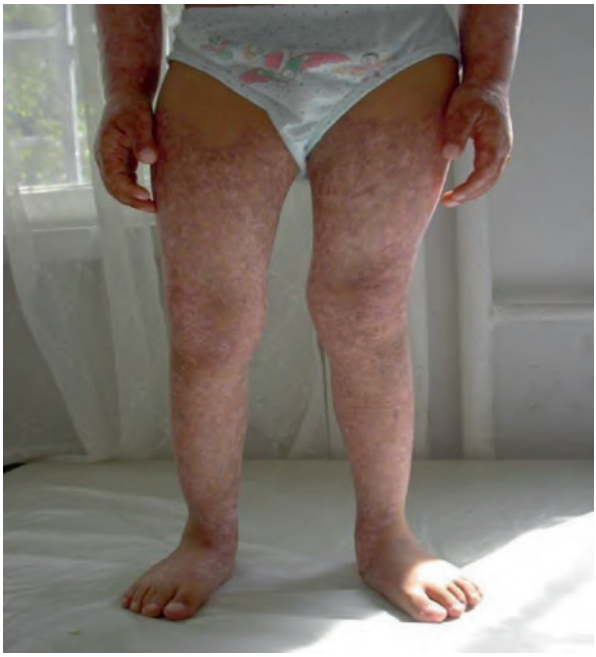

Fig. 14.4 Reticulated erythematous patches with brownish pigmentation on the lower limb

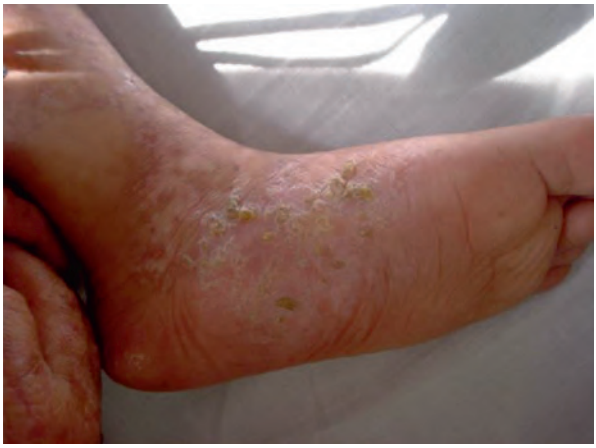

Fig. 14.5 The hyperkeratotic appearance of the foot

Based on the Case Description and the Photograph, What Is Your Diagnosis?

1. Bloom's syndrome
2. Rothmund–Thomson syndrome
3. Dyskeratosis congenita
4. Baller-Gerold syndrome
5. Xeroderma pigmentosum
6. Werner Syndrome

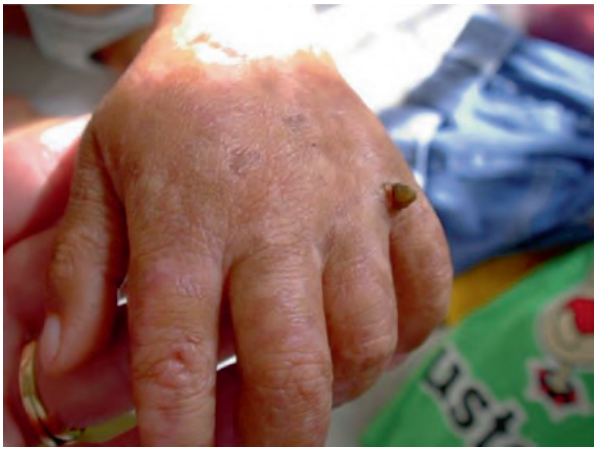

Fig. 14.6 Warty hyperkeratosis on the hand and small cutaneous horn measuring 0.5 cm in length

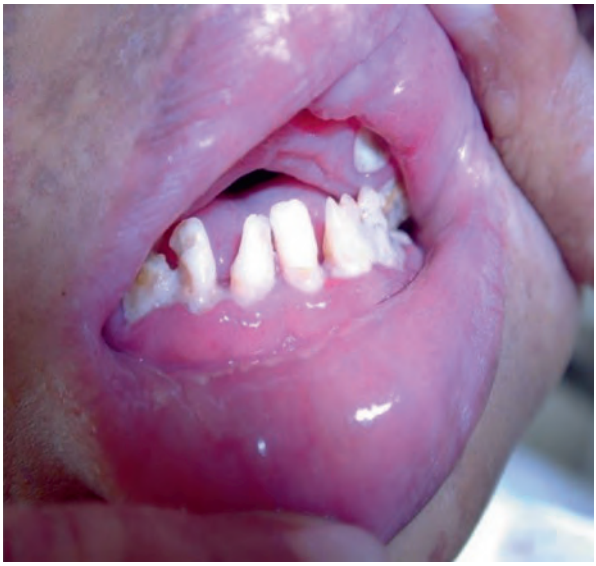

Fig. 14.7 Dental abnormalities with widespread caries

Diagnosis

Rothmund–Thomson syndrome.

Discussion

The clinical features of photodistributed poikiloderma and hyperkeratotic lesions with cornu cutaneum suggested Rothmund–Thomson syndrome (RTS). Our case also demonstrates many of the RTS changes, including initial cataract, dental and

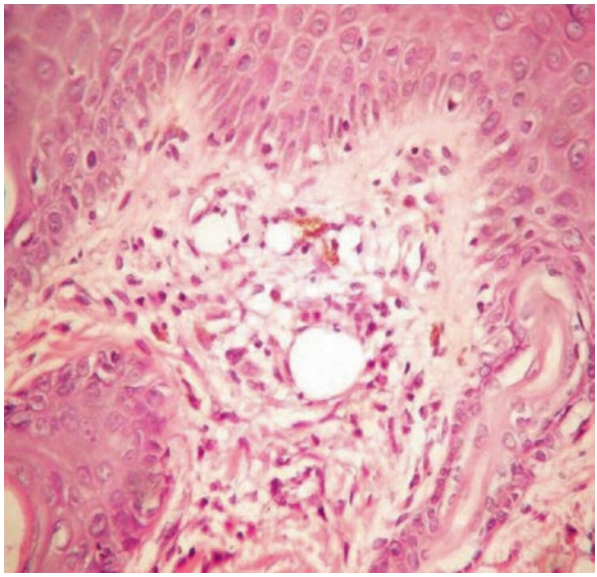

Fig. 14.8 Histology of skin demonstrating dermal melanophages with pigmentary incontinence

gastrointestinal abnormalities. Pediatric monitoring of growth and development and dermatological surveillance for malignancy were instigated.

Rothmund–Thomson syndrome, also known as congenital poikiloderma, is a multisystem disorder that affects the skin, eyes, and skeletal system. It is a rare genodermatosis (OMIM #268400, with around 400 patients reported in the literature. RTS was initially described in 1868 by the German ophthalmologist Rothmund who reported 10 children with poikiloderma, growth retardation, and rapidly progressive bilateral juvenile cataracts. In 1936, the English dermatologist Thomson observed three similar patients with poikiloderma who displayed skeletal defects but no cataracts. The eponym Rothmund-Thomson syndrome is coined in 1957 [1].

RTS presents in infancy with a characteristic facial rash (poikiloderma) and heterogeneous clinical features, including short stature, sparse or absent hair, juvenile cataracts, skeletal abnormalities, radial ray defects, and predisposition to specific malignancies. Premature aging is observed in adult age. Presentation of this syndrome is typically variable. Sometimes only a few of these features are present in an individual case [2].

Poikiloderma, the diagnostic hallmark of RTS, is characterized clinically by erythema and mottled pigmentation. As the patients age, the affected skin becomes atrophic. The poikiloderma is typically recognizable during early infancy, between 3 and 6 months of age. An erythematous rash starts bilaterally on the cheeks, and it subsequenly spreads on the extremities and buttocks [3]. It is often mistaken for mottled pigmentation.

Histologically, these changes result from basal vacuolar change with consequent melanin incontinence and variable dilation of blood vessels in the superficial dermis. RTS individuals can also have photosensitivity, graying hair, alopecia, and dystrophic nails [3].

Gastrointestinal abnormalities have been described, including esophageal stenosis, pyloric stenosis, annular pancreas, anal atresia, and rectovaginal fistula [4]. Dental deformities include microdontia, rudimentary or hypoplastic teeth, and disorders of dental breakthrough [2].

Variable immune defects ranging from combined immune deficiency to immunoglobulin deficiency are also described in RTS patients. However, immune defects do not appear to be a consistent feature of RTS [5].

RTS predisposes subjects to the development of malignancies: bone tumors at an early age, and skin tumors during adult years, as well as gastrointestinal and hematological neoplasia [6, 7].

Stinco et al. [8] identified 61 patients with RTS and malignancy. The mean age at diagnosis was 18.7 years (range 3–49 years. The most frequent malignancy (62%) was osteosarcoma, of which three were multicentric and 12 developed before the age of ten. Epithelial tumors such as squamous and basal cell carcinomas are presented most often in adulthood, with a mean age of 34.

RTS is caused by germ-line mutations in RECQL4, a RecQ helicase family member [5].

Deoxyribonucleic acid (DNA) replication is the process by which a molecule of DNA is duplicated. It is a multistep process involving a large number of protein complexes. Accurate and efficient replication is essential for human health. Disruption of DNA replication can lead to genomic instability, associated with many point mutations or more prominent chromosomal anomalies [9].

Germline mutations in genes involved in DNA repair pathways and DNA damage responses can predispose to genetic syndromes that are often called “genome instability syndromes.” Common features of these syndromes include a high incidence of cancers and developmental abnormalities, including short stature, microcephaly, and neurological deficiencies [9, 10]. Overall, cancer is the most common disease associated with genomic instability.

The RecQ DNA helicases, a conserved group of enzymes, are critical to ensure proper DNA damage repair. Humans possess five RECQ helicase genes, and their mutations are associated with the genetic disorders, all associated with an increased risk of cancer [11, 12].

Two clinical subforms of RTS have been defined based on clinical and molecular analysis: type I RTS, negative for the RECQL4-mutation scan, and type II RTS, related to deleterious RECQL4 mutations. The RTS-I genetic defect is so far unknown. Whether RTS I and II represent distinct syndromes or intersecting nosological entities remains unclear. RTS-II, or Thomson-like type, is characterized by poikiloderma, skeletal defects, and cancer predisposition (osteosarcoma and less frequently squamous cell carcinoma of the skin, hematological tumors, and other malignancies). RTS-I or Rothmund-type is characterized by poikiloderma, ectodermal dysplasia, and bilateral juvenile cataracts [13, 14].

Mutations in the RECQL4 gene can lead to several clinical phenotypes with overlapping features: RTS, RAPADILINO, and Baller-Gerold (BGS).

The distinguishing feature of BGS is craniosynostosis, which can lead to death in early childhood without surgery. The similarities between BGS and RTS are so

strong that some authors suggested that BGS should be considered a severe form of RTS.

RAPADILINO syndrome (RAdial hypo/aplasia, PAtellae hypo/aplasia and cleft PAlate, DIarrhea and DIslocated joint, LIttle size and LImb malformation, NOse slender and NOrmal intelligence) lacks the primary dermal manifestation - poikiloderma that is a hallmark feature in both RTS and BGS [13].

Cancer predisposition, together with premature aging, is shared by RTS-II, Bloom (OMIM#210900), and Werner (OMIM#277700) syndromes [15].

Bloom syndrome (Bloom-Torre-Machacek syndrome or congenital telangiectatic erythema) is caused by mutations in the BLM gene. It is characterized by growth deficiency, mild immunodeficiency, poikiloderma with extreme photosensitivity, type 2 diabetes mellitus, and hypogonadism. The increased risk of malignancy in Bloom syndrome (carcinomas, leukemias and lymphomas, and osteosarcoma) leads to a shortened life expectancy [16].

Werner Syndrome (adult progeria) is an autosomal recessive disorder characterized by premature aging, short stature, bilateral cataracts, and scleroderma-like skin changes. The patients are predisposed to many types of neoplasia, including soft tissue sarcoma, osteosarcoma, meningioma, myeloid disorders, melanomas, and thyroid carcinomas [10].

Photodistribution of the poikiloderma is a feature of xeroderma pigmentosum and RTS. Xeroderma pigmentosum, first described by Hebra & Kaposi (1874), is an autosomal recessive disorder. The incidence is approximately 1 in 250,000 newborns. It is characterized by severe photosensitivity, photophobia, and premature skin aging. These patients have an estimated 10,000-fold increased risk of nonmelanoma skin cancer (NMSC) and a 2000-fold increased risk of melanoma below 20 years. The median age at the onset of NMSC is approximately eight years [10].

Clericuzio-type poikiloderma with neutropenia (PN) syndrome is a rare autosomal recessive disorder characterized by poikiloderma, nail abnormalities, and noncyclic neutropenia. The disease was first described in Navajo Indians in 1991. Patients may be predisposed to recurrent infections due to neutrophil functional defects [17].

Another condition to consider in the differential diagnosis of RTS is dyskeratosis congenita (DC), also known as Zinsser-Engman-Cole syndrome. Patients with DC present with the classic triad of poikiloderma, nail dysplasia, and oral leukoplakia associated with a high risk of bone marrow failure and cancer.

Pediatric patients presenting with poikiloderma require thorough clinical examination. Our case illustrates the importance of maintaining a broad differential when approaching a patient with early-onset poikiloderma. Early diagnosis may prompt adequate clinical follow-up and early treatment of systemic manifestations.

Key Points

- Poikiloderma can be a key presenting symptom of inherited skin disorders, with potentially serious consequences.
- Poikiloderma almost always precedes more severe manifestations of these genodermatoses.

- Rothmund-Thomson syndrome is an autosomal recessive genodermatosis presenting with poikiloderma and heterogeneous clinical features, including short stature, sparse or absent hair, juvenile cataracts, skeletal abnormalities, radial ray defects, premature aging and predisposition to specific malignancies.
- Continual screening for malignancy is warranted due to the high prevalence of osteosarcoma and skin cancer in these patients.

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Chapter 15
A Rare Variant of Penile Disease

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

An 18-year-old male was referred to our hospital due to a cauliflower-like lesion, which was approximately 8 centimeter in size (Fig. 15.1), pruritic with a foul odor. The disease course was about 4 months, associated with hyaline secretion through the urethra with mild febrile episodes without gauging and weight loss. Physical examination revealed a large keratotic mass with itching, advancing toward the coronal sulcus from the dorsal layer of the glans without urethral meatus involvement (Fig. 15.1). Poor penile hygiene was observed. Inguinal region examination showed no palpable lymphadenopathy.

Histopathological examination result reported a well- differentiated penile verrucous squamous cell carcinoma (verrucous SCC) without vascular or lymphatic invasion. He was referred for a partial penectomy, with only a 4 cm penile stump remaining due to the extension of the lesion and the safety margin of the surgery, spatulation and maturation of the urethra during surgery. The surgical sample, including lesion and inguinal lymph node was sent for pathological examination, as a protocol at the hospital. The patient was discharged 5 days after surgery, stable, with a clean operative wound without purulent secretion. No recurrence or metastasis was observed at six months follow-up.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_15

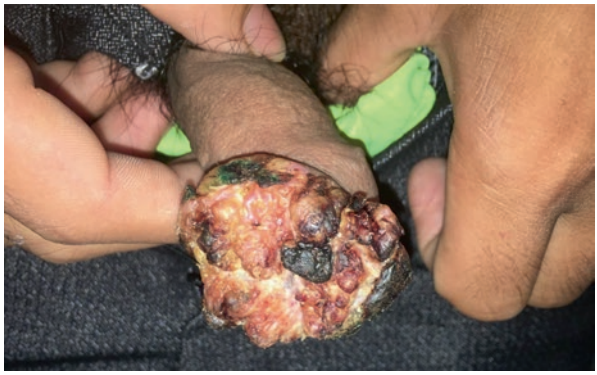

Fig. 15.1 Large cauliflower-like tumor at gland

Based on the Case Description and Photographs, What Is Your Diagnosis?

1. Verrucous squamous cell carcinoma
2. Penile sarcoma
3. Urethral carcinoma
4. Genital warts

Diagnosis

Verrucous squamous cell carcinoma

Discussion

Penile cancer is a rare type of cancer which accounts for less than 1% of cancer in men [1]. Its prevalence is higher in developing countries. It more frequently affects uncircumcised, white men with low income. Squamous cell carcinoma is the most common type and 33% of SCCs originate from premalignant lesions. Possible mechanisms consist of those stimulate malignant transformation such as chronic irritation, tobacco smoking, and poor penile hygiene. They induce chronic inflammation, metaplasia, and differentiation [2]. Certain types of viral infections such as HPV may also lead to penile cancer through DNA damage [3, 4].

Verrucous SCC accounts for 3–8% of penile cancers and 20% of verruciform lesions. It is a rare variant of exophytic, papillomatous, low-grade, and well-differentiated SCC. As verrucous SCC mostly present with squamous epithelial hyperplasia and keratinization, misdiagnosis is common, when diagnostic biopsy

fails. Therefore, biopsy is strongly recommended for definitive diagnosis. Its etiology is not fully understood [5].

Although most of current data regarding verrucous SCC are based on case reports and case series, surgery is the mainstay of the treatment. The main strategy is wide excision of the mass or partial penectomy. Radical penectomy can be performed in rare cases. Recurrence of penile verrucous SCC is high [1, 4]. In early recurrence, additional resection and even radical penectomy can be performed. Distant metastasis is extremely rare and is not seen in most of patients with penile verrucous SCC. Therefore, inguinal lymphadenectomy is reserved for only a few patients. Hatzichristou et al. performed inguinal lymphadenectomy in selected patients with penile verrucous SCC; however, no specific lesion could be detected [6]. Thus, prophylactic inguinal lymphadenectomy is not recommended for this patient population. Early diagnosis and prevention are of utmost importance for the management of penile cancer. Neonatal circumcision, smoking cessation, and HPV vaccination have been suggested to decrease the incidence of penile cancer.

Key Points

- Penile cancer is a rare type of urological cancer.
- Predisposing factors include phymosis, poor hygiene, and smoking. Circumcision in early childhood has been shown to be protective against penile cancer.
- About 95% of penile cancers are squamous cell carcinomas, while verrucous type is a rare variant with frequent recurrences, but with a favorable prognosis.

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Chapter 16
A Red Nodule in a Girl

Sara Scrivani and Marco Brusasco

An 8-years old girl presented in hospital because of a single nodular mass on her right forearm (Fig. 16.1a).

She was in good health, without a family history of melanoma or other skin tumors, no previous sunburns or dermatologic disease referred, as well as she never took drugs prior to medical visit.

The lesion was not painful or pruritic and it arose two years before although the size of nodule has gradually increased over the last six-seven months. Physical examination revealed a pink-red nodule with smooth surface, slightly translucent, measuring about 7 × 6 mm, it was moreover firm and it never bled. No regional lymphadenopathy has been detected and finally skin surrounding the nodule appeared normal.

The dermoscopic analysis exhibited a slight pigmentation, especially on the edge and an atypical vascular pattern characterized by dotted and linear vessels with irregular distribution (Fig. 16.1b). Because of the rapidity of growth and the dermoscopic features of the nodule, it has been promptly removed by excisional skin biopsy (Figs. 16.2 and 16.3).

