

## Skin diseases of the great folds.

This chapter faces the skin diseases affecting the axillary, inguinal and neck folds, that is the joint folds between the trunk, limbs and head. The neck is a true fold especially in the first months of life, when the disorders affecting the axillary and inguinal folds often involve even the neck. However, even later some skin diseases, such as acanthosis nigricans and pseudoxanthoma elasticum, affects both the axillary folds and the neck.

These folds share some physiological characteristics such as the increased mobility, which explains the increased tendency to ulcerate of hemangioma in these sites, the increased temperature and, finally, the increased humidity leading to dilution of the defensive factors of the skin and increased pH.

These physiological characteristics are magnified in the first years in the developed countries by the use of the disposable diaper, aimed at containing urine and feces. The external layer of the disposable diaper indeed increases by itself temperature and humidity in the involved area. The vasodilation caused by the increased temperature makes the diaper area a localization factor for many skin disorders, from psoriasis to Langerhans cell histiocytosis.

The increased dilution of the defensive factors level with the folds localizes more frequently in these regions bacterial and mycotic infections.

The increased sweating, mainly in the axillary region, and the consequent use of cosmetic products, is responsible for irritant and allergic contact dermatitis, starting from the peripuberal age. Finally the presence of apocrine glands in the axillary and perineal regions is responsible in these sites for some disorders such as apocrine bromhidrosis and chromhidrosis and for Fox-Fordyce disease or apocrine miliaria. The apocrine sweat in the axillary region, starting from

the peripuberal age, can be responsible for bad smell (apocrine bromhidrosis), to which bacterial proliferation contributes. The bad smell seems indeed due to the epsilon-3-methyl-2-exanoic acid (5). Apocrine chromhidrosis or sweating of various color mainly occurs in hyperpigmented populations. It is due to lipofuscin pigments of the sweat. This entity should be differentiated from pseudochromhidrosis, that is on the other hand due to metabolic products of bacteria.

The neck, the axillary and inguinal regions are characterized by the presence of superficial lymph nodes. This is why these sites should be searched for when suspecting a disease able to induce regional lymphadenopathy. On the other hand, in cat-scratch disease the great inguinal or axillary enlargement of lymph nodes should induce to search for the primary peripheral skin focus.

### Inherited disorders

Pseudoxanthoma elasticum, Darier's disease and Hailey-Hailey disease are here treated.

*Pseudoxanthoma elasticum* (PXE) is a disorder inherited by an autosomal dominant or recessive trait, due to a mutation of gene ABCC6, belonging to the transmembrane transporter family binding ATP -ATP-Binding-Cassette- (9).

Its name derives from its yellow discoloration reminiscent of xanthomatous disorders. This yellow discoloration and the lack of elasticity with formation of folds reminiscent of aged skin (Fig. 1396) is due to the degeneration of the elastic fibers, that are fragmented with specific staining (Fig. 1398) and calcified. The degenerative process of the elastic fibers, besides the charac-



Fig. 1395: Pseudoxanthoma elasticum: small yellowish papules along the creases of the skin outline in a 10-year-old boy.