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_16

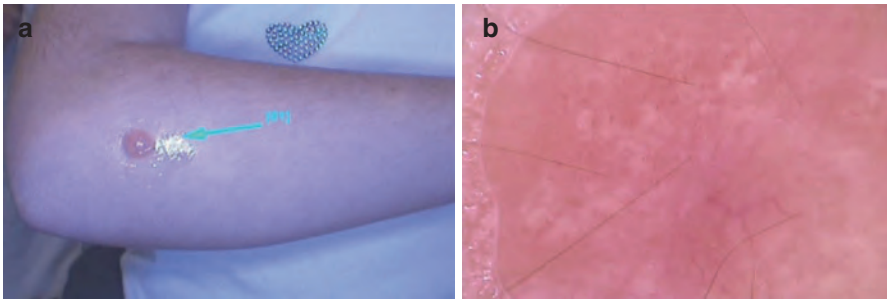

Fig. 16.1 Pink-red, firm, sharp edge nodule of forearm of 6-years-old girl (**a**). Dermoscopy of nodule is characterized by atypical vascular pattern made up dotted and linear vessels irregularly distributed (**b**)

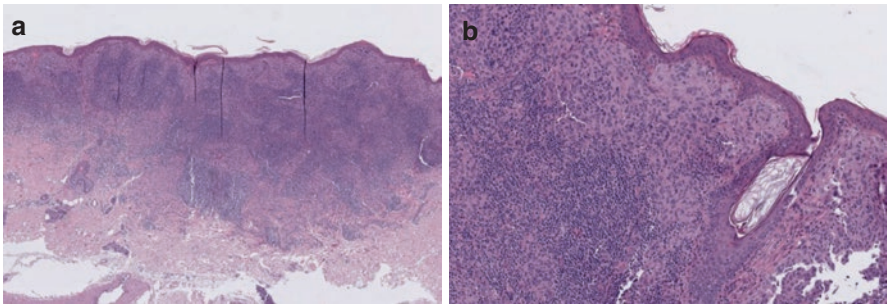

Fig. 16.2 Haematoxylin & eosin stain: Asymmetrical, intradermal melanocitic lesion (**a** H&E 10×) characterized by nests of melanocytes prone to confluence with low tendency of maturity. Mitotic figures appear in superficial layers and in depth of nodule (**b** H&E 40×). *Courtesy of Dr. Roberta Manuguerra*

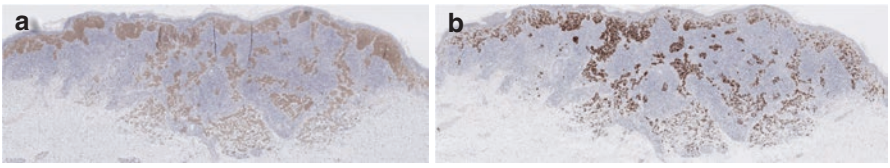

Fig. 16.3 Immunohistochemical staining show BRAF (**a**) and p16 (**b**) expression

Based on the Case Description and the Photographs, What Is Your Diagnosis?

1. Spitz nevus
2. Atypical Spitz tumor
3. Amelanotic melanoma
4. Melanocytic tumor of uncertain malignant potential (MELTUMP)

Diagnosis

MELTUMP

Discussion

MELTUMPs, i.e., melanocytic tumors of uncertain malignant potential, are a subset of histologically ambiguous melanocytic lesions, whose nature is difficult to determine by pathologists. As defined by Abraham et al. MELTUMP is a provisional diagnosis due to the lack of clearly defined sign of benignity or malignity, suggesting that only a long-term follow-up can determine the biological behaviour of these lesions [1].

In the cauldron of MELTUMP are grouped different equivocal melanocytic tumours, such as atypical Spitz nevus, atypical blue nevus, melanocytoma, "borderline melanoma", "minimal deviation melanoma", "dermal-based melanocytic lesion".

Diagnosis of MELTUMP is probably dependant from pathologist's confidence towards difficult melanocytic lesions [2], but it could also reflect a different mutational burden, more than a benign lesion but less than a malignant one [3].

After a diagnosis of MELTUMP, first of all, the lesion should be re-evaluated considering all clinical and anamnestic data of the patient (age, history of the lesion, clinical and dermoscopical features). If diagnosis of MELTUMP persists, a wide local excision is suggested, usually with a margin of 1 cm [2, 4].

Actually there aren't indications to sentinel lymph node biopsy (SNBL). As demonstrated in atypical Spitz nevus, also in MELTUMP there is a significant fraction of cases with positive SNBL (from 16% to 50%), nevertheless invasion of other lymph nodes is exceptional and positive SNBL doesn't correlate with development of systemic disease [2].

After wide local excision a clinical 6-month follow up for at least 5 years with local lymph node ultrasound is recommended [2, 4].

At now, the exact data about incidence of MELTUMP are indefinable, both in adults and in children because of the diagnostic challenge of MELTUMP and its rarity as Berk et al. illustrated observing only 13 MELTUMP in pediatric population from 1995 and 2008 [5].

Majority of MELTUMPs has a good prognosis, especially in pediatric age, but metastatic cases has been described, suggesting to revise the diagnosis to melanoma in these ones.

Key Points

- Nodular lesions of the skin, if not clearly benign, should be excised and followed up both in adult and in children
- MELTUMP is a diagnostic challenge for pathologists
- MELTUMP requires a strict clinical and dermoscopic follow up after surgical excision

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Chapter 17
A Yellowish-Orange Nodule of the Chest

Alessandra Massa, Alfredo Zucchi, and M. Beatrice de Felici del Giudice

A 3-year-old female referred to our dermatologic department with a nodular lesion on the chest. The lesion appeared 4 months earlier as a little yellow-reddish papule and gradually increased in size. It was completely asymptomatic without any pain, itching or bleeding. There were neither relevant personal medical history nor any previous trauma. On physical examination, an exophytic, well-circumscribed solitary nodule of 10 millimeter in diameter was detected above the sternum. The lesion was characterized by a shiny, yellowish-orange colour, with a very mild scaling of the edges (Fig. 17.1a and b). No further skin lesions were detected on the remaining body surface.

A complete surgical excision of the lesion was performed and histopathology showed a well defined dermal nodule composed of mononuclear and multinucleate histiocytes of Touton-type (Fig. 17.2a and b).

What Is Your Diagnosis?

1. Mastocytoma!
2. Pyogenic granuloma
3. Juvenile xanthogranuloma
4. Giant molluscum contagiosum
5. Spitz nevus

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_17

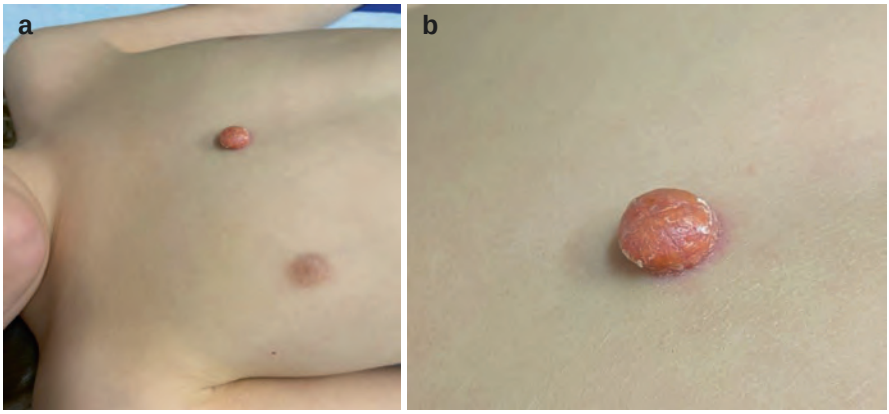

Fig. 17.1 (**a**, **b**) Clinical features: a solitary polypoid nodule of the sternum, with a shiny, yellowish-orange colour, measuring 1 cm of diameter

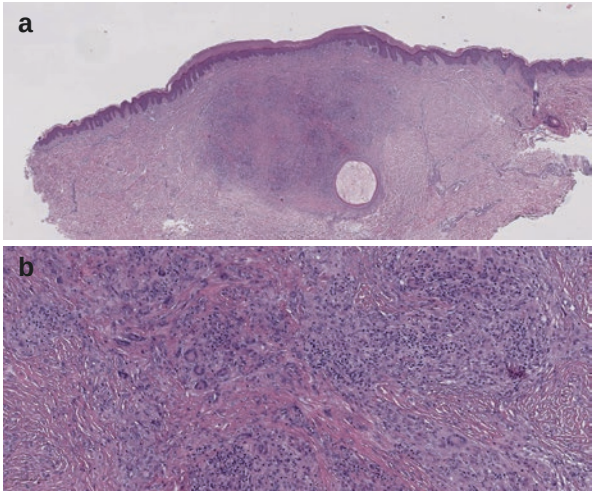

Fig. 17.2 (**a**, **b**) Histopathologic features: well-circumscribed dermal nodule (**a**; H&E, ×4) composed of mononuclear and multinucleate histiocytes of Touton-type (**b**; H&E, ×20) (Courtesy Dr. Roberta Manuguerra)

Diagnosis

Juvenile xanthogranuloma.

Discussion

Juvenile xanthogranuloma (JXG) is considered the most common form of non-Langerhans cell histiocytic (non-LCH) disorder of childhood [1]. The positivity for factor XIIIa, typical of proliferating dendritic cells of JXG, is an immunophenotype shared with many other dendritic non-LCH [2].

The pathogenesis is still unknown, although it is generally considered as a proliferative reaction to unidentified stimuli, such as infections or trauma [1].

JXG usually occurs in early childhood with more than 15–20% of patients having lesions at birth and 75% of cases appearing during the first year of life [1]. Clinically it appears as solitary or multiple well-defined yellow-orange-brown papules or nodules with a smooth surface and firm consistency [1]. Lesions are usually asymptomatic and can occur anywhere, nevertheless the head and neck region and the upper trunk are involved more frequently [3].

Although the majority of JXGs involve only the skin, there are also extracutaneous cases [2] and ocular involvement is the most frequent [4]. Most patients with extracutaneous involvement, however, have multiple cutaneous lesions at the time of diagnosis [1].

More rarely JXG can be systemic, appearing as multiple cutaneous and/or subcutaneous nodules with the involvement of 2 or more visceral organs, especially eyes, liver, spleen, lungs, and central nervous system [2].

Furthermore, JXG has been associated with juvenile chronic myelogenous leukemia and other diseases such as urticaria pigmentosa, insulin-dependent diabetes mellitus, aquagenic pruritus, and even cytomegalovirus infection [1].

The diagnosis of JXG is essentially clinical and is oriented by the history, progression, and morphology of lesions. In some cases, diagnosis needs to be confirmed by histology or immunohistochemistry [2].

Pathologically the lesions exhibit a dense infiltration of numerous histiocytes within the superficial dermis. Mononuclear cells may show an elongated appearance. Multinucleated giant cells (Touton cell) have a central wreath of nuclei while the cytoplasm near the periphery of the cell is pale and foamy in appearance [1]. Immunohistochemistry of JXG classically shows a positivity for CD68 or Ki-M1P and anti F XIIIa, vimentin, and anti-CD4 [1]. The differential diagnosis of JXG depends on clinical presentation and includes both benign and malignant entities. Langerhans cell histiocytosis (LCH) should be contemplated as alternative diagnosis, particularly in patients with multiple skin lesions and systemic involvement. Histologic examination can be helpful defining the diagnosis [2]. Some forms of non-LCH such as benign cephalic histiocytosis, necrobiotic xanthogranuloma, and multicentric reticulohistiocytosis should also be contemplated in the differential diagnosis. Moreover, when single, differential diagnosis include mastocytomas, Spitz nevus, neurofibromas, dermatofibromas, sarcoidosis and xanthomas.

The prognosis of JXG is usually excellent with most lesions resolving spontaneously within approximately 3–6 years. Solitary lesions that cause functional impairment or psychological distress can be surgically removed or treated using other ablative methods. A “wait and see” approach is the first-line option for the vast majority of asymptomatic and solitary lesions. Conversely, in case of functional impairment or psychological distress, they can be surgically removed or treated with other ablative methods [2].

Treatment of systemic disease depends on the degree of visceral dysfunction caused by these multiple benign lesions. Therapies as surgical resection, radiation

therapy and/or chemotherapy should be initiated when JXG starts to interfere with vital function. Ocular exams are always recommended for high-risk patients.

Key Points

- Juvenile xanthogranuloma is a rare benign histiocytic proliferation predominantly diagnosed in early childhood
- Common clinical presentation is as solitary or multiple yellow-orange-brown papules or nodules but it exhibits a wide spectrum of clinical manifestations, each requiring an appropriate treatment
- Usually it is a self-limiting disease with a spontaneous resolution, although cases with a extracutaneous involvement have been reported
- Conservative management is the treatment of choice for the limited forms, nevertheless excision may be considered due to functional or diagnostic reasons

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Chapter 18
A Young Man with Clubbed Fingers and Toes

Meng Zhang, Hao Guo, Song Zheng, Xing-Hua Gao, Jiu-Hong Li, and Zhen-Ting Lin

An 18-year-old man presented to our department with progressive enlarged hands and feet with clubbed fingers and toes for over 5 years (Fig. 18.1). the patient complained of arthralgia frequently since childhood. He was born to healthy nonconsanguineous parents, without family history of similar diseases. Five years ago, he noticed the gradually thickening and furrowing of his forehead skin, seborrhea and hyperhidrosis (Fig. 18.2). Meanwhile, cutis verticis gyrata exhibited on his scalp (Fig. 18.3). His height and weight are within normal level in his family. The patient denied smoking and drinking history, and no previous cardiopulmonary disease.

Based on the Case Description and the Photograph, What Is Your Diagnosis?

1. Acromegaly!
2. Pachydermoperiostosis
3. Secondary hypertrophic osteoarthropathy
4. Thyroid acropachy
5. Chronic inflammatory rheumatic diseases

On physical examination, thickening and furrowing of the patient's facial skin to form a "leonine appearance to the face". Seborrhea, digital clubbing, watch-glass nails, cutis verticis gyrata, and swelling of elbow and knee joints was observed. Meanwhile, face, palmar and plantar hyperhidrosis were apparent.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_18

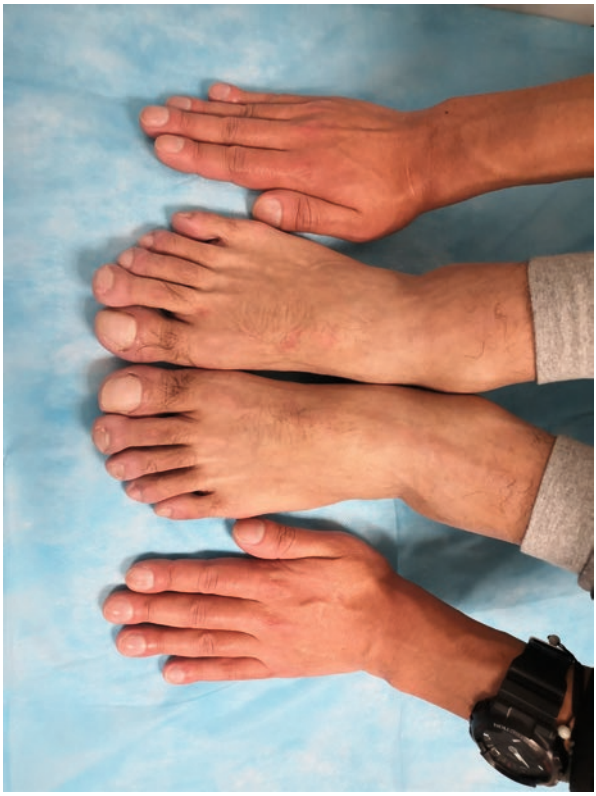

Fig. 18.1 Enlarged hands and feet with clubbed digitals and watch-glass nails of the patient

Laboratory tests, including myocardial enzyme spectrum, thyroid function, growth hormone and insulin-like growth factor 1, were within normal ranges. Inflammatory markers C-reactive protein(CRP) was slightly raised. Serum and urinary levels of PGE2 were unavailable. Radiological examination in another hospital showed cortical thickening and periostosis in the long bones of his lower extremities.

The patient's main plea was to improve his facial appearance, we recommend staged cosmetic surgery. However, the patient later lost the visit.

Diagnosis

Pachydermoperiostosis.

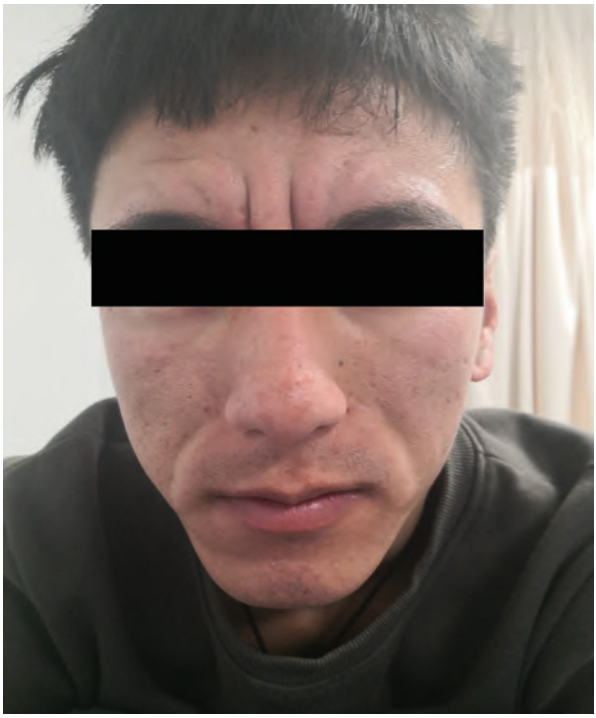

Fig. 18.2 Thickening and furrowing of the patient's forehead skin to form a leonine appearance, seborrhea and hyperhidrosis was found on his face

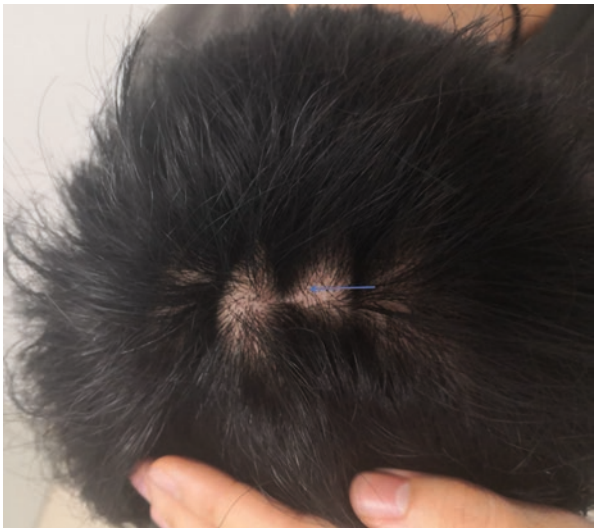

Fig. 18.3 Cutis verticis gyrata exhibited on the patient's scalp (blue arrow), as his hair is too long and thick, the figure is not very clear here

Discussion

Pachydermoperiostosis(PDP) is a rare genetic disorder entity, also named primary hypertrophic osteoarthropathy(PHO), or Touraine-SolenteGolé syndrome [1, 2]. Mutations in HPGD gene and/or SLCO2A1 gene, which disturbed prostaglandin E2 (PGE2) catabolism resulting in increased PGE2 levels is suggested in the pathogenesis. In Asia, especially in China and Japan, mainly is SLCO2A1 gene [1, 3]. Typical cases usually occur in male patients, while fewer females were affected and they generally showed atypical PDP phenotypes with less severe skin and skeletal symptoms post-menopause [3, 4]. The estimated prevalence of PDP is 0.16% [5]. Generally, the disease does not endanger one's life expectancy, but can affect the patient's quality of life [2, 5].

The classical 3 characteristics of PDP are pachydermia (leonine appearance of the face and cutis verticis gyrata), digital clubbing and periostosis of the long bones. Additional common manifestations include seborrheic hyperplasia, long eyelashes, blepharoptosis, hyperhidrosis, arthropathy, peri-articular oedemas, synovial effusions and periodic watery diarrhoea [1–6]. Diagnostic criteria require at least 2 of the following items including family history, clubbing, hypertrophic skin changes, bone pain, or radiographic changes [5]. Generally, the diagnosis of PDP is straightforward when all 3 characteristics are present. Radiological examination usually showed cortical thickening and subperiosteal bone formation in the long bones [1, 2, 5]. Laboratory tests, especially for the patients with bone pain, inflammatory markers such as C-reactive protein(CRP) usually raised. Also elevated are urinary PGE2 and its major metabolite (PGE-M) [1, 3–5]. Histological findings in pachydermia frequently include dermal mucin deposition, elastic fiber degeneration, dermal fibrosis and adnexal hyperplasia [2].

The differential diagnosis of PDP includes acromegaly, secondary hypertrophic osteoarthropathy, thyroid acropachy, and chronic inflammatory rheumatic diseases [5, 6]. And acromegaly is the most important one, which is associated with the excessive secretion of growth hormone (GH) leading to elevated insulin growth factor-1 (IGF-1) levels, and characterised by somatic overgrowth and physical disfigurement notably affecting hands and feet [6]. These can be identified by laboratory tests. Other differential diagnosis can be readily differentiated by asking about the history in details, and performing some laboratory tests.

Management of PDP is symptomatic. As the pathogenesis of it is the elevated of PGE2 level, which simulate the activity of osteoblast, promote fibroblast growth and increase collagen and extracellular matrix production [1]. Etoricoxib, a cyclooxygenase(COX)-2-selective NSAID, is proved to be effective, especially patients with bone and joint symptoms [1, 3]. Joao et al. utilized prednisone and hydroxycarbamide to treat a patient of PDP associated with extramedullary haemopoiesis, achieved the control of clinical symptoms and progressive reduction of the mass [4]. It has also been reported that zoledronate acid can inhibit bone destruction and absorption, which is beneficial to relieve bone pain [5]. To improve the leonine appearance of face, cosmetic surgery is effective. The therapy was performed in two

stages. In the first stage, implanted an expander to enlarge and ensure adequate skin tissues. In the second stage, resection of the furrowed and redundant skin was performed [7]. Xiang et al. reported 3 cases to treat the facial manifestations of PDP with botulinum toxin type-A(BTX-A), showing good outcome in reducing wrinkles and sebum production [6], which is proved to be a cosmetic technique, as an alternative therapy of surgery.

Key Points

- Pachydermoperiostosis is a rare entity associated with gene disorder of HPGD and SLCO2A1, characterized by pachydermia, digital clubbing and periostosis.
- Management of pachydermoperiostosis is symptomatic. Etoricoxib is effective to improve the bone and joint symptoms, and cosmetic surgery and injection of botulinum toxin type-A are main methods to improve facial appearance of pachydermoperiostosis patients.

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Chapter 19
An Enlarging Eczematous Patch of the Hip

Marco May Lee, Francesca Satolli, and M. Beatrice de Felici del Giudice

A 10 year-old boy was referred to our dermatologic clinic after the appearance, 4 months earlier, of one erythematous patch on the right hip that enlarged slowly but progressively (Fig. 19.1a). The lesion, only mildly itchy, was xerotic with a cigarette paper-like surface and it showed slightly infiltrated and red edges (Fig. 19.1b). The child was overall healthy. His brother was followed up for dermatomyositis and his father had a history of atopic dermatitis. An incisional biopsy was performed revealing an atypic cutaneous T-cell lymphoid infiltrate with epidermotropic phenomena. A second larger biopsy showed a band-like lymphocytic infiltrate in the papillary dermis with lymphocytes of medium size with hyperchromatic nuclei, some of which arranged in single file along the basal layer of the epidermis with discrete epidermotropism. T-cells were CD3+/CD4+/CD5+, with partial loss of CD2, CD7 and CD8. Epidermis was orthokeratotic. The evaluation of the rearrangement of T cell receptor beta gene documented policlonality (Fig. 19.2a and b).

Narrowband UVB treatment with acitretin was started after clinical and histological evaluation with complete remission.

What Is Your Diagnosis?

1. Atopic dermatitis
2. Tinea corporis
3. Mycosis fungoides
4. Contact dermatitis
5. Psoriasis

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_19

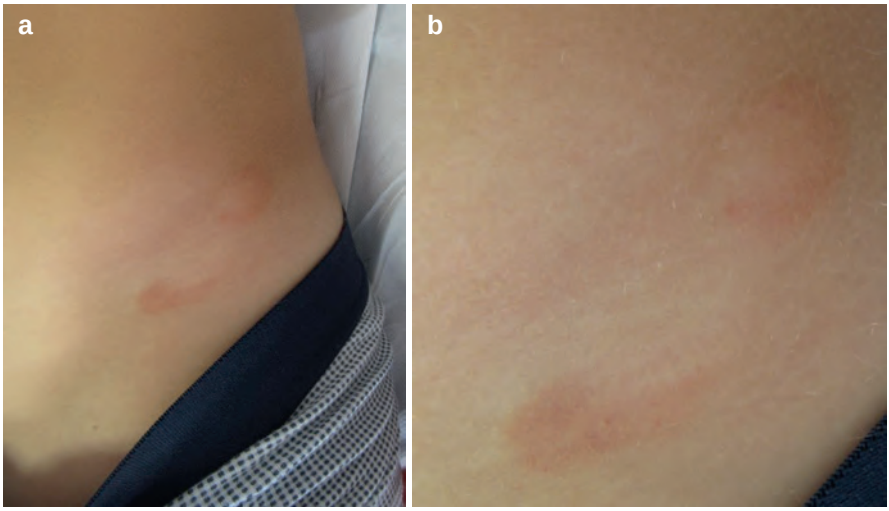

Fig. 19.1 (**a**, **b**) Clinical features of mycosis fungoides (patch stage): enlarging patch of the hip, with cigarette paper-like surface and slightly infiltrated erythematous edges

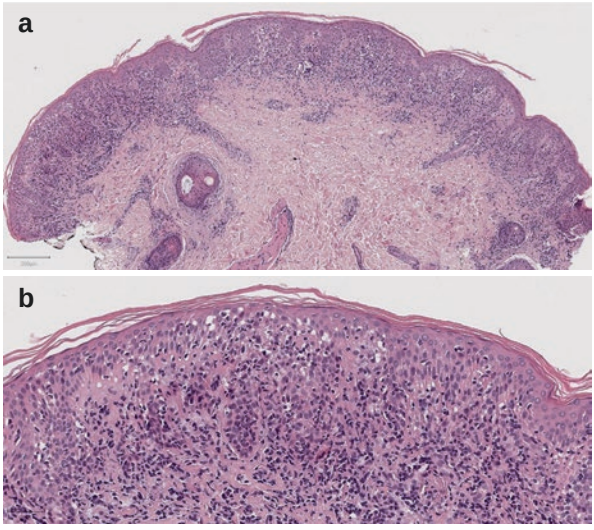

Fig. 19.2 (**a**, **b**) Histopathologic features of mycosis fungoides (patch stage): band-like infiltrate in an expanded papillary dermis (**a**; H&E, ×10) composed of small lymphocytes surrounded by a clear halo, mildly atypical, with epidermotropism (**b**; H&E, ×20) (Courtesy of Dr. Roberta Manuguerra)

Diagnosis

Mycosis fungoides.

Discussion

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma in adults and children [1]; however, based on an American database of 1902 patients, juvenile-onset MF represented only 2% of all MF/Sezary syndrome cases [2]. Despite the rarity, when clinically appropriate, a diagnosis of MF has to be considered also in children, in order to avoid delayed diagnosis and consequent worse prognosis [3].

In our case we found xerotic, partially erythematous and mildly pruritic lesions, a clinic that matches the classic MF variant. This is the most common type in adults but not in children, in which the hypopigmented MF represents over the half of pediatric cases [3].

Another type to consider in children, even if rare, is the folliculotropic MF, that in addition to clinical features of classical variant such as patches, plaques and tumors, is characterized by a secondary alopecia due to the prevalent perifollicular atypical T cell infiltrate with mucine deposition and follicle's destruction [4].

Differential diagnosis include some inflammatory and common entities such as atopic dermatitis, psoriasis, vitiligo and pityriasis alba. A skin biopsy is mandatory for a definitive diagnosis. The main histopathologic clue is an epidermotropic lymphoid infiltrate with a T-helper phenotype (CD3+, CD4+, CD8-) even if they can also express a cytotoxic T-cell phenotype (CD3+, CD8+, CD4−). Atypical lymphocytes with cerebriform nuclei and aggregates in the epidermis (the so call Pautrier's microabscesses) are pathognomonic [3].

There are no guidelines for the treatment of MF in children. Topical corticosteroids and phototherapy narrowband UVB (NB-UVB) are regarded as the first-line treatment for pediatric MF due to the strong efficacy and the few side effects [1, 5]. In our case we added systemic retinoid to the standard NB-UVB phototherapy, in order to achieve complete and stable remission without any recurrences after 2 years.

Key Points

- MF is rare in children and it can be misdiagnosed with other inflammatory dermatosis
- When a suggestive clinic is present, the diagnosis of MF must be considered also in childhood
- When suspecting MF is always mandatory performing a biopsy and obtain a histological confirmation to achieve a rapid diagnosis and enhance the prognosis

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Chapter 20
Basal Cell Carcinoma in Young Patient

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

A 15-year-old female presented with recurrent hyper-pigmented papule on her left cheek. The lesion appeared when she was 10 years old. It was diagnosed as benign tumor at many hospitals and excised two years ago. However, the lesion reappeared at the same area. The patient self-treated by an unknown topical medicine from a pharmacy. The lesion grew slowly, with the appearance of many black spots and telangiectasias and became more hyper-pigmented. There was no specific history of sun or radiation exposure (Fig. 20.1).

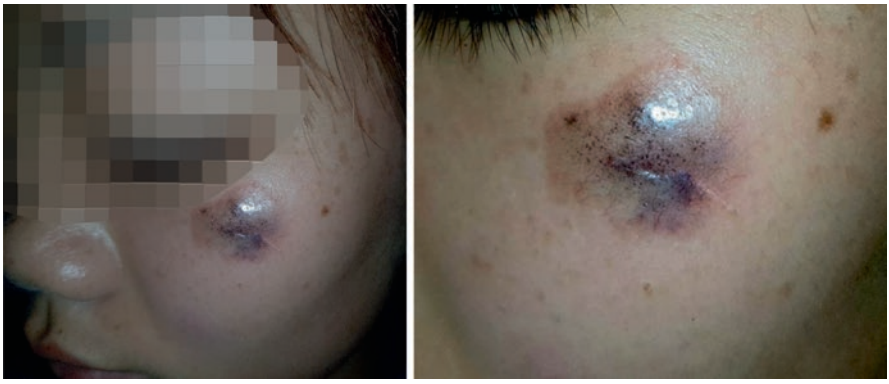

Fig. 20.1 Well-defined, hyper-pigmented papule on left cheek with telangiectasia, but no pain or itch

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_20

Based on the Case Description and Photographs, What Is Your Diagnosis?

1. Benign tumor
2. Melanoma
3. Basal cell carcinona

Histopathology (Fig. 20.2)

Diagnosis

Nodular basal cell carcinoma.

Dicussion

Basal cell carcinoma (BCC) is both the most common skin cancer [1] and the most common cancer found in humans [2]. Most BCCs occur in sun-exposed areas. Basal cell carcinoma susceptibility appears to consist of a combination of ultraviolet (UV) radiation exposure and polymorphic genes [3]. Basal cell carcinoma is a rare disease in the pediatric population that usually presents in children with predisposing genetic condition. There is often a delay in the diagnosis of BCC in the pediatric population because of a low index of suspicion [4]. A study of more than 36,000 pediatric dermatology patients by Orozco-Covarrubias et al. found only seven patients had BCC, with five children of the 7 had xeroderma pigmentosum; one had

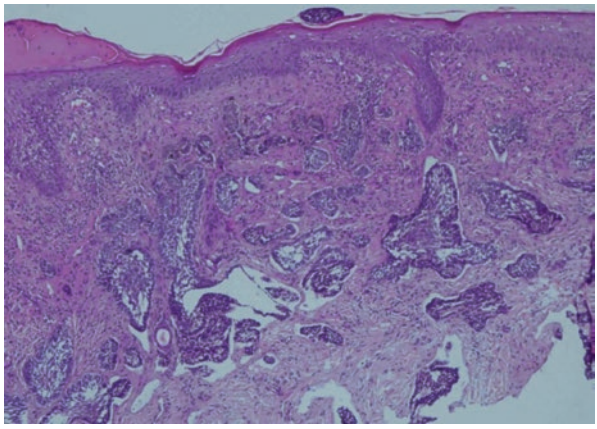

Fig. 20.2 Nodular aggregates of basaloid tumor cells are observed in the dermis. Also present, are a basaloid epithelial tumor arising from the epidermis; a palisade with a cleft forming from the adjacent tumor stroma and a mucinous stroma. Centrally, the nuclei are crowded with scattered mitotic figures and necrotic bodies. (Hematoxylin-eosin stain)

basal cell nevus syndrome; and in one, the basal cell developed in a field exposed to previous radiation [5]. The lesional symptoms of patients with childhood onset BCC include lesion increase in size, bleeding, tenderness, color change and cosmetic concerns [6].

Regarding our clinical case, the lesion on cheek which had reappeared after normal excision, changed color and slowly increased in size and was diagnosis as BCC, with histopathology confirmation.

Key Points

– Basal cell carcinoma (BCC) is a rare disease in the pediatric population
– Usually presents in children with predisposing genetic conditions or special history of sun- radiation exposure.

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Chapter 21
Centrofacial Lentiginosis

Uwe Wollina

A 14 months-old Caucasian girl was presented with multiple facial hyperpigmentation by the concerned parents. The birth was on time and previous development was uneventful.

There was no positive family history for facial hyperpigmentation.

Based Upon History and Clinical Appearance, What Is Your Diagnosis?

1. Melanocytic nevi.
2. Facial Lentiginesx.
3. Reticulate acropigmentation of Dohi.
4. Carney complex.
5. Peutz–Jeghers syndrome.

On examination we observed well defined flat brownish macules of up to 4 mm diameter. The girl had a Fitzpatrick phototype I with fair complexion and greenish eyes (Fig. 21.1). The pigmented lesions were restricted to the face. No oral hyperpigmentation was found. The general status was normal according to her age.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_21

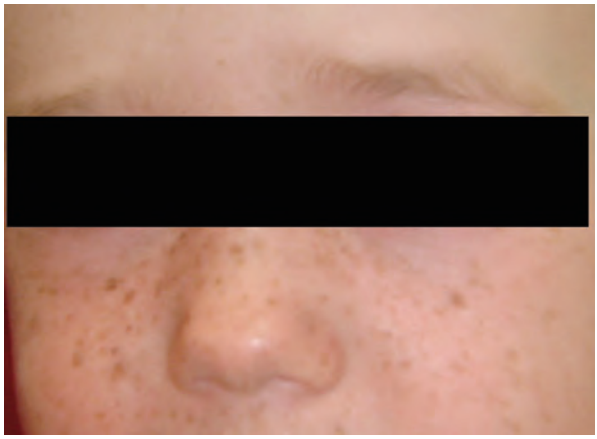

Fig. 21.1 Centrofacial lentiginosis

Diagnosis

Centrofacial lentiginosis suspicious for Carney complex.

Discussion

Carney complex is a rare genetic disorder associated with multiple endocrine neoplasias. One fourth of cases occur sporadically, three fourth are inherited. Germline mutations of the Carney complex gene 1 in a regulatory subunit 1A of protein kinase A (PRKAR1A) has been detected in the majority of patients. This gene is located on chromosome *17q22-24*.

Another gene locus is on chromosome *2p16*, however, no specific gene could be identified so far. In addition, inactivating mutations of phosphodiesterase genes (*PDE11A* or *PDE8B*) have been observed in patients suffering from micronodular pigmented or non-pigmented hyperplasia [1].

Although lentiginosis is the major cutaneous symptom, blue nevi, café-au-lait spots or cutaneous myxomas are other possible cutaneous findings. The dermatological symptoms are of diagnostic relevance.

Endocrine manifestations can occur in thyroid and pituitary glands, ovary and testicles. Non-endocrine manifestations include cardiac myxomas, benign breast lesions, melanocytic schwannoma, and osteochondromyxoma [2]. Diagnostic criteria are summarized in Table 21.1.

The highest mortality is associated with surgery for cardiac myxomas. Rarely, malignant tumors develop such as malignant large cell calcifying Sertoli cell tumors in elderly male patients, thyroid carcinoma or adrenocortical carcinoma [3, 4].

Table 21.1 Diagnostic criteria for Carney complex

Major diagnostic criteria
Lentiginous macules
Myxoma[a] (cutaneous and mucosal)
Cardiac myxoma[a]
Breast myxomatosis[a]
Primary pigmented nodular adrenocortical disease (PPNAD)[a]
Acromegaly as a result of growth hormone (GH)-producing adenoma[a]
Large-cell calcifying Sertoli cell tumor (LCCSCT)[a]
Thyroid carcinoma[a] or multiple, hypoechoic nodules on thyroid ultrasound in a child younger than age 18 years
Psammomatous melanotic schwannomas (PMS)[a]
Blue nevus[a]
Breast ductal adenoma[a]
Osteochondromyxoma[a]
Supplementary criteria
• Affected first-degree relative
• Inactivating pathogenic variant in PRKAR1A
Findings suggestive of or possibly associated with Carney complex, but not diagnostic for the disease
• Intense freckling
• Blue nevus
• Café au lait macules or other "birthmarks"
• Elevated IGF-I levels, abnormal glucose tolerance test (GTT), or paradoxic GH response to TRH (thyrotropin-releasing hormone) testing in the absence of clinical acromegaly
• Cardiomyopathy
• Pilonidal sinus
• History of Cushing's syndrome, acromegaly, or sudden death in extended family
• Multiple skin tags or other skin lesions
• Lipomas
• Colonic polyps (usually in association with acromegaly)
• Hyperprolactinemia
• Single, benign thyroid nodule in a child younger than age 18 years or multiple thyroid nodules in an individual older than age 18 years
• Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors

[a]Denotes after histologic confirmation [5]

Key Points

- Carney complex is a rare genetic disorder associated with multiple endocrine neoplasias.
- Both spontaneous and inherited cases occur.
- Cutaneous symptoms are of diagnostic importance.
- There is an increased risk of mainly benign tumors such as myxomas.
- Among possibly associated carcinomas, thyroid carcinoma is most important.

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Chapter 22
Disabling Pansclerotic Morphea of Childhood

Uwe Wollina

A 16-year-old boy with an 11-year history of disabling pansclerotic morphea of childhood was admitted to the hospital due to worsening of his general health status and a nonhealing large ulcerated wound on the calve. On admission, a gangrenous soft tissue infection was suggested. His family history was negative for rheumatic diseases (Figs. 22.1 and 22.2).

Based upon history and clinical appearance, what is your diagnosis?

1. Gangrene.
2. Necrotic tumor.
3. Arterial leg ulcer.
4. Ulcerative morphea.
5. Streptococcal necrotizing soft-tissue infection.