Fig. 1396

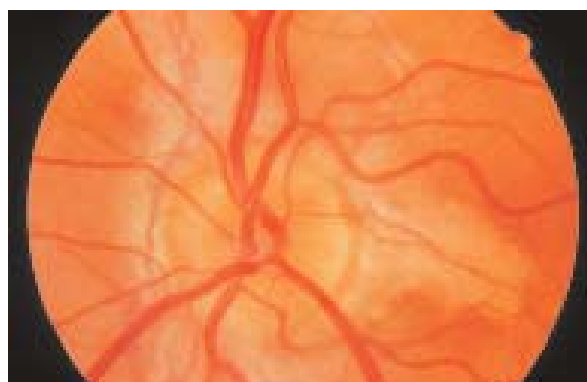


Fig. 1397

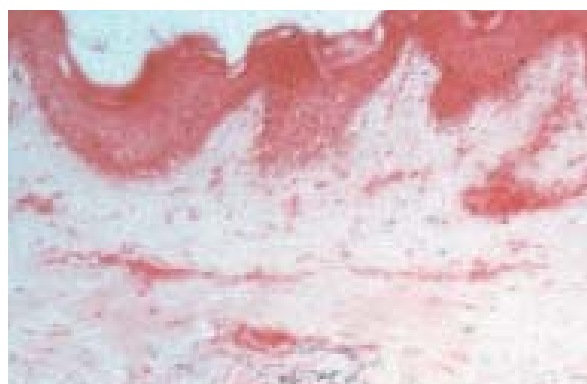


Fig. 1398

Fig. 1396, 1397, 1398: Pseudoxanthoma elasticum with aged skin due to alteration of the elastic fibers (Fig. 1398) in a 20-year-old woman with folliculitis (Fig. 1396). Angioid streaks of the retina (Fig. 1397, courtesy of Prof. Mario Bellizzi).

teristic cutaneous features, is also responsible for alterations of membranes and vessels rich in elastic fibers level with eyes, heart and in other internal organs, such as the stomach. As in all the diseases, the involvement of the other organs is variable. The severe involvement of the skin is not indeed associated with as severe involvement of other organs.

Angioid streaks are the most characteristic sign of pseudoxanthoma elasticum in the eyes (Fig. 1397). These streaks represent fracture lines of the Bruch membrane of the retina, which is rich in elastic fibers, with consequent visualization of the underlying chorioid. The angioid streaks, which are also seen in 10% of patients affected by beta-thalassemia (1), are red-colored in subjects with light complexion - from where the adjective "angioid"- and grey-brown in dark-skinned subjects. The angioid streaks surround the optic disk or start from it in a radial distribution (Fig. 1397).

The calcification of the elastic of the vessels leads to the early appearance of findings reminiscent of arteriosclerosis, affecting both the heart -angina, infarct- and the peripheral vessels, causing claudicatio intermittens.

Among the symptoms and signs affecting the other organs there are gastric hemorrhages, that occur in 10% of patients, sometimes during pregnancy (7).

The cutaneous lesions start on the sides and nape of the neck. After the neck the most frequent affected site are armpits. However, whatever fold can be affected. Initially, even in the first decade, yellowish macules appear in the creases of the cutaneous outline. Later on the macules turn into flat-topped papules (Fig. 1395). With years comedo, folliculitis and anelastitic, excessive for age folds appear on the neck (Fig. 1396). Cases of perforating PXE were reported. Yellowish micropapules can appear also on the visible mucosae.



Fig. 1399

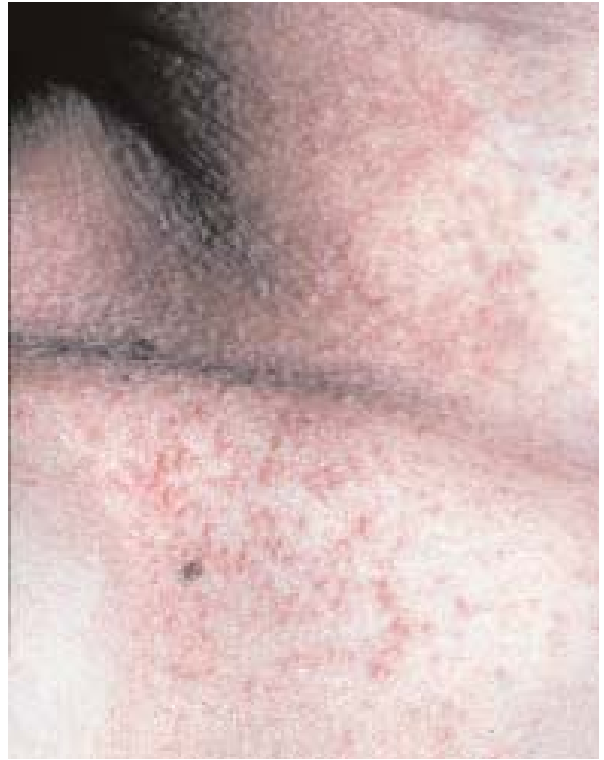


Fig. 1400



Fig. 1401



Fig. 1402



Fig. 1403

Fig. 1399, 1400, 1401, 1402, 1403: Darier's disease: initial papules in a 7-year-old boy. Mature lesions on the side of the neck (Fig. 1400), thorax (Fig. 1401), forehead (Fig. 1402) and armpits (Fig. 1403).