The boy presented with a generalized sclerosis of the skin and multiple cutaneous ulcerations. Joint contractures had led to immobility, toes, fingers and outer ears were partially mutilated. His body weight was only 18 kg. He suffered from dilated cardiomyopathy with an ejection fraction of 32%. The vital lung capacity was reduced to 70%. Radiographs of the bones revealed osteoporosis.

Laboratory investigations: increased C-reactive protein of >100 mg/l (normal <5 mg/l), eosinophila 8%, hemoglobin 7.5 mmol/l, serum iron 230 µg/l (normal 10–26 µmol/l), transferrin 1.58 mg/dl (normal 2.0–3.6 g/l). Antinuclear antibodies, anti-Scl-70, and anticentromere antibodies were all negative.

Biopsy confirmed a moderately differentiation squamous cell carcinoma of skin with tumor necrosis on the left lower leg. He also had a smaller squamous cell carcinoma of the dorsum of his left hand. Antibiotic therapy was initiated. Palliative

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_22

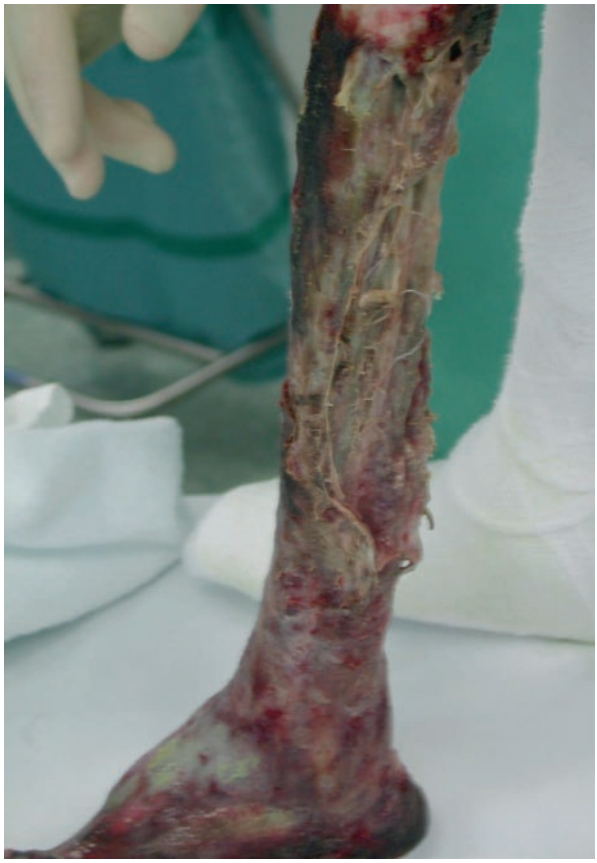

Fig. 22.1 Presentation of the leg on admission. From Doede et al. [1]

ablation of the proximal femur was performed. The boy, however, died 9 days after surgery.

Diagnosis Aggressive squamous cell carcinoma in disabling pansclerotic morphea of childhood.

Discussion

Disabling pansclerotic morphea of childhood is an orphan connective tissue disease [2]. The disease often starts before the age of 14 years. The onset of the disease is indistinguishable from morphea. The course, however, is rapidly progressive with generalized fibrosis of all soft tissue layers, leading to chronic ulcerations, joint contractures, and immobility. The mortality is nearly 100%, since no effective treatment is available. Most patients have a survival of less than 10 years [1, 3].

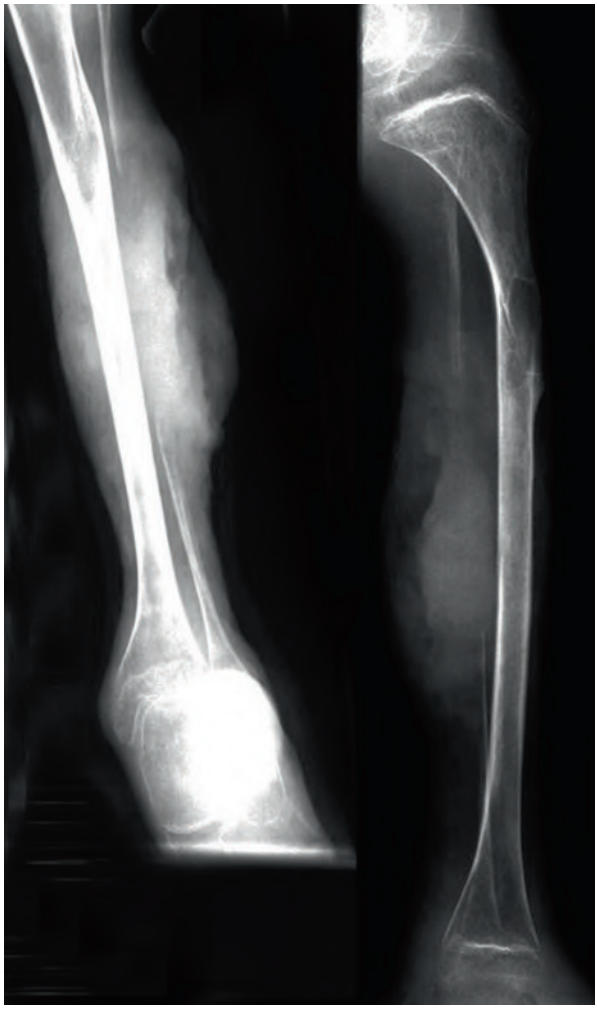

Fig. 22.2 X-ray of the affected leg demonstrating fibular infiltration of a tumor mass. From Doede et al. [1]

Table 22.1 Squamous cell carcinoma (SCC) in disabling pansclerotic morphea of childhood

References	Gender	Duration of morphea	SCC localization
[3]	M	10 years	2 × foot
[4]	F	12 years	Lower lip
[5]	M	10 years	Lower leg and hand
[6]	M	23 years	Ankle + popliteal metastases

The patients are at risk to develop aggressive squamous cell carcinoma with a potential to metastases (Table 22.1; [4–9]. Therefore, these patients need a regular follow-up for early diagnosis.

Key Points

- Pansclerotic morphea of childhood is a progressive and most severe type of morphea.
- There is no specific and effective treatment available.
- The disease has a high morbidity and mortality.
- Squamous cell carcinoma is the most common associated skin malignancy.

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Chapter 23
Giant Squamous Cell Carcinoma in Xeroderma Pigmentosum

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

A 16-year-old boy presented to our hospital because of a huge mass on the face and a large ulcer on the scalp. Physical examination revealed a giant necrotic, ulcerating mass involving the two third upper part of the face (Fig. 23.1) and an ulcer sized 10 × 7 cm on the cranial vertex of the scalp (Fig. 23.2). The mass covered almost the two eyes and half of the nose with multiple bleedings and pus-discharging. This mass had been gradually progressing for the last 7 years. There were also diffuse hypo-hyperpigmented atrophic lesions all over the body (Fig. 23.3). His skin was unnaturally dry and rough. Telangiectasias! were observed over some lesions. These lesions have increased over the skin since the age of three. There was no palpable lymph node. He had a significant alteration of general condition with a BMI (body mass index) of 13.6 kg/m^2. He has a family history of consanguinity, but no other person in the family has similar presentation.

Based on the case description and photographs, what is your diagnosis?

1. Carcinoma in ichthyosis
2. Squamous cell carcinoma in xeroderma pigmentosum
3. Porphyria
4. Cutaneous lymphoma

Diagnosis

Giant squamous cell carcinoma in xeroderma pigmentosum.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_23

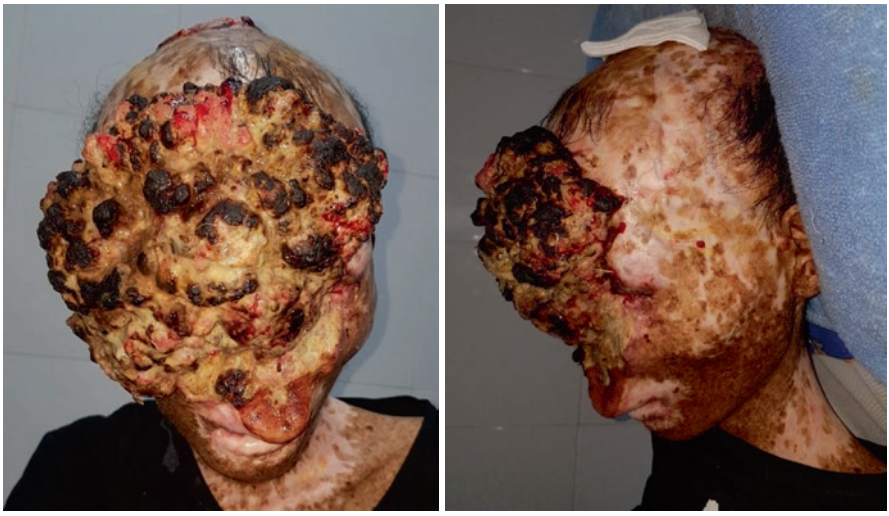

Fig. 23.1 Giant mass involving the two third upper part of the face, covering almost the two eyes and half of the nose

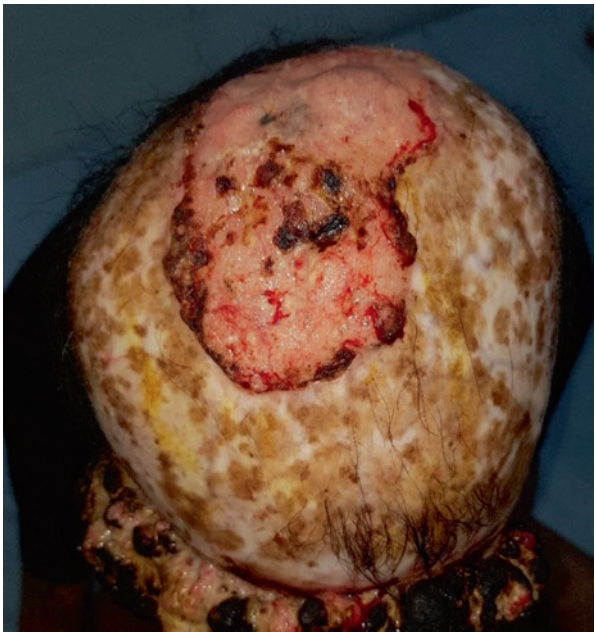

Fig. 23.2 Large ulcer on the cranial vertex of the scalp

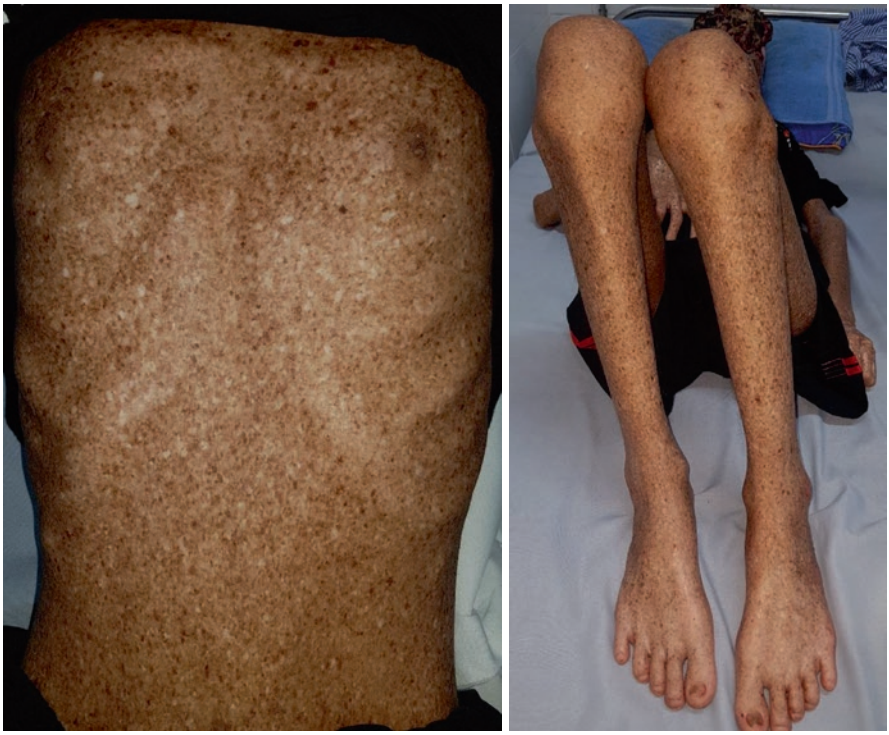

Fig. 23.3 Diffuse hypo-hyperpigmented atrophic lesions all over the body

Discussion

Xeroderma pigmentosum (XP) is an autosomal recessive genetic disorder that appears in early childhood, in which the ability to repair damage to DNA caused by ultraviolet (UV) light is deficient [1]. It is associated with extreme sensitivity to sunlight resulting in sunburn, pigment changes in the skin with increase in the frequency of skin cancers. In children with XP, there is a 10000-fold increased risk of skin cancer under 20 years of age [2]. The mean age for skin cancer is 8 years compared to 60 years in the healthy individuals [3].

Clinically, XP patients develop skin sensitivity to sunlight in early years (as early as 6 months) of childhood with sunburn, actinic keratosis, xerosis, poikiloderma, ocular abnormalities, and malignant neoplasms of the skin, especially in sun-exposed areas [1]. The most common neoplasms are squamous cell carcinoma and basal cell carcinoma. The central nervous system (CNS) is often affected in XP patients. The CNS does not have direct UV radiation exposure making the

mechanism of disease unclear, but unrepaired oxidative damage has been proposed as a possible cause [4]. Neurodegeneration occurs in an estimated 24% [2], including loss of intellectual functioning, deterioration of neurologic status, impaired hearing, abnormal speech, areflexia, ataxia, peripheral neuropathy, and loss of the ability to walk and talk.

The laboratory diagnosis of XP can be established with studies that include cellular hypersensitivity to UV radiation and chromosomal breakage studies and gene sequencing to identify the specific gene. Prenatal diagnosis is possible by amniocentesis or chorionic villi sampling [5]. Unfortunately, all these investigations are not available in our center and were, therefore, not undertaken for this patient. Clinical presentation provided the clue to the diagnosis.

In term of treatment, there is no cure for xeroderma pigmentosum. Investigative therapies using gene therapy and antioxidants to reduce oxidative damage may result in future treatment options [6]. Current management of XP patients mostly focuses on prevention of skin cancers by sunscreen use, protective clothing (long sleeves and pants, shirts with collars, tightly woven fabrics, wide-brimmed hat), restriction of outdoor activities to night-time. Frequent consultation and examination by dermatology and ophthalmology is recommended every 6 months to monitor for skin and ocular damage. Decreasing UV radiation exposure may not decrease neurodegenerations. Patients often require Vitamin D supplementation to compensate for sun avoidance [7]. Systemic treatment with retinoids has showed some benefits in reducing the number of skin cancers [8]. Surgical excision is the most common modality used for the treatment of XP-related neoplasms. However, lesions at some sites may not be amenable to adequate surgical intervention. In addition, significant esthetic deformities may result from multiple excisions. Therefore, early diagnosis and management are crucial in this disease. In our case, his poor socioeconomic background precludes these early interventions. The parents of this patient did not seek medical advice for him and he was brought late to hospital in spite of his early presentation at the age of 3-year-olds.

Key Points

- Early diagnosis is very important for the prognosis of XP patients
- Current management of XP patients focuses on prevention and treatment of skin cancers

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Chapter 24
Linear Lesion on the Scrotum

Katerina Damevska, Anita Najdova, Nora Pollozhani, and Elena Mircevska Arsovska

A 5-year-old boy presented with 3 years history of asymptomatic, slowly progressive lesions on the scrotum first appeared when he was 3 months of age. His parents have noted that from time to time, the lesion swells. The patient was otherwise healthy and had no history of local skin trauma or discharge from the site. A physical examination revealed multiple, soft, translucent, cystic lesions, 1–5 mm in diameter, on the scrotal median raphe (Fig. 24.1). No other skin lesions were observed, including mucous membranes, scalp, hair, and nails.

Based on the case description and the photograph, what is your diagnosis?

1. Testicular tumor
2. Milia
3. Viral warts
4. Median raphe cyst
5. Apocrine hidrocystoma
6. Linear epidermal naevus

Diagnosis

Median raphe cyst.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_24

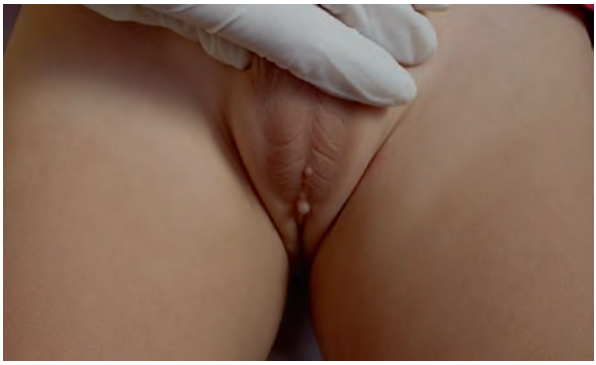

Fig. 24.1 Linear arranged skin-colored cysts on the scrotal median raphe

Discussion

The scrotum extends the keratinized squamous epithelium with underlying dartos muscle and associated external spermatic fascia. The underlying dermis with its rich vasculature contains hair follicles, eccrine, apocrine, and sebaceous glands [1].

Testicular and scrotal problems in children may be both congenital and acquired. Acute pathologic conditions comprising the bulk in the older children. In contrast, impalpable testes and neoplasms comprise most of the lesions in infants. Benign testicular neoplasms occur more frequently than primary malignancies [2].

Median raphe cysts are rare congenital lesions along the male external genitalia. Several terms have been used in the past to describe the condition, including mucoid cyst of the penile skin, genitoperineal cyst of the median raphe, parameatal cyst, hydrocystoma, and apocrine cystadenoma [3].

The cysts can occur at the parameatus, glans penis, penile shaft, scrotum, or perineum. The penile shaft is the more common location, whereas the perineum is the least common site. These cysts are generally asymptomatic or unrecognized during childhood [4].

The exact mechanism of formation of these cysts is not fully understood. Three different mechanisms have been described, including fusion defect of urethral folds, presence of ectopic periurethral glands of Littre proliferating into epithelial cavities, and development from urethral columnar epithelium followed by separation. Most authors believe that abnormal closure of the urethra during embryogenesis is the cause of median raphe cysts. The cysts can be defined into four types based on pathological findings: urethral, epidermoid, glandular, and mixed [5].

A median raphe cyst in pediatric age is usually a spot diagnosis. Specific location (any site along the midline of the ventral side of the male genital area) is highly suggestive of the diagnosis.

Dermoscopy can assist in clinical evaluation, showing a translucent image and the absence of a punctum. Translucency is highly suggestive of a cystic entity; however, a definitive diagnosis can only be achieved histologically [6]. The cysts are centered in the dermis and are not connected with either the epidermis or urethra [5].

Navarrete et al. [6] emphasize the importance of Doppler ultrasonography before biopsy in adult patients. An ultrasound excludes Mondor's disease or sclerosing lymphangitis, as well as a urethral diverticulum. These conditions could be clinically and dermoscopically indistinguishable from a median raphe cyst. Moreover, ultrasonography is the best imaging modality to diagnose testicular tumors, with a sensitivity of almost 100% for the detection of a testicular mass [7]. MR is used in exceptional cases where scrotal ultrasonography findings are inconclusive. Tumoural markers can help in the decision between orchiectomy or testis sparing surgery.

Median raphe cysts should be differentiated from other conditions such as epidermal cysts, pilonidal cysts, dermoid cysts, and urethral diverticula, perianal location condyloma, viral wart, hemorrhoid, hypertrophied papilla, and testicular tumors [5].

Testicular tumors are rare in children under 15. The increased risk is associated with cryptorchidism and gonadal dysgenesis. Prepubertal-type teratomas and prepubertal yolk sac tumours are the most frequent testicular tumors in children. Other tumors are epidermoid cyst and stromal tumor (Leydig cell and Sertoli cell) [7].

Teratomas are derived from all three germ layers (endoderm, mesoderm, and ectoderm). Prepubertal-type teratomas do not have significant cellular atypia and no metastasis. They are divided into mature (contain adult cells) and immature (contain embryonic cells).

On ultrasonography, they generally form well-defined heterogeneous masses. They may show cystic parts (mucoid, keratinous, or serous content) and peripheral solid parts (cartilage, fibrosis, scars, or calcifications). Mature teratomas are predominantly cystic with predominant sebaceous fat content, whereas immature teratomas are larger, encapsulated, with solid areas. Teratomas are poorly vascularized on color Doppler [7].

Apocrine hidrocystoma is a benign tumor arising from the apocrine sweat gland. It presents as a solitary translucent nodule, usually on the face, head, and neck. The size of the tumor varies between 3 and 15 mm. Multiple lesions are also reported, but rarely on the genitalia. Its color can vary from skin-colored to blue. The differential diagnosis of apocrine hidrocystoma includes eccrine hidrocystoma, blue naevus, poroma, and epidermal cyst. If the cyst occurs on genitalia, the median raphe cyst should always be ruled out. Simple excision can be both a diagnostic and therapeutic option when the apocrine hidrocystoma has an atypical location. The histopathologic findings, such as decapitation secretion, PAS-positive, and D-PAS-negative granules, can help distinguish the disease [8].

Key Points

- Scrotal pathology is relatively common in children. Benign testicular neoplasms occur more frequently than primary malignancies.
- Median raphe cyst is an uncommon condition in young patients. Only a few hundred cases have been published in the literature.
- The cysts can occur at any site on the ventral side of the genital area, including the parameatus, glans penis, penile shaft, scrotum, or perineum.

- In most patients, the cysts are asymptomatic during childhood but may become symptomatic during adolescence or adulthood.
- The diagnosis is generally based on characteristic clinical findings, and biopsy is rarely performed for diagnosis.
- Excision is the treatment of choice with minimal chance of recurrence.

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Chapter 25
Multiple Hyperpigmentation on the Face

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

An 18-year-old male patient was admitted to the hospital with many asymptomatic hyperpigmentation on his face. This condition began about 2 years ago, when he initially developed many abnormal skin pigmentations. They were all concentrated in light-exposed areas such as the face, neck and forearms with increasing number of lesions. During the examination, the physician found two large hyperpigmented macules on the left nasolabial fold and cheek. The lesion on the left nasolabial fold also had mild ulceration at the centre and had a pearly quality with telangiectatic vessels and a "rolled" border.

Based on the case description and photographs of patient's lesions at admission (Fig. 25.1), what is your diagnosis?

1. Basal cell carcinoma (BCC)
2. Squamous cell carcinoma (SCC)
3. Xeroderma pigmentosum (XP)
4. Melanoma
5. Benign nevus

Figure 25.1 shows two particularly large hyperpigmented areas on the face and the lesion of the nasolabial fold has many typical features of a basal cell carcinoma (a pearly or translucent quality, telangiectatic vessels with a "rolled" border and an ulcer. Additionally, some dryness is noticeable in the light exposed area. The biopsy results taken from both sides confirmed the diagnosis of basal cell carcinoma.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_25

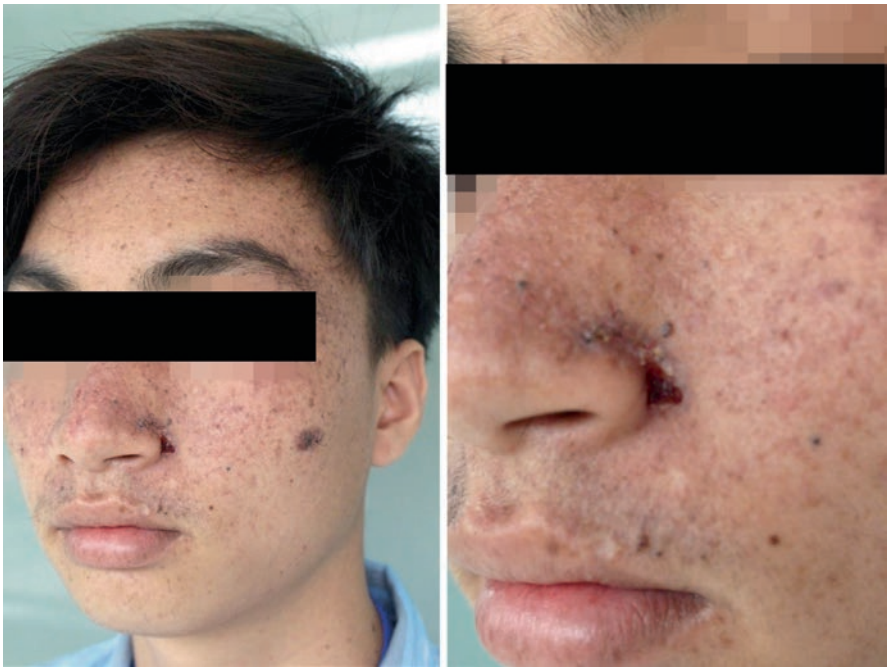

Fig. 25.1 18-year-old with marked photosensitivity manifested by many hyperpigmentations on his face

Diagnosis

Basal cell carcinoma/Xeroderma pigmentosum.

Discussion

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer worldwide that arises from cells of the basal layer and appendages of the epidermis. It is also the most common cancer in the United States, constituting 25% of all cancers, which translates to over 2,000,000 cases diagnosed annually [1]. In contrast, Asians are less likely to have BCC than Caucasian, but BCC is still the most common maglinant skin tumor. Although BCCs rarely metastasize, they can be locally destructive and highly morbid and therefore require conscientious work-up and management [2].

The development of BCC is the result of interactions between genetic factors and environmental factors. Table 25.1 lists the factors involved in the formation of BCC

Risk factors of skin cancer in general, most authors mention the role of sun exposure and UV light. Ultraviolet radiation is a well-known risk factor in the

Table 25.1 BCC causes and associations [1]

Sun exposure
Gene mutations
Exposure to artificial ultraviolet (UV) light
Ionizing radiation exposure
Arsenic exposure
Immunosuppression
Xeroderma pigmentosum
Personal and family history of previous nonmelanoma skin cancer (NMSC)
Skin type

development of non-melanoma skin cancers. Ultraviolet radiation is comprised of wavelengths range from 100 to 400 and is subdivided into UVA, UVB, and UVC. Ultraviolet exposure consists of 95% UVA and 5% UVB as UVC is filtered out completely by the ozone layer [3]. Any prolonged sun exposure or increased sun sensitivity condition, they all increase the risk of developing skin cancer, including BCC.

Like other cancers in general, the incidence of BCC increases with age and it is not common in young people, especially children. Persons aged 55–75 have about a 100-fold higher incidence of BCC than those younger than 20 [4]. Therefore, early-onset BCC (especially under age 40) needs to consider for cause or risk factors. BCCs in young patient were believed to be associated with environmental carcinogens, i.e. UV radiation and smoking [5]. Recent reports have also suggested an inverse relationship between body mass index (BMI) and early-onset BCC [6]. Some authors have hypothesized that estrogen exerts a potentially protective effect in obese individuals. Human papillomaviruses (HPV) are also other clinical factors reported to play a role [1]. Several observational studies have reported a significant positive association between HPV DNA or seropositivity and BCC, though most case-control studies have failed to demonstrate a clear association.

There are also several genetic syndromes and disorders that have been associated with the development of numerous and early-onset BCCs, such as Gorlin syndrome, Bazex syndrome, Rombo syndrome, Brooke-Spiegler syndrome and Xeroderma pigmentosum. Xeroderma pigmentosum (XP) is a very rare genetic disorder that increased sensitivity to UV radiation, early development of pigmentary changes and skin cancers. XP is inherited in an autosomal recessive pattern with 100% penetrance. In XP, there is an impaired nucleotide excision repair (NER) system. In normal individuals, the body repairs the damaged genetic material (DNA) of skin cells when exposed to UV radiation but in persons with XP, the body does not fix the damage due to molecular defects in genes involved in NER [7]. There are two subclasses of NER system: Global genome repair (GGR) pathway and Transcription-coupled repair (TCR) pathway. The global genomic repair (GGR) removes lesions throughout the genome regardless of whether any specific sequence is transcribed or not. The other is the transcription-coupled repair (TCR), which removes lesions only from the transcribed DNA sequences [8]. Both pathways lead to unwinding of

the DNA helix and excision of small fragments of affected DNA, and when affected, they result in developing the signs and symptoms of xeroderma pigmentosum.

XP is characterized by dermatological manifestations like severe sunburn, persistent erythema, marked freckle-like pigmentation of the skin, dry pigmented skin, keratosis, and neoplasm. Patients of XP with multiple primary lesions develop skin cancer. In contrast with what is observed in the general population, in XP patients, NMSC develops at a younger age than melanoma, with an average age of onset of 8 years for NMSC such as BCC or SCC [9]. Usually XP is diagnosed at a very young age base on clinical manifestations and family history consistent with autosomal recessive inheritance, and confirmed by molecular testing.

It is still extremely difficult to treat XP at present. Patients mostly live in disadvantaged areas and lack of understanding about disease. Treatments only include protecting patient from the effects of the sun and educating patients and families on early detection of skin cancers. In contrast, BCC has a very good prognosis. Because of the rarity of metastases, the most commonly used treatments of BCCs are currently surgical-based. Patients reported that at the initial treatment was Mohs micrographic surgery (MMS). Mohs surgery provides an intraoperative control of margin status. Therefore this surgery minimizes the amount of normal tissue that must be resected and has better cure outcome. Studies and reviews have found a 5-year cure rate of more than 90% for primary tumours and for recurrence that are recorded for this type of treatment [10].

Key Point

- Basal cell carcinoma (BCC) is the most common non melanoma skin cancer
- Typical clinical features of a basal cell carcinoma includes pearly or translucent quality, telangiectatic vessels, “rolled” border and ulceration.
- Early-onset BCC (especially under age 40) needs to consider for cause or risk factors: UV radiation, smoking, BMI, genetic syndromes and disorders.
- The signs and symptoms of xeroderma pigmentosum are a result of an impaired nucleotide excision repair (NER) system.
- Mohs micrographic surgery (MMS) is the most useful therapy for tissue conservation purposes and has more than 90% 5-year cure rate.
- XP treatment is still very difficult and mainly for prevention of complications, especially skin cancer.

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Chapter 26
Perianal Vegetations in a 1-Year-Old Child

Runping Fang, Shifei Zhu, and Tingting Qu

A 1-year-old boy was held by his parents for medical treatment. Six months after his birth, he had two small papules on his anal skin and didn't care. Half a month ago, dozens of papules were found in the boy's anus and perianal area, showing skin color and partially fusing into linear arrangement. Most of these papules are the rice-sized, with prickles on the surface, showing cauliflower-like appearance (Fig. 26.1). After inquiring about the medical history in detail, we found that the boy's uncle suffered from condyloma acuminatum, he often be alone with the boy and rub the boy's anus with his genitals.

Based on the case description and the photograph, what is your diagnosis?

1. Bowenoid papulosis
2. Squamous cell carcinoma
3. Condylomata acuminatum
4. Sebacous gland hyperplasia!

After seek medical advice, the patient was given Xiaoyou Decoction to wash the affected area, and recovered after 1 month.

Biopsies for cutaneous pathology were obtained from a single perianal lesion. Pathology showed that hyperkeratosis and parakeratosis of the epidermis, hypertrophy of the spinous layer, and massive vacuolar cells in the granular layer and the upper part of the spinous layer. Dermal papillomatous hyperplasia with telangiectasia and infiltration of inflammatory cells around superficial dermal vessels (Fig. 26.2).

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_26

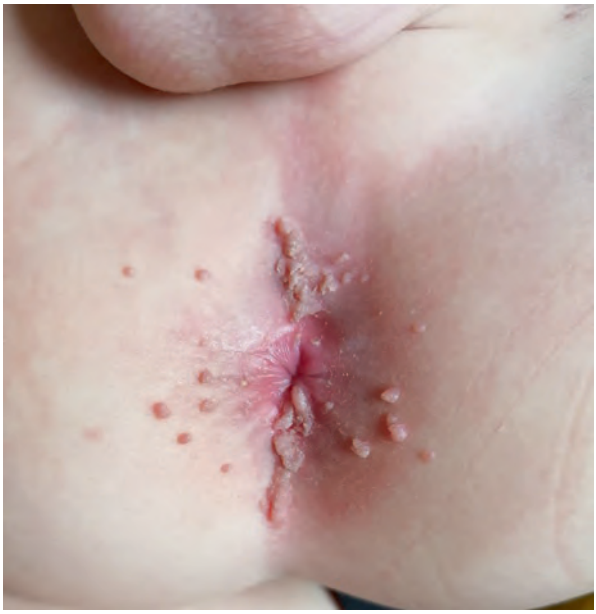

Fig. 26.1 Clinical manifestation of the patient. Multiple rice-sized vegetations can be seen on the anus and perianal skin

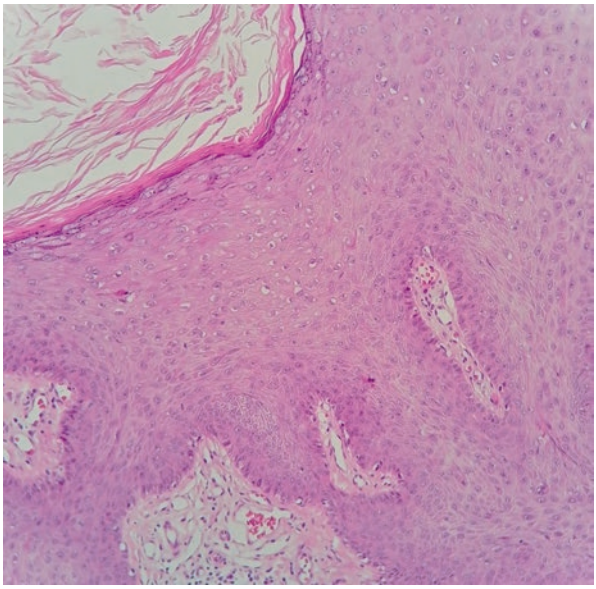

Fig. 26.2 Numerous corn-like cells are seen above the epidermis (HE ×20)

PCR-DNA detection of perianal lesions showed that the low-risk human papillomavirus increased, the normal value was 0–500, and the detection value was 2.46×10^4, Syphilis serological test was negative.

Diagnosis

Pediatric perianal condyloma acuminatum.

Discussion

Condyloma Acuminatum (CA) is a common sexually transmitted disease caused by human papillomavirus (HPV) type 6, 11, 16, 18 and 33. The incubation period is 1–8 months, with an average of 3 months. It mainly occurs in sexually active people. The peak age of onset is 20–40 years old, accounting for more than 80%. Genital and perianal sites are the best occur location for condyloma acuminatum. Female vaginitis and male redundant prepuce are the auxiliary factors for the occurrence and growth of condyloma acuminatum. Men see more at foreskin frenum, coronal sulcus, glans, urethral orifice, penile body, perianal and scrotum. Women are more common in large and small labia, posterior syndesmosis, vestibule, vaginal port, cervix and anus, pudendal and perianal areas. Occasionally, it occurs in armpit, umbilical fossa, oral cavity, breast and toe. The lesions were small and reddish papules at the beginning, then gradually increased, and the surface was uneven and rough. Usually no special feeling, and then further increase the formation of verrucous processes and spread to the periphery. According to the general morphology, it can be divided into papule type, nipple type, cauliflower type, cockscomb type and mushroom type. Wart surface often wet, white, red or dirty gray, occasionally foreign body feeling, itching or sexual pain, can burst, exudate, bleeding or infection [1].

A large number of epidemiological data show that HPV infection is closely related to the occurrence of genital cancer. It has been reported that vulvar condyloma acuminatum transformed into squamous cell tumor after 5–40 years, which is often caused by HPV16, HPV18, HPV31 and HPV33 infection. Condyloma acuminatum is a kind of benign proliferative lesions, after treatment, the prognosis is generally good, clinical see wart disappear is cured, but all kinds of treatment will have the possibility of recurrence, retreatment is still effective. The diagnosis of condyloma acuminatum is based on the analysis of medical history, clinical manifestations and necessary laboratory examination. According to the history of extramarital sexual intercourse or sexual partner infection, genital perianal condyloma acuminatum is not difficult to diagnose. If necessary, laboratory examination can help to make a definite diagnosis. Polymerase chain reaction (PCR) is the most sensitive method to detect HPV infection in vitro, It can also be used for type specific analysis. It has the characteristics of high sensitivity, simple and rapid method, and has been widely used in clinic. Pathological findings of vacuolar cells have characteristic diagnostic value. Condyloma acuminatum needs to be differentiated from Bowenoid papulosis, squamous cell carcinoma, sebaceous gland hyperplasia and other diseases.

Bowenoid papulosis is mainly associated with HPV16 infection. The clinical manifestations are clusters of flat brownish-red or brown small papules in the vulva, scattered in distribution or clustered in line or ring, with slow development and histopathological manifestations was carcinoma in situ [2].

Squamous cell carcinoma is more common in the elderly, with obvious upward proliferation of skin lesions, infiltrative growth into the tissue, prone to rupture and infection, hard nature, easy to bleed, with foul odor. Histopathological examination shows that the cells are abnormal and there are no vacuolized cells [3].

Sebaceous hyperplasia, also known as fordyee's disease, are small needle-size, isolated, non overlapping yellow-white clusters papules distributed in penis、glans and mucous membrane of labia, with a diameter of about 1 mm. It is a benign disease and generally does not require treatment. However, lesions can be unsightly and bothersome. The main concern is the clinical resemblance with other neoplastic lesions such as sebaceous adenoma and basal cell carcinoma. Mature sebaceous tissue can be seen by histological examination [4].

Based on the patient's medical history, clinical manifestation, and supplementary examination results, the diagnosis is Pediatric perianal condyloma acuminatum. It is worth mentioning that, how to prevent infants from sexual assault is a common problem for families, society and government.

There are many methods for the treatment of condyloma acuminatum, including laser, freezing, surgery, and drugs. In this case, considering that the child is young and the skin is delicate, we give traditional Chinese medicine to soak and wash, which has achieved good curative effect without causing damage to the skin.

Key Points

- Condyloma acuminatum is a sexually transmitted disease in which virus invades epidermal cells.
- The disease occurs in children suggests that human moral issues is involved.

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Chapter 27
Periocular Squamous Cell Carcinoma in a Child with Xeroderma Pigmentosum

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

Case Report

An 18-year-old boy, accompanied by his father, presented with an ulcerative mass on the right periorbital region and multiple brownish spots on the face, neck, upper chest, and limbs.

According to the father, brownish spots started to appear when the patient was 2 months old and increased in number along with time. The patient is the second child of six siblings. The patient's older brother had the same condition and died at the age of 7. The patient's parents and four siblings, including one male and three females, do not have similar symptoms. He has normal birth history and complete immunization. There was no history of drug or food allergy. The family has not sought any treatment for the skin complaints.