Once diagnosed, patients should avoid traumas of the eyes, sporting physical activity, foods rich in cholesterol and smoking. Moreover, the arterial pressure should be controlled.

*Darier disease* is an inherited disorder transmitted by an autosomal dominant trait. It is due to a mutation of the gene *ATP2A2* (10), which has been mapped on chromosome 12q23-24.1 (2). This gene regulates the pump of calcium and thus the processes of cell proliferation, differentiation and adhesion.

Darier disease is clinically characterized by keratotic papules not related with the hair follicles -although in the past included in the chapter of follicular keratosis- and histologically by suprabasal acantholysis, hyperkeratosis and dyskeratosis.

Acantholysis is the earliest phenomenon leading to the characteristic suprabasal clefting. The dyskeratotic process gets evident only in the prickly and granular layer with formation of the corps ronds, that is partially and prematurely keratinized cells with a light halo around a central, roundish, homogeneous nucleus. In the horny layer the corps ronds give raise to the grains, that is keratinocytes with pycnotic, elongated nuclei, surrounded by homogeneous dyskeratotic material.

The disease usually starts in the peripuberal period, often during summertime, being worsened by sun, hot climate and sweating.

It is clinically characterized by skin-colored or brownish, greasy, crusted papules in seborrheic sites, thus hairline, forehead (Fig. 1402), retroauricular, laterocervical, supraclavicular (Fig. 1400), axillary (Fig. 1403), inguinal and trunk (Fig. 1399, 1401) regions.

The acral involvement is almost constant, although not always much evident. In children the hands can be first affected. Red and/or white streaks longitudinally crossing the nail lamina are the most characteristic acral sign. Pits and keratotic papules affect the palmar and plantar regions.

Some infections such as primary Herpes Simplex virus infection on preexisting dermatitis, also known as Kaposi-Juliusberg eruption, can complicate and be superimposed to Darier disease.

As other inherited disorders, also Darier disease can exist in a segmentary variant, due to a post-zygotic mutation. The same mutation may partially affect the germinal cells and thus manifest itself in a generalized Darier disease in the offspring of the subject with a segmental variant.

Initial Darier disease should be differentiated from acne and seborrheic dermatitis. When the typical papules and confluent plaques lack, the summertime worsening and the acral lesions are useful in the differentiation from these trivial disorders.

The treatment of Darier disease consists of keratolytics, emollients, antimicrobials aimed at reducing the bad smell caused by sweating and finally of topical and systemic retinoids. The latter, especially acitretin, are useful in summertime worsening, combined with photoprotection measures. Women in fertile age can use isotretinoin, which is less effective but does not require two years of sterility.

The mechanisms of intercellular adhesion are also involved in *Hailey-Hailey disease* or benign chronic familial pemphigus. It is an inherited disorder transmitted by an autosomal dominant trait and due to a mutation of the gene *ATP2C1*. The latter, which also regulates the pump of calcium (4) has been mapped on chromosome 3q21-q24.

Hailey-Hailey disease is histologically characterized by acantholysis and suprabasal clefting without dyskeratosis and immune deposits. Thanks to these findings Hailey-Hailey disease can be easily differentiated from Darier's disease and from autoimmune bullous disorders.

Clinically, it is characterized by vesicular and blistering very painful lesions localized on the axillary ((Fig. 1404), inguinal, submammary (Fig. 1405) and neck folds.

The symptomatic treatment consists of topical corticosteroids and antibiotics. Dermabrasion is at least transitory effective, probably because the adnexal structures giving raise to the new-formed epidermis do not express the defect of cell adhesion (6).