The patient was in a good general condition with normal vital signs. Dermatologic examination showed hyper-pigmented, crustal, lentiginous, multiple macules on the face, neck, and upper and lower limbs, hypo-pigmented atrophic lesions on the face and neck; ulcerative mass was seen on the right periorbital region (Fig. 27.1). These patches were seen on sun exposed area and some were grouped. White spots appeared on areas that are unexposed to the sun. Telangiectasias were observed over some lesions. These lesions have increased in size since the age of 3. There was no palpable lymph node. The patient also winces when exposed to the sun. This complaint was accompanied by burning sensation, pain and itching.

The histopathological examination of the biopsied specimens revealed poor differentiated SCC (Fig. 27.2)

Based on the case description and photographs, what is your diagnosis?

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_27

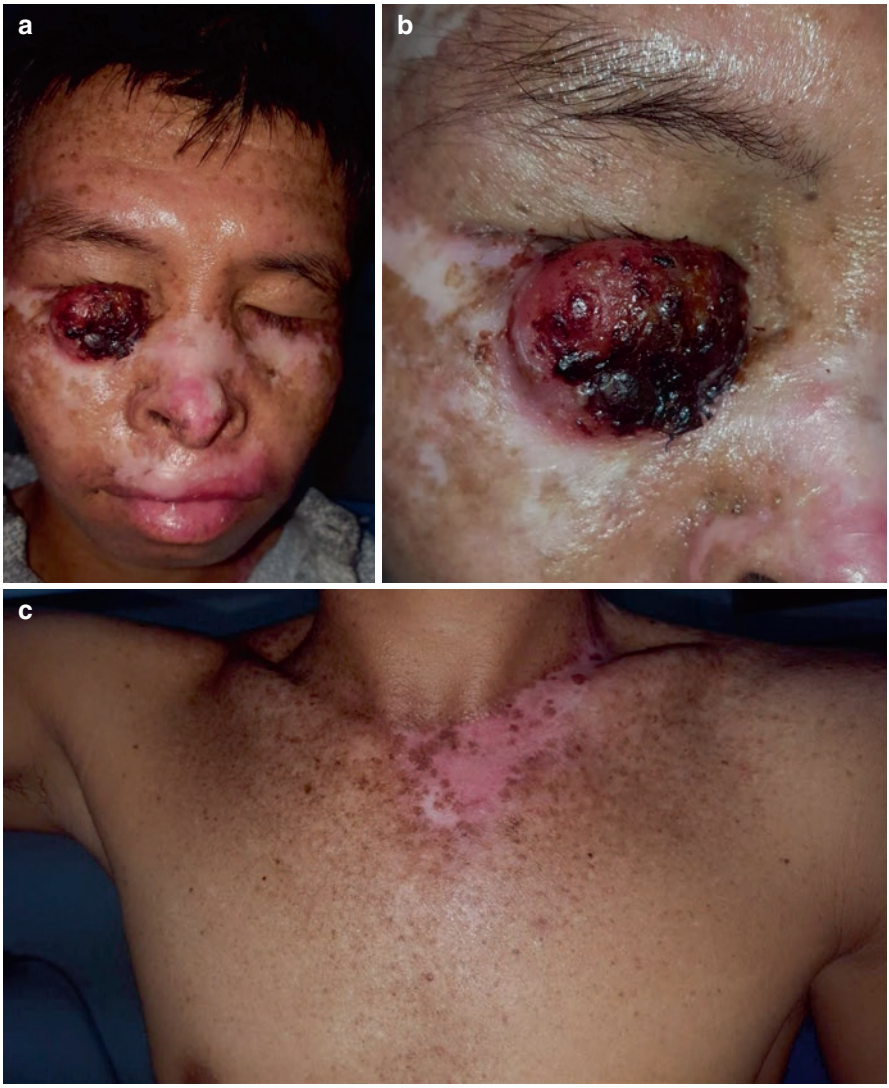

Fig. 27.1 (**a**–**c**) Hyper-hypopigmented atrophic macules, multiple lentigines at sun exposure areas and necrotic mass in the right periorbita

1. Carcinoma in ichthyosis
2. Squamous cell carcinoma in xeroderma pigmentosum
3. Squamous cell carcinoma in porphyria
4. Cutaneous lymphoma

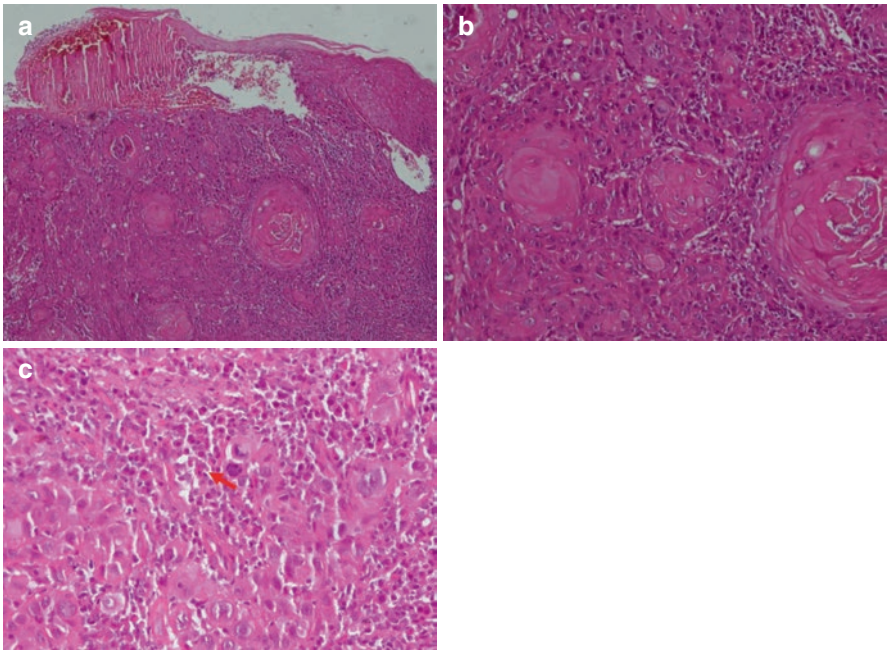

Fig. 27.2 Histopathology. (**a**) (X40)–(**b**) (X100). Inflammatory cell with necrotic tissue. (**c**) (X200). Atypical squamous cell, pleomorphic, prominent nucleoli, eosinophilic cytoplasm (red arrow)

Diagnosis

Squamous cell carcinoma in xeroderma pigmentosum.

Discussion

XP was first described in 1874 by dermatologist Moritz Kaposi, who coined the term "xeroderma" in reference to the dry skin of his four patients with XP [1]. XP is an autosomal recessive disease due to DNA gene mutation abnormalities, characterized by hyperpigmented and dry skin. XP is usually diagnosed at the age 1–2 when the child start to have sun exposure.

We report a case of XP in an 18-year-old boy who presented with necrotic mass under the right eye, which slowly developed from brownish spots 10 months prior to admission. These pigmented lesions were clearly seen on sun-exposed skin. From an early age, the patients are sensitive even to minimal sun exposure. Initially, the

lesions presented as erythema, vesicles, and edema. At the age of 2 years, solar lentigines, xerosis and pigmentation are often found which may be followed with the development of actinic keratosis, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), keratoacanthoma, and malignant melanoma. Skin cancers occur in XP with much greater frequency and at a younger age compared with the general population. The risks of skin cancer were found to be 1000-fold and 2000-fold higher, respectively, than in the general population in a study of 106 XP patients. The average age for developing melanoma malignancies in XP patients is at the age of 8 years. In a study including 830 XP patients, 45% of patients had BCC or SCC with majority of site on the head and neck. Ocular manifestations in XP include the development of scar tissues and skin cancers that require excision. Ocular abnormalities can be accompanied by dry eyes, red conjunctiva, swelling, and early pterygium. Prolonged exposure can cause scarring and impaired vision. Ocular cancer, especially SCC, has been reported in many patients with significant sun exposure and poor ocular protection [2–6].

The diagnosis of XP is based on history, physical examination and laboratory tests. The diagnosis of XP is established by finding trophoblast cells obtained early in pregnancy. Prenatal diagnosis can be done by measuring exposure to UV light which will trigger DNA synthesis in amniotic fluid cell cultures. Another test that can be useful is electroencephalography examination. Histologic findings were hyperkeratosis and an increase in melanin pigment and some rete ridges can extend where other rete ridges may show atrophy. Another feature was apoptosis of keratinocyte cells and the images of varieties of tumors that are complications of XP. The histologic findings in our case were inflammatory cells accompanied by tissue necrosis, keratinization, atypical squamous cell proliferation, pleomorphic, prominent nucleoli, which support a diagnosis of squamous cell carcinoma.

Treatment of patients with XP includes lifetime protection from sun exposure and early detection of neoplasms. The management requires a multidisciplinary team including dermatologists, genetics professionals, ophthalmologists, oral surgeons and neurologists. Sun protections, such as face coverings, hat, sunglasses, and in many patients can cause social isolation and may lead to psychological adverse effects such as depression and anxiety. Patients must be educated to protect all body surfaces by wearing UV-absorbing glasses and protective clothing. The doctor must examine the patient approximately every 3-6 months for early detection skin cancer. Premalignant lesions, such as actinic keratosis can be treated with liquid nitrogen, topical 5-fluorouracil, or imiquimod. Surgical excision is the treatment of choice for skin cancers in XP patients. Due to the high number of cancers that may occur in neighboring sites, margins should be as narrow as possible, with frequent follow-up and re-excision when needed (Fig. 27.3).

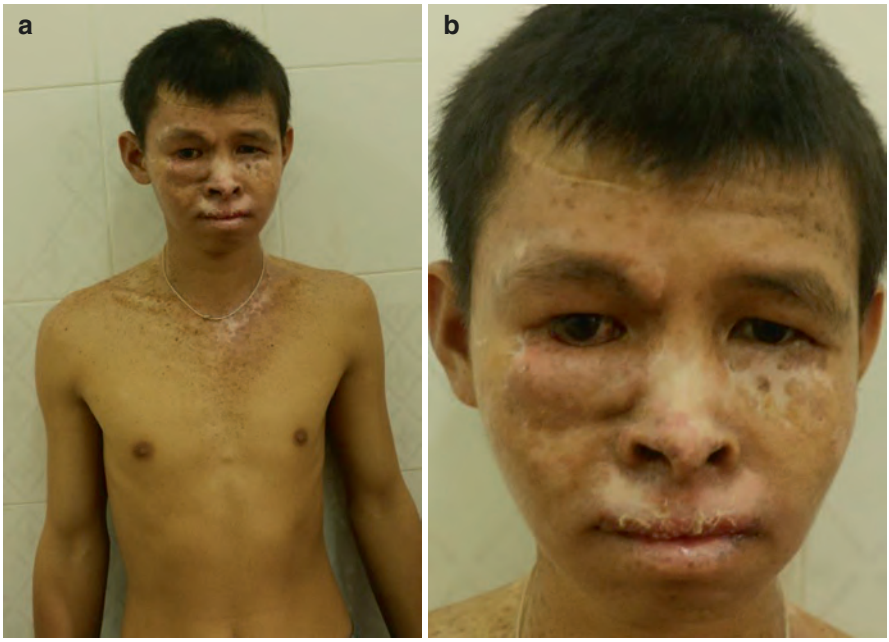

Fig. 27.3 (**a**–**b**) Two months post-operation, the patient could easily open his right eye but hyper-hypopigmented macules, multiple lentigines in sun exposed areas were still evident

Key Points

- Skin cancers, including squamous cell carcinoma, occur in XP with much greater frequency and at a younger age compared with the general population.
- Treatment of patients with XP includes lifetime protection from sun exposure and early detection of neoplasms.

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Chapter 28
Recurrent Vulvar Rashes in a Girl

Ke-Yao Li, Jian-Ping Tang, Yan-Ling Jiang, and Bin Zhou

The girl had no obvious cause of erythema in vulvae at about 1 year old (Fig. 28.1), The parents considered "diaper dermatitis" and did not give special treatment. After that, the rash gradually expanded, and the rash became like a blister, with no pain and itching. Then the scope of the rash gradually expanded. Multiple visits to local hospitals, the diagnosis of "vulvar eczema?", and the treatment with antiallergic

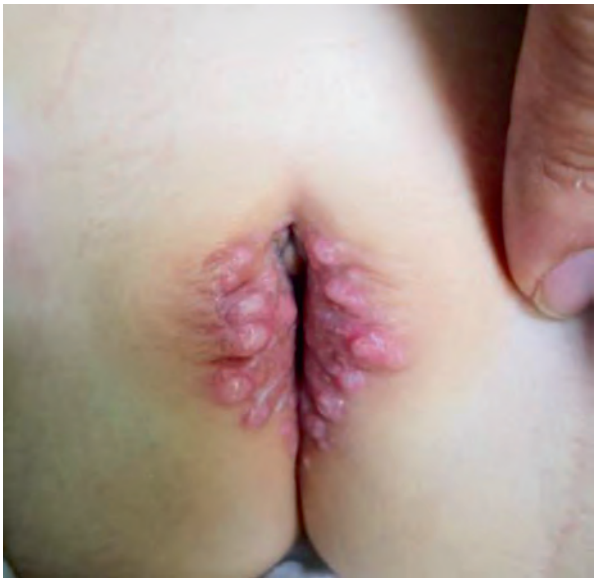

Fig. 28.1 A girl, aged 22 months, attended the hospital due to recurrent vulvar rashes for more than half a year

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_28

drugs (specific drug name is unknown) was ineffective. Then the patient went to the outpatient department of our department to diagnose “Molluscum Contagiosum? Sexually transmitted diseases?” In consideration of the special location of the rash, the treatment of diagnostic treatment like curettage of Verruca, external use of recombinant human interferon antiviral, transfer factor oral solution to improve the immunity of children, ozone hydrotherapy and external washing were not effective. Biopsies showed Langerhans cell histiocytosis, and evaluation of systemic conditions showed no systemic involvement.

Based on the case description and the photograph, what is your diagnosis?

1. Molluscum Contagiosum?
2. Condyloma acuminatum?
3. Herpes simplex?
4. Fordyce disease?
5. Langerhans cell histiocytosis?

She was hospitalized, skin biopsy showed Langerhans cell histiocytosis, and evaluation of systemic conditions showed no systemic involvement. Therefore, the girl was diagnosed with Langerhans cell histiocytosis (skin type).

Diagnosis

Langerhans cell histiocytosis (skin type).

Discussion

Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a rare clonal disease originated from bone marrow monocyte macrophage system. Sustained immune stimulation leads to uncontrolled proliferation of CD1 α + /cd207 + dendritic cells [1]. The annual incidence rate of children and adults was (4~8)/1 million and (1~2)/100 million respectively, and the overall mortality was 10~20% [2]. LCH can occur at any age, but it is common in children, especially in infants. The most frequently involved sites are bone, skin and lymph nodes [3], The rash of LCH is pleomorphic, which mainly occurs on the scalp, face, trunk and buttocks. Papules, macular papules, hemorrhagic papules, nodular ulcers or small ecchymosis can be seen. Female genital tract involvement is rare. In this case, only female genital tract involvement is rare, but vulva is the most common site of involvement (Fig. 28.2).

Langerhans cells are derived from peripheral dendritic antigen processing cells of bone marrow and are an important part of local immune response, These cells are found throughout the body, but mainly in the upper basal layer of the epidermis. They are also found in the dermis, lymph nodes and stratified squamous epithelium of tonsil and oral cavity. In the genital tract, Langerhans cells were found in vulva,

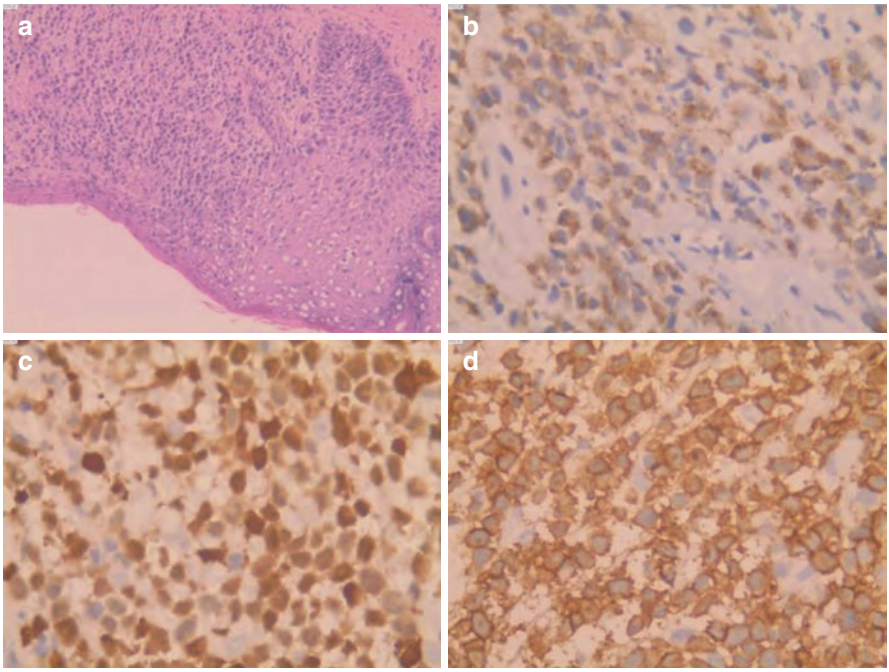

Fig. 28.2 Pathological picture (**a**) HE ×400. (**b**) Langerin ×400. (**c**) S-100 ×400. (**d**) CD1a ×400

vagina and cervix. Langerhans cells were affected by chemical stimulation, especially smoking and human papillomavirus infection. This may be the reason why LCH can occur in vulva [4].

The treatment of LCH located in vulva is not recommended, so individualized treatment should be selected according to the clinical symptoms. Current treatments include surgery, radiotherapy, topical corticosteroids, topical nitrogen mustard solution, thalidomide, systemic chemotherapy and various combinations [5].

This case of female onset about 1 year old, and the rash was only located in the vulva. The rash was a solid blister like rash with symmetrical distribution. The patient had no pain, pruritus and other conscious symptoms, and the rash gradually expanded. The manifestations of the rash have certain characteristics, but no specificity. Although it is very rare, but it has been reported in the literature. No damage to the system was detected, and it is diagnosed as LCH (skin type). After topical use of 0.3% tacrolimus, the rash subsided.

Key Point

- Langerhans cell histiocytosis (LCH), is a rare clonal disease originated from bone marrow monocyte macrophage system.
- The treatment of LCH located in vulva include surgery, radiotherapy, topical corticosteroids, topical nitrogen mustard solution, thalidomide, systemic chemotherapy and various combinations.

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Chapter 29
Scattered Pigmented Papules in an Infant

Le Huu Doanh, Nguyen Van Thuong, and Michael Tirant

A 5-month-old baby boy was admitted to our hospital with scattered pigmented papules. The onset was at the age of 3 months with many papules on his scalp, then progressed to his abdomen, back and groins. Some papules were self-healing although new lesions had continued to develop.

He is the third child of his parents, by normal vaginal delivery and is vaccinated to date. No member of his family had similar lesions like him.

Examination revealed many scattered skin-colored papules, 1–2 mm in diameter, some were rose-yellowish, crusted, hemorrhagic, the distribution was mainly on his head, trunk and groins. The old lesion left hypopigmented macules. He had no scratch due to itching and no nail involvement.

He had no fever, no hepatosplenomegaly. The rest of his examination was normal (Fig. 29.1).

Investigation

Complete blood count, liver and kidney function test were normal.

Histopathology revealed exocytosis of mononuclear cells to epidermal, infiltration of eosinophils and lymphocytes in papillary dermis. Immunohistochemistry was positive staining for S100, CD1a, CD45 and CD4, negative for CD20 (Figs. 29.2, 29.3, and 29.4).