Among the inherited disorders there is also *dystrophic recessive epidermolysis bullosa inversa*, that can prevalently affect the axillary



Fig. 1404



Fig. 1405

Fig. 1404, 1405: Hailey-Hailey disease with involvement of the axillary (Fig. 1404) and submammary (Fig. 1505) folds in a young woman.



Fig. 1406: Dystrophic recessive epidermol. bullosa inversa.

and inguinal (Fig. 1406) folds. The involvement of these folds is not usually evident at birth in this form of epidermolysis bullosa, manifesting itself in the second-third year.

### Nevi

Among the characteristic lesions of the neck, besides accessory tragi, about which we talked in the previous issue, there are *cysts of the thyroglossal duct* and the less frequent fistulas, which are due to incomplete obliteration of the thyroglossal duct. The cysts are clinically characterized by a soft nodule, moving upwards with protrusion of the tongue and swallowing. Fistulous tracts may be also present and manifest themselves in case of infection. A carcinomatous degeneration of these residua was reported (11). Due to this reason, a careful removal of these residua is indicated.

*Hemangioma* of the folds, especially in the inguinal region, can ulcerate.

*Hygroma* is localized on the neck (Fig. 1407) and axillary region. Hygroma is nowadays treated with streptococcal sclerosing extracts.



Fig. 1407

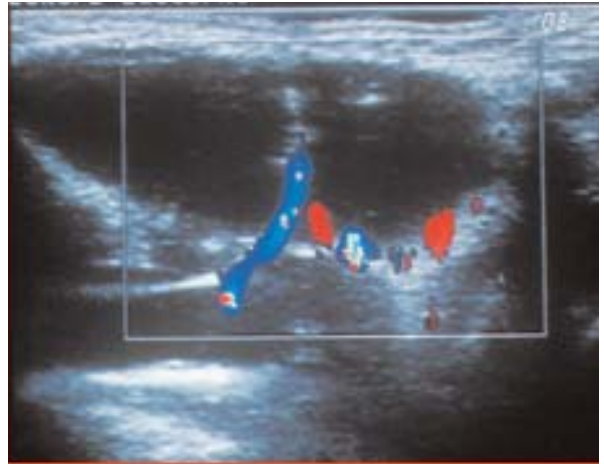


Fig. 1408

Fig. 1407, 1408: Newborn with cystic hygroma of the neck (Fig. 1407). Echocolor Doppler (Fig. 1408) shows two large cavities separated by a septum, with blood vessels remaining at their periphery.

### Infections

The dilution of the defensive factors, which is due to the humidity, is responsible for increased number of bacteria and fungi level with the folds. However, in the immunocompetent child rarely bacterial infections occur in these sites.

In the newborn and in the unweaned baby *bullous pyoderma* (Fig. 1409, 1410) starts from

the perianal region (Fig. 1410) or anyway from the diaper area. This infection is caused by *Staphylococcus aureus* group II phage 71.

The latter produces toxins able to cause intraepidermal clefting and more or less extensive vasodilation. Bullous pyoderma, staphylococcal scarlatina, 4 S syndrome and toxic shock syndrome are parts of the spectrum of the same disorder.



Fig. 1409



Fig. 1410

Fig. 1409, 1410: Neonatal bullous pyoderma starting from the folds of the neck in the newborn as in Fig. 1409 and from the inguinal folds in the newborn as in Fig. 1410.



Fig. 1411



Fig. 1412

Fig. 1411, 1412: Axillary (Fig. 1411) and inguinal (Fig. 1412) cat-scratch disease with minimal primary cutaneous lesions (arrows).



Fig. 1413: Scrofuloderma.

Axillary hydradenitis and Fox-Fordyce disease usually affect the adult.

Among the infections affecting the folds, cat-scratch disease and scrofuloderma should be mentioned.

*Cat-scratch disease*, which is due to *Bartonella henselae*, a Gram-negative microorganism, is a usually benign disease, mainly affecting the first two decades of age. It is clinically characterized by a minor cutaneous lesion. The latter is followed by a much more significant satellite adenopathy (Fig. 1411, 1412) that can persist several months. General signs may be present. The use of antibiotics is debatable, especially in the mild cases of immunocompetent child.

*Scrofuloderma*, which is much rarer, is a post-primary tuberculosis. The skin is secondarily interested by an underlying tubercular focus,

usually a lymph node (Fig. 1413). The most frequently affected site is the latero-cervical region, usually after a specific infection of a lymph node.

Among mycoses involving the greater folds, *tinea inguinalis*, which is usually due to *Epidermophyton floccosum*, affects also children, especially when obese (Fig. 1414). The treatment consists of topical antimycotics, that should be continued till the disappearance of any sign of inflammation, that is about one month.

### Parasitic diseases

Among the most frequently affected sites of *scabies* there is the axillary region, both in children and adults. Characteristically in children this site presents gross nodules, till 1.5 cm in size, that make the diagnosis much easier (Fig. 1415, 1416). Once scabies has been treated, nodules persist for several months. The worst thing is that the nodules undergo periodical episodes of reddening and swelling, with intense itching, which raise the suspicion of a relapse of scabies. The differential diagnosis from the latter is based on the number of lesions. When the



Fig. 1414: Tinea inguinalis in a 9-year-old boy.

nodules do not increase in number, although inflamed and itching, we are not dealing with a relapse of scabies. The latter should be suspected when many new lesions occur. When we are dealing only with a flare up of preexistent nodules, the treatment against mites is not effective and may be responsible, when repeated many times, for an irritant dermatitis and thus for



Fig. 1415



Fig. 1416

Fig. 1415, 1416: Nodular scabies of the axillary region.

further worsening of itching. On the other hand, a topical, anti-inflammatory corticosteroid treatment is indicated. The latter improves the inflammation but is not able to prevent further episodes of inflammatory swelling.

The armpit is also the most frequently affected site of *pediculosis corporis*, which is due to *Pediculus humanus*. The latter usually resides on the clothes and moves to the skin only for its blood meals. *Pediculosis corporis* therefore occurs only in those people who are not able to change and wash periodically their clothes. It is responsible for itching and consequent scratching with secondary infections and hyperpigmentation, giving raise to the condition known as “vagabond’s skin”. The diagnosis is made by identifying the parasites on the clothes.

### Dermatitis

*Atopic dermatitis* affects the axillary and inguinal regions much less frequently than other

constitutional dermatitis. On the other hand, the neck is frequently affected in atopic dermatitis, both in the first months of age, when the neck is indeed a fold, and even later in the child and adolescent.

In the first months the neck can be the only or the first site affected. More often other sites, mainly the face are affected. The atopic lesions at this age are often exudative (Fig. 1417) and stinking. These exudative lesions rarely go on beyond the first year.

In children and adults the neck, when involved in atopic dermatitis, more often presents infiltrative lesions. In hyperIgE syndrome and in the severe forms of atopic dermatitis the neck can be uniformly infiltrated, hyperpigmented, apparently dirty. In hyperIgE syndrome the axillary (Fig. 1418) and inguinal regions are often affected.

Various forms of *psoriasis* in children affect the diaper area. In children this area is often the first site affected in psoriasis. The latter can be characterized by erythematous, confluent, non



Fig. 1417



Fig. 1418

Fig. 1417, 1418: Exudative atopic dermatitis of the neck (Fig. 1417); axillary lesions in hyperIgE syndrome (Fig. 1418).



Fig. 1419



Fig. 1420

Fig. 1419, 1420: Fixed patches of psoriasis (Fig. 1419) and eruptive napkin psoriasis (Fig. 1420) in the diaper area.



Fig. 1421



Fig. 1422

Fig. 1421, 1422: Inverted psoriasis with lesions of the axillary and inguinal folds.

specific lesions, reminiscent of diaper rash, that are later on followed by an eruptive psoriasis in other sites -napkin psoriasis- (Fig. 1420). In other cases psoriasis manifests itself with round, fixed, well defined, scarcely hyperkeratotic patches (Fig. 1419). A history of more or less severe and persistent diaper rash is also reported in children, whose psoriasis starts in the first 12 years.