Chest x-ray, abdominal ultrasound and bone scans, were all normal.

Based on the case description and photographs, what is the diagnosis?

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_29

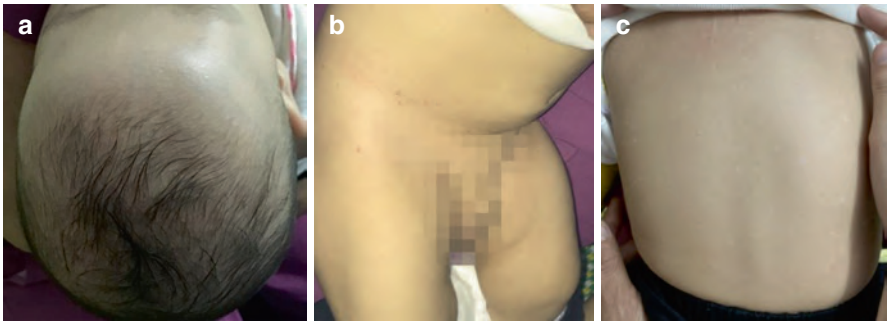

Fig. 29.1 (**a**) Scattered skin-colored papules in the scalp. (**b**) Rose-yellowish, crusted, hemorrhagic papules on the groin. (**c**) Self-healing lesions leaving hypopigmented macules

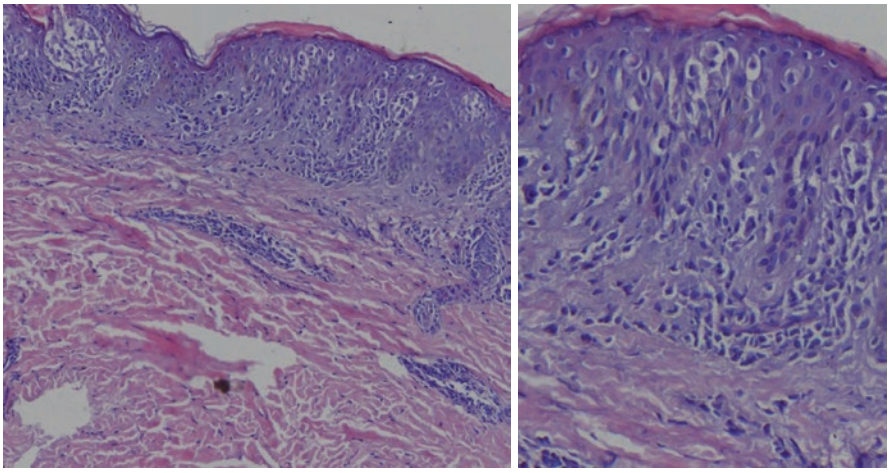

Fig. 29.2 HE stain—exocytosis of mononuclear cells to epidermal, infiltration of eosinophils and lymphocytes in papillary dermis

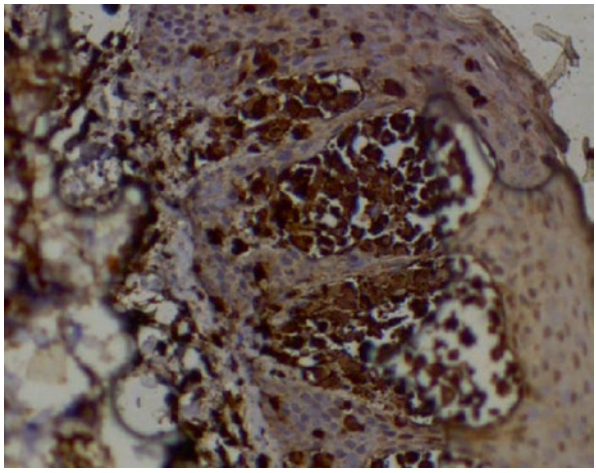

Fig. 29.3 Immunohistochemistry CD1a (+)

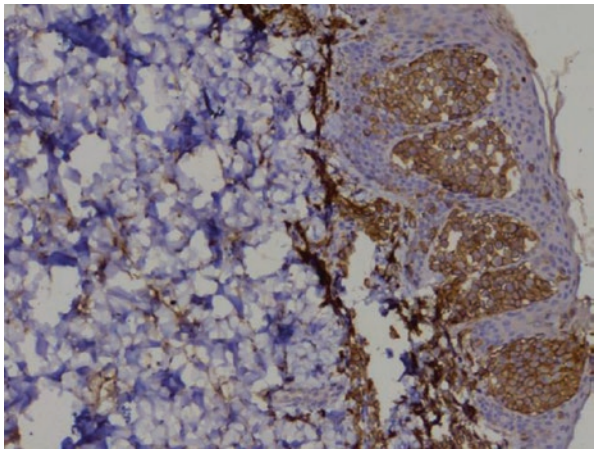

Fig. 29.4 Immunohistochemistry S100 (+)

1. Cutaneous Langerhans cell histiocytosis
2. Benign cephalic histiocytosis
3. Seborrheic dermatisis
4. Atopic dermatitis

Diagnosis

Cutaneous Langerhans cell histiocytosis.

Discussion

The histiocytoses are a group of rare disorders characterized by pathologic accumulation of cells derived from the monocyte, macrophage, and dendritic cell lineage. The Working group of Histocyte Society classified the histiocytoses as Langerhans cell-related, non-Langerhans cell-related, or malignant. Among histiocytic disorders, Langerhans cell histiocytosis (LCH) is the most common one, affecting an estimated 4–5 per million children 0–15 years of age each year. The median age of diagnosis is 3.5 years, and the highest incidence rate is observed before 1 year of age, with a decreased incidence observed thereafter. While most prevalent in children, the disorder presents in all ages and has also been reported in the elderly. There is a 2:3 male:female ratio [1].

Current knowledge redefined LCH as an heterogeneous neoplasm of dendritic cells driven by activating mutations in the MAPK pathway. BRAF-V600E mutation is found in 38–69% patients.

LCH is currently categorized by involvement of single or multiple organ systems, single or multiple sites within a particular organ system, and the presence of risk organ involvement, which includes the liver, spleen, and bone marrow.

The most commonly affected organs are: bone (80%), skin (33%), pituitary (25%), liver (15%), spleen (15%), hematopoietic system (15%), lungs (15%), lymph nodes (5–10%), and the central nervous system excluding the pituitary (2–4%). Systemic signs, such as fever, lethargy, and weight loss, may be noted in patients with either single-system or multisystem disease. Fever has been observed in 50% of pediatric patients.

In considering patients of all ages, skin is the second most frequently involved organ system after bone. Nevertheless, in patients 2 years of age, cutaneous disease is the most common manifestation. Cutaneous involvement is typically representative of multisystem disease because 87–93% of patients also have systemic involvement. Cutaneous lesions associated with fever (52%), hepatomegaly (52%), splenomegaly (48%), bone damage (39%), and lung damage (36%) are the most common manifestations of systemic involvement. Isolated cutaneous disease accounts for only 2% of total cases.

Patients can present with a broad variety of skin manifestations. The most typical ones are small, translucent rose-yellowish crusted papules or papulo-vesicles on the trunk, in the intertriginous areas and the scalp, associated with eczematous scaling which resembles “candida intertrigo” or “seborrheic dermatitis”. Lesions can also present as hemorrhagic papules and nodules associated with petechiae reminiscent of vascular lesions or “varicella-like eruptions”. Vesicles, pustules, and nail involvement have been described. Nail involvement can present as paronychia, nail-fold destruction, onycholysis, subungual hyperkeratosis, longitudinal grooving pigmented and purpuric striae of the nail bed. Mucosal lesions most commonly are nodulo-ulcerative and involve the perioral, the peri-genital, and the perianal areas as well as the gingiva. Mucosal lesions and external otitis media seem to be associated with a higher risk for multisystem LCH. Purpura with nail involvement might be a poor prognostic sign, but this should be evaluated in larger clinical trials. This broad variety of skin and mucosal manifestations frequently leads to a delayed diagnosis as skin lesions are misinterpreted as eczema, miliaria, scabies, varicella, seborrheic dermatitis, folliculitis, or candidiasis. LCH should be kept in mind as a rare, but important, differential diagnosis when the above-mentioned lesions are seen, especially if they are resistant to therapy and are spreading.

A histopathologic diagnosis is by far the most reliable and accurate diagnostic tool for a definitive diagnosis of LCH and should always be performed if it doesn’t put the patient at an increased risk. Histopathologically, typical findings in a skin biopsy show a dense and band-like infiltration of the papillary dermis with LCH cells. These cells are oval shaped with an eosinophilic cytoplasm and typically display an irregular, vesicular, and infolded (kidney-shaped) nucleus. Typical immunehistochemical markers of LCH cells are CD1a, S100B, CD207 (Langerin), and fascin. Stabilin-1 and CD34 are not expressed [2].

In children with LCH confined to the skin, a watch-and-wait strategy is the best approach. Topical treatment can be tried with corticosteroid ointments, but topical

steroids have shown little efficacy. A skin rash that does not respond to topical steroids is considered a clue for LCH. Other topical treatment options include imiquimod and tacrolimus as well as intralesional corticosteroid injections, CO2 laser therapy, or excision of single LCH nodules. Nitrogen mustard ointment can be applied to treat skin lesions in adults [3].

Several case reports exist that show a significant improvement after narrowband ultraviolet B irradiation in adults and children. This treatment might work well with papules and eczematous lesions, but not when nodules are present. Photochemotherapy is effective in some adult patients. In case of ineffective local therapy, systemic glucocorticoids, thalidomide, or antimitotic drugs, such as low-dose methotrexate, can be tried. Thalidomide can ameliorate skin lesions, but the treatment is associated with neurologic toxicity and fatigue. Thalidomide should not be used in women with child-bearing potential if the skin is the only organ affected. There is one case report in which a patient went into complete remission after oral isotretinoin therapy (1.5 mg/day for 8 months).

Single-system LCH has an excellent prognosis, with a survival rate of nearly 100%. The 5-year recurrence rate is 20%, and recurrence typically involves the same organ system but may involve a different location. Cutaneous lesions that regress mostly heal without defects, but may be followed by scarring, hypo-, or hyperpigmentation.

Key Points

- LCH is newly defined as a rare, heterogeneous neoplasm of dendritic cells. CD1a/S100B/CD207-positive mononuclear cells with beanshaped nuclei infiltrate organ involvement.
- Skin is the second most frequently involved organ system after bone in considering patients of all ages, and is the most common manifestation in patents 2 years of age.
- Cutaneous finding is variable, including translucent, roseyellowish, crusted papules or papulovesicles, eczematous lesions, hemorrhagic papules and nodules, petechiae, noduloulcerative mucosal lesions, and nail involvement.
- In children with LCH confined to the skin, a watch-and-wait strategy is the best approach.
- Single-system LCH has an excellent prognosis, with a survival rate of nearly 100%.

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Chapter 30
The Wrinkled Part of the Whole Body Is Black in a Boy

Ke-Yao Li, Jian-Ping Tang, Yan-Ling Jiang, and Bin Zhou

The child first developed a black neck calmness 9 years ago (Fig. 30.1), and no special treatment was given because of no special discomfort. Later, the armpit, groin, and popliteal were gradually involved. Later, he went to the local hospital, considered "acanthosis nigricans" and treated with topical drugs (the details are unknown), but there was no obvious curative effect. The child was born at 40 weeks of gestation, with deafness, and his height and weight after birth were 3SD lower than children of the same age. The parents of the child complained that the child had poor physique since childhood, prone to get sick, and had been hospitalized for pneumonia many times.

Based on the case description and the photograph, what is your diagnosis?

1. Acanthosis nigricans?
2. Hypocorticism?
3. Donohue syndrome?

Check genetic testing, It turns out to be Donohue syndrome (Fig. 30.2).

Diagnosis

Donohue syndrome.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_30

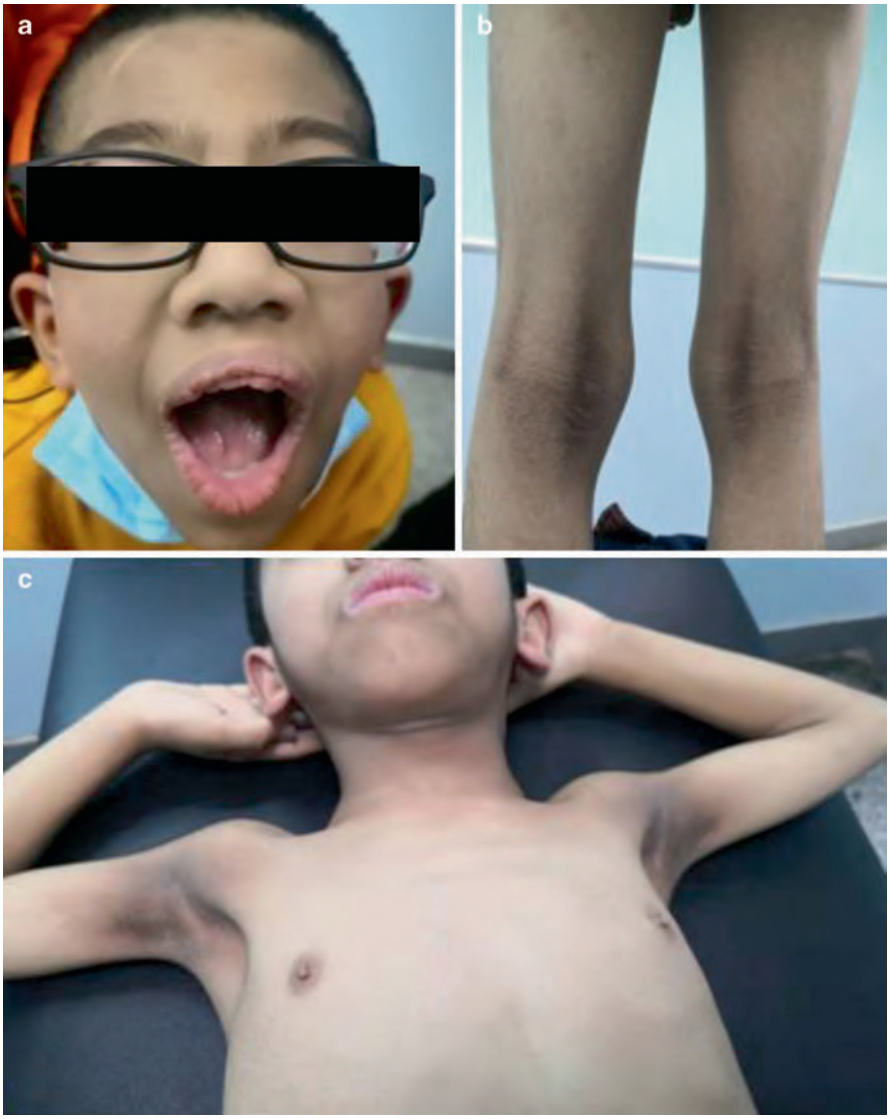

Fig. 30.1 Clinical manifestation of the patient (**a**) Rash on his face. (**b**) Black wrinkles on the lower limbs. (**c**) Black wrinkles on the armpit

Discussion

Donohue syndrome (Leprechaunism) is characterized by insulin resistance and distinct clinical and facial features [1]. Donohue syndrome is the most severe type of insulin receptor disorder with autosomal recessive inheritance and the majority of

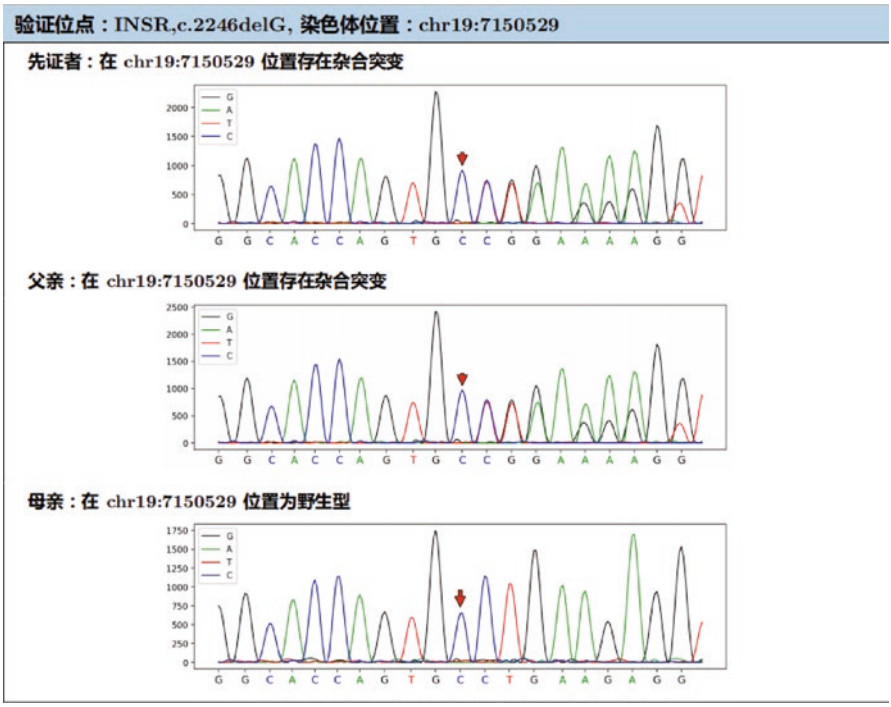

Fig. 30.2 Genetic test result

syndrome [2]. Donohue syndrome is a rare disorder with an incidence of one in four million live births [3]. It is an autosomal recessive disorder caused by a functional defect in the Insulin Receptor gene on chromosome 19p13. Children with Donohue syndrome present with severe intra- and extrauterine growth retardation. Intrauterine growth retardation is typically seen acutely from 7 months gestation. Birth weights are typically <0.4th percentile. Postnatally there is severe failure to thrive with marasmus and malnutrition despite feeding [4]. Severe hyperinsulinism combined with fasting hypoglycemia and postprandial hyperglycemia are the hallmarks of Donohue syndrome [4].

Due to their accelerated fasting state and disordered homeostatic response to hypoglycemia, these children fail to gain weight or length despite adequate feeding. They lose muscle mass and are at risk of sepsis due to immunodeficiency.The only current treatment option in Donohue syndrome is IGF-1 therapy [4].

Key Point

- Donohue syndrome (Leprechaunism) is characterized by insulin resistance and distinct clinical and facial features.
- Donohue syndrome is the most severe type of insulin receptor disorder with autosomal recessive inheritance and the majority of syndrome

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Chapter 31
Tiny Hyperpigmented Macule on Lower Lip

Tugba Kevser Uzuncakmak and Zekayi Kutlubay

A 9-year-old female presented to our department for dermatological examination of her hyperpigmented skin lesions on her face. Clinical examination revealed several light brown lentiginous proliferation on sun-exposed areas on the face, neck, and extensor surfaces of the upper extremity. Also, a 1 mm, black macular lesion on the left side of the lower lip noted which occurred 1 month ago and multiple, shiny, pinkish 2–3 mm papular lesions on the left lateral aspect of the nose were noted (Fig. 31.1). Her lentiginous lesions on her face first appeared when she was 2 years old and she applied in the different dermatology departments for her lesions before, but not routinely. Her elder brother also has similar lesions on the same localizations and he also has a history of multiple basal cell carcinoma excisions on his face, previously. She was otherwise healthy.

On the dermoscopic examination, diffuse dark pigmentation was detected on the lesion located on the lip (Fig. 31.2) and telangiectatic vessels on a pink structureless basis were observed on the lesions located on the cheek. Both the lesions on her lip and one of the papular lesions on the cheek were excised. Histologically, focal lentiginous atypical melanocytic proliferation was detected in the pigmented lesion (Fig. 31.3). The lesion on the nose was consistent with basal cell carcinoma, histologically.

Based on the case description and the photograph, what is your diagnosis?

- Rothmund-Thompson Syndrome
- Gorlin-Goltz Syndrome
- Xeroderma pigmentosum
- LEOPARD Syndrome

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_31

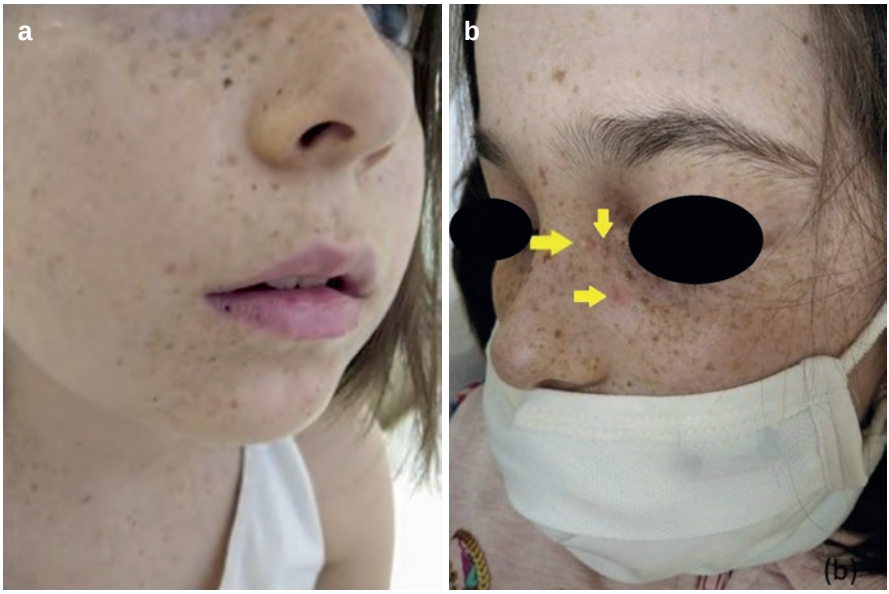

Fig. 31.1 (**a**) Multiple light brown lentiginous proliferations on the face and neck and a 1 mm, black macular lesion on the left side of lower lip. (**b**) Multiple 2–3 mm shiny, papules on the lateral aspect of nose

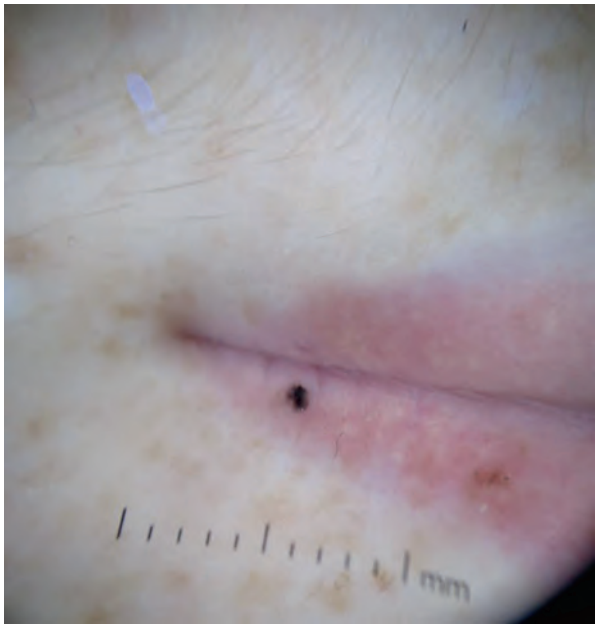

Fig. 31.2 An irregular dark hyperpigmentation on the lower lip (DermLite Photo 3Gen LLC, Dana Point, CA, U.S.A.)

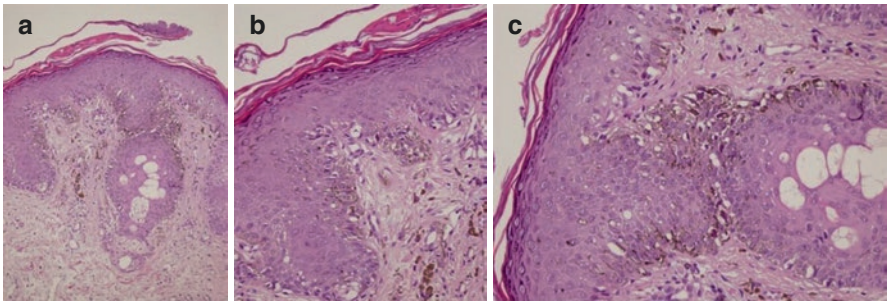

Fig. 31.3 (**a**) Increased melanocytes along the basal epidermis (H&E, ×200) (**b**, **c**). Increased atypical melanocytes with prominent nucleoli and enlarged nuclei (H&E, ×400)

Diagnosis

Lentigo maligna and basal cell carcinoma in Xeroderma pigmentosum.

Discussion

Xeroderma pigmentosum (XP) was first defined in 1874 by Hebra and Kaposi, was named as xeroderma pigmentosum due to dry skin, pigmentary changes in affected patients [1]. It is a rare hereditary disorder and reported to affect 45 per million in Japan and this ratio is estimated to be 1 per million in the USA without any gender predilection [1, 2].

The skin lesions of XP begin in the first 2 years of life and typically the skin looks healthy at birth. Diffuse erythema, lentiginous pigmentation, and scaling may occur 6 months after birth, usually on sun-exposed areas, especially on the face. These features usually diminish during the wintertime due to the decreased UV exposure [1]. Poikiloderma, including mottled hyperpigmentation and hypopigmentation, telangiectasias, skin atrophy, and early skin aging are the other main cutaneous findings. Telangiectasias may occur both in the sun-exposed areas and in unexposed skin and even on mucosal surfaces.

Different cutaneous malignancies, including squamous cell carcinoma, malignant melanoma, basal cell carcinoma, and fibrosarcoma may occur [3, 4]. The risk of nonmelanoma skin cancer development has been reported to be 10,000-fold greater in XP patients and the risk for melanoma development was found to be 2000 times greater in this patient group [2].

There is not a single gene defect in XP patients and there are individual variations, affecting the prognosis of XP. Minimizing sun exposure and detecting the skin changes in their earliest stages are major points in the management of XP. Sunblocks should be used, even in the winter months. The exposed surfaces of

the skin should be shielded with protective, double-layered clothing and broad-brimmed hats. Precancerous lesions and small or localized BCCs can be treated with topical agents such as 5-FU or imiquimod or cryotherapy. Larger skin lesions and SCCs should be treated surgically with clear free margins due to the increased risk of recurrence [3]. Systemic acitretin can be offered to prevent the development of skin cancers.

Rothmund-Thomson syndrome (RTS), or poikiloderma congenital, is a rare autosomal recessive disorder characterized by a combination of poikilodermatous skin changes, growth retardation, and juvenile cataracts [3]. The characteristic skin lesions occur between the age of 3–6 months as an erythematous, oedematous blistering facial rash. As the lesions reach the chronic stage, poikilodermatous changes including atrophy, telangiectasias, and pigmentary changes become more prominent especially on the face, extensor surfaces of extremities, and buttocks with sparing of the chest, abdomen, and back. In this syndrome, a possible genetic mutation in the RECQL4 gene, encoding for the RECQ helicase, which is responsible for correcting double-stranded DNA breaks has been suspected. The loss of this gene leads to an accumulation of unrepaired DNA damage results in increased risk for cutaneous and skeletal malignancies. These patients should be followed up by a multidisciplinary team, including a dermatologist, an oncologist, an ophthalmologist, and an orthopedic surgeon. A life-long follow-up, including regular skin examinations to screen for SCC and BCC, should be recommended. They also should be advised to avoid sun exposure to prevent the development of cutaneous malignancies.

Gorlin Goltz Syndrome (GGS), also known as naevoid basal cell carcinoma, is an autosomal dominant condition that is characterized by unusual facial appearance, dental cysts, palmar pits, and multiple BCCs, clinically. Multiple BCC usually appear at the age of puberty and the age of 35. The presence of the other skeletal abnormalities, calcification falx cerebri, odontogenic cysts, palmoplantar pits, medulloblastoma and positive family history for GGS may help in the differential diagnosis.

LEOPARD syndrome is the acronym of the main features including lentigines (multiple), electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, and deafness [5]. Autosomal dominant inheritance has been reported in familial cases. The diagnosis of this complex dysmorphogenesis disorder may be very difficult in early childhood and can be clinically suspected in patients who have three main features: characteristic facial features, hypertrophic cardiomyopathy, and café au lait spots in the first months of life. The lentiginous proliferation may be present at birth or develop during childhood. They become more numerous and darker with age. The occurrence of malignant melanomas has been reported sporadically in the LEOPARD syndrome.

Key Points

- Xeroderma pigmentosum is a rare autosomal recessive hereditary disorder that may affect the skin, ocular and neurologic systems.
- Patients with XP have severe photosensitivity, an increased number of lentigines (freckle-like pigmentation) in sun-exposed areas, and extreme sensitivity to sunlight resulting in acute severe sunburns.
- In XP patients, cutaneous malignancy risk is much higher and these malignancies usually appear earlier than in the general population.
- A life-long follow-up, including regular skin examinations to screen for malignancies, should be recommended.
- Patients should be advised to avoid sun exposure to prevent the development of cutaneous malignancies.
- Topical 5 fluorouracil cream, imiquimod 5% cream, and systemic acitretin can be offered for actinic damage and to prevent further development of cutaneous malignancies.

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Chapter 32
Xeroderma Pigmentosum with Cutaneous Malignancy

Inne Arline Diana, Srie Prihianti Gondokaryono, R. M. Rendy Ariezal Effendi, and Reiva Farah Dwiyana

An 8-year-old boy presented to the hospital with her mother, complaining of hypopigmented and hyperpigmented macules on expose areas mainly on the face, neck, upper chest, back, arms, hands, and leg, with multiple tumors on the right retro auricular, face, and scalp which bleed easily with friction (Figs. 32.1, 32.2, and 32.3)

Based on the case description and the photograph, what is your diagnosis?

1. Xeroderma pigmentosum (XP) with suspect squamous cell carcinoma (SCC) on right retro auricular and basal cell carcinoma (BCC) on scalp and face.
2. Xeroderma pigmentosum (XP) with suspect BCC on the right retro auricular, scalp, and face.

Seven years prior to consultation (PTC), the mother noticed hypopigmented macules alternating with normal to hyperpigmented skin on exposed area increase in size and number. The patient temporarily applied the topical treatment from a dermatologist, but there was no improvement. The patient also complained of half photophobia with normal visus. One year PTC, the mother noticed multiple painful tumors on scalp and face. The tumors were slow growing as brown-black, bleed easily, erosion on the surface and sometimes covered with pus. One month PTC, his mother, noticed that the tumor at the right retroauricular region was increased in size with pain. Daily outdoor patient's activity were between 09.00–11.00 AM and 02.00–03.00 PM since 4 years-old without photoprotection and no severe sunburn.

The hematological examination was within normal limit. Ophthalmology examination revealed limbal stem cell deficiency and xerosis cornea with dry eyes.

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F. Satolli et al. (eds.), *Clinical Cases in Pediatric Skin Cancers*, Clinical Cases in Dermatology, https://doi.org/10.1007/978-3-030-93666-2_32

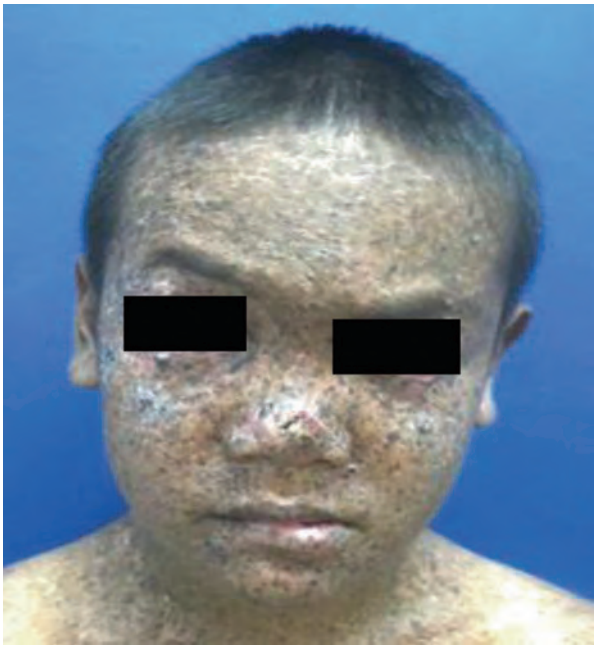

Fig. 32.1 Hypopigmented and hyperpigmented macules on exposed areas mainly on the face, neck, tumor on the tip of the nose 2 × 1 × 0.5 cm and on the scalp 0.3 × 0.3 × 0.2 cm

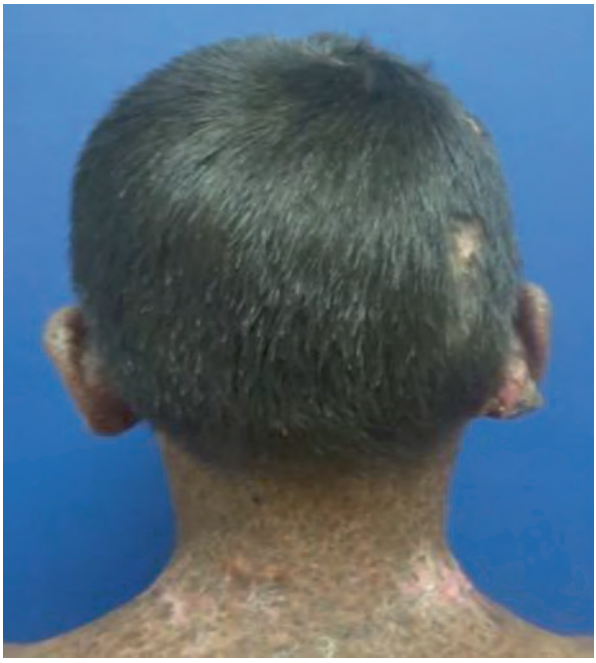

Fig. 32.2 Hypopigmented and hyperpigmented macules and scar on upper chest, and back

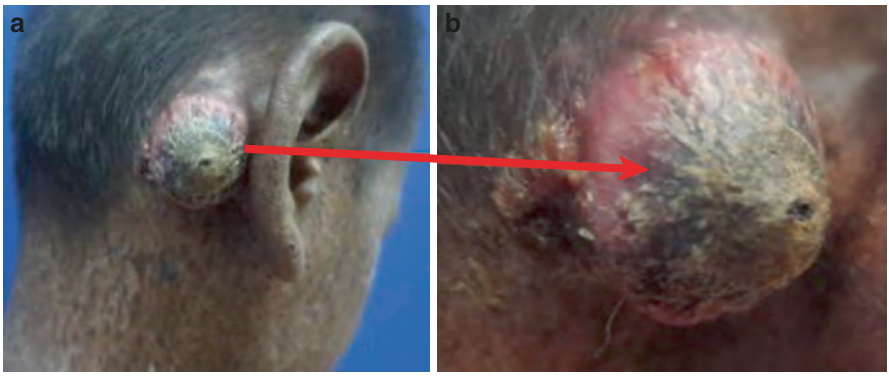

Fig. 32.3 (**a**, **b**) Tumor at the right retro auricular region, 4 × 4 × 3 cm

Surgery wide excision with frozen section and reconstruction tumor on the right retro auricular were positive for squamous cell carcinoma. Biopsy and dermoscopy from the tumor on the face and the scalp were positive for basal cell carcinoma.

Diagnosis

Xeroderma pigmentosum with squamous cell carcinoma on right retro auricular and basal cell carcinoma on scalp and face.

Discussion

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by cutaneous photosensitivity a decreased ability to repair DNA damage by UV radiation and the early development of cutaneous and ocular malignancies [1–3]. Abnormalities will arise if the patient has two identical alleles at the locus genes. In children whose parents are carriers-heterozygous, the opportunity is 25% become sick, 50% as asymptomatic careers, and the other 25% are unaffected and not a carrier [4]. Men and women can be affected at the same frequency [5]. Consanguinity is the most common cause of disorders autosomal recessive. In this case, there was no history of a similar disease in the previous generation, consanguinity between the patient's parents, siblings, or the biological families of his grandparents. The patient is the third child in the family, the second child has the same complaint as the patient, but the first child does not have a similar disease. In 75% of cases, the initial symptoms can be found at 6 months to 3 years [1]. The combination of a genetic in the ability to repair DNA damage due to UV rays exposure from the environment will cause clinical manifestations in patients with XP [1–3]. Photosensitivity

to wavelengths of UV light, especially 290–340 nm [1, 6]. Continuity of sun exposure will cause dry skin (xerosis), changes in pigmentation such as freckle-like pigmented lesions accompanied by photophobia and chronic conjunctivitis. Ocular involvement occurs in 80% patients with XP arising early in childhood [1]. Patients with XP have a susceptibility 10,000 times to squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) compared to other populations in general, and 2000 times for melanoma susceptibility. The median age of onset nonmelanoma skin cancer reported in patients with XP is 8 years [2] or before 10 years old [6], although it can also first arise at the age of 3 or 4 years [7].

Recently, there are eight subtypes of XP, namely XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, and G, due to genetic mutations in the nucleotide excision repair (NER) pathway. Sunburn after minimal UV light exposure occurs in 50–64% of cases [1]. Severe sunburn after mild exposure to UV light occurs in XP-A, XP- B, XP-D, XP-F, XP-G. While, XP-C, XP-E, and XP-V, do not easily experience sunburn. Skin disorders of XP are usually pigmentation changes, such as freckle-like hyperpigmented macules, lentiginous, hypopigmentation spots and hyperpigmentation (mottled), keratosis, ulceration, telangiectasia, and also atrophy [1, 8].

This patient may be included as type XP-C because of a skin disorder regarding the whole body, no severe sunburn reaction after exposure sunlight, no neurological abnormalities were found. But, in this case, SCC was obtained, as well as BCC are found in areas that are unprotected to UV rays, such as the head, neck [9].

The treatment in XP patients includes establishing an early diagnosis, lifelong protection against UV rays, as well as routine skin examination for diagnosis and treatment of malignancies in the skin [1, 8]. DNA damage in XP is cumulative and irreversible, so there is no curative therapy in this disease [10]. Early diagnosis and protection of the sun can prevent the occurrence of malignancies in the skin, and extend life expectancy [7, 10]. The process of UV protection can be thought of as wrapping the XP patients in layers of protection: an outer layer of environmental UV management (limiting activities that are exposed to sunlight, using LED lights or protecting incandescent lamps fluorescent, halogen and mercury-vapor lights with protectors [7, 11], using UV-ray filter films on windows, and using UV-meters) [11], a middle layer of mechanical barriers (protective clothing such as wearing dark colored shirts and trousers, covered layered clothing, glasses, hats, hoods with plastic protectors, gloves, and socks and UV-absorbing eye glasses) [7, 11], and an innermost layer of protection next to the skin (sunscreen/blocking lotions). The recommendation types of sunscreens are chemical and physical sunscreen with SPF more than 30 and applied every 2–3 h [11].

Ocular care for patients with XP should be protected by wearing UV absorbing glasses with side shields, giving artificial tears for dry eyes, methylcellulose eye drops can be used to keep the cornea moist, while surgical action can be done for cases of neoplasms of the eye [2].

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