Inverted psoriasis affects the axillary and inguinal regions (Fig. 1421, 1422). This variant is frequent in children and often associated to involvement of the medial commissura of the eyelids. The above mentioned sites can be the only affected areas or more often fixed patches of psoriasis are present on the scalp or in other sites. Inverted psoriasis may be a transition form towards other forms of psoriasis.

Also *seborrheic dermatitis* can affect the axillary and inguinal regions. However the nosological problem of seborrheic dermatitis in children is complex. We are not sure that a disorder comparable to seborrheic dermatitis of adults does exist in children. At this age we never see the erythematous circinate medi thoracic lesions, that are characteristic in adults, nor we see the characteristic chronic-recurrent clinical course of adults.

Because of the lack of sebum secretion and of whatever laboratory marker confirming the diagnosis of seborrheic dermatitis, under the heading of seborrheic dermatitis merge, according to different Authors, many very different skin disorders ranging in severity from the condition known as "cradle cup" to Leiner's erythroderma. When in the modern era Leiner's erythroderma resulted an expression of various primary immune deficiencies, this form left seborrheic dermatitis.

Many cases of dermatitis of the scalp indeed belong to atopic dermatitis and the discussion is open on the existence of a minimal dermatitis of the scalp in the first months that is not atopic dermatitis and can be classified as seborrheic dermatitis.

There is indeed an inflammatory disorder of the axillary and inguinal region, sometimes affecting even the neck in the first months, that does not turn into atopic dermatitis or psoriasis.

However, a disorder like that is always less frequent today.

Also cases of acute erythroderma starting from the diaper area and self-regressing within two months become always less frequent today. In the past these cases often turned into classical atopic dermatitis or psoriasis.

With regard to *diaper rash*, it is useful to distinguish the chronic-recurrent forms, which do not regress with any treatment and only regress when withdrawing diapers, from the acute forms of short duration.

The chronic-recurrent forms are probably expression of increased susceptibility to psoriasis, because, when following these patients, the number of cases developing a classic psoriasis is directly related to the length of the period of observation.

On the other hand, the acute forms of short duration have always a precise causal factor, usually an inflammatory or infectious episode, a treatment which modifies urine and/or feces, a delayed change of diaper or an irritant contact in the diaper area. These acute forms regress when the causal factor regresses.

In diaper rash the role played by *Candida albicans* has been overestimated, whereas that one of *Staphylococcus* and other bacteria has been underestimated. When performing systematically a bacteriological examination in the most severe forms, we find *Staphylococcus aureus* with the same frequency or even more frequently as compared with *Candida albicans*. However, as in atopic dermatitis and in whatever condition altering the local defense of the skin, the presence of *Candida* and *Staphylococcus* does not play a primary and pathogenic role, but it is only secondary to the altered conditions of the skin.

This is why no drug has been so far approved by American FDA specifically for the treatment of diaper rash. The most adequate treatment of diaper rash should be aimed at decreasing temperature and humidity in the diaper area, at decreasing the inflammation and finally, in the most severe cases, at decreasing the number of bacteria and fungi. These goals can be achieved with frequent change of diaper, with the use of a traditional cotton diaper without any external



Fig. 1423



Fig. 1424

Fig. 1423, 1424, 1425, 1426: Diaper rash of the convex area (Fig. 1423, 1424), that in females (Fig. 1424) is characterized by an inverted W-shape. Diaper rash involving the depth of the folds (Fig. 1425) and micropustular (Fig. 1426). In all 4 cases *Candida* and *Staphylococcus* were isolated. None of these features is characteristic of superimposed *Candida*.



Fig. 1425



Fig. 1426



Fig. 1427: Acanthosis nigricans.



Fig. 1428: Linear IgA dermatitis.

plastic layer when the child is awake, with anti-inflammatory lotions containing protease inhibitors and, in the most severe cases with probable superimposed infection, with a soap containing chlorexidine and lotions containing fusidate sodium and well tolerated antimicrobials.

*Acanthosis nigricans* is the term proposed by Unna (8) to indicate a disorder mainly affecting the neck and the axillary and inguinal regions, characterized clinically by thickened, dark brown skin with greater evidence of the groove and relief pattern (Fig. 1427) and histologically by hyperkeratosis and hyperplasia of the dermal papillae in absence of true acanthosis, melanic hyperpigmentation and inflammatory infiltrate. The hyperplasia of the skin is probably due to the presence of excessive growing factors.

*Acanthosis nigricans* is a syndrome with countless clinical forms. The paraneoplastic form was first reported. However, the most frequent form is associated to obesity. In the latter the factor stimulating the proliferation of the skin is insulin in obese subjects with insulin-resistance (3).

### Autoimmune disorders

Among the bullous autoimmune disorders of childhood *IgA linear dermatitis* more frequently affects the inguinal region (Fig. 1428), whereas dermatitis herpetiformis can affect the axillary region. After dermatitis herpetiformis linear IgA dermatitis is the more frequent autoimmune bullous disorder of children. Its name is due to the immunofluorescence findings, showing linear deposits of IgA level with the dermal epidermal junction.

*Systemic vitiligo* may affect the diaper area in the first years and later on the genital and inguinal region, less frequently the neck.

*Crohn's disease* in children may start with granulomatous lesions of the perigenital (Fig. 1429) and perianal area. The histological examination can be a clue to the diagnosis, showing a giant cell granuloma (Fig. 1430, 1431).

Besides this specific manifestation, other less specific lesions may be present, such as fissurae, fistulae, abscesses, perianal skin tags, necrotic

zing vasculitis, necrotizing fasciitis and amyloidosis. As ulcerous colitis, Crohn's disease can be complicated by pyoderma gangrenosum, erythema nodosum and aphthae.

### Tumors

Among the tumors of children affecting the folds, especially the inguinal folds, *Langerhans*

*cell histiocytosis* should be remembered, both the self-regressing, exclusively cutaneous form (Fig. 1432) and the multisystemic one (Fig. 1433).

Both forms can start at birth or in the first months with trivial lesions reminiscent of diaper rash. The presence of purpuric, lichen-like papules of uniform size -about 1 millimeter- and of deep ulcers in the axillary (Fig. 1432) and inguinal (Fig. 1433) folds should raise the suspicion



Fig. 1429



Fig. 1430

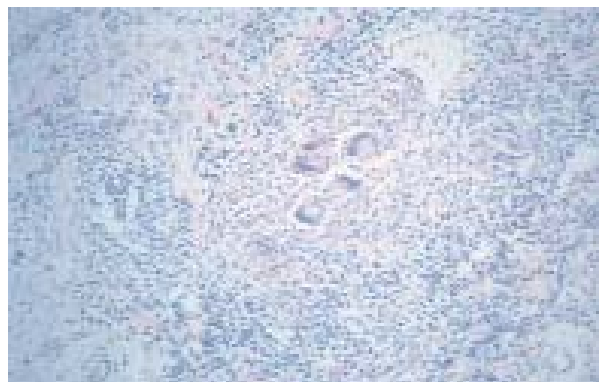


Fig. 1431

Fig. 1429, 1430, 1431: Crohn's disease in a 5-year-old boy started from the inguinal-anal folds and penis (Fig. 1429). The histological examination showed a giant cell, granulomatous infiltrate (Fig. 1430, 1431).



Fig. 1432



Fig. 1433

Fig. 1432, 1433: Self-resolving (Fig. 1432) and fatal (Fig. 1433) Langerhans cell histiocytosis.

of Langerhans cell histiocytosis. As the prognosis of this disorder is extremely variable, ranging from the spontaneous regression in a few months to the exitus in a few weeks, also chil-

dren with exclusively cutaneous lesions of histiocytosis should be monitored with a pediatric oncohematologist till the complete and stable regression of the cutaneous lesions.

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