Hashimoto-Pritzker Langerhans cell histiocytosis in a neonate

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Title figure:
Paul Langerhans in 1878 (Source: www.wikipedia.org)

We present a male infant born at 40 weeks of gestation by elective Caesarean section due to active hepatitis C infection of the mother with a viral load of 8'000'000 IE/ml. This was the first pregnancy of the 20-year-old mother. Apart from active hepatitis C infection and atopic dermatitis as a child, the mother was healthy, and the pregnancy had been uneventful.

The mother's hepatitis C had been diagnosed nine years earlier and thus far had been untreated as there was no higher degree liver fibrosis and treatment is contraindicated during pregnancy (1). Serologic screening was also positive for hepatitis A, negative for HIV, syphilis and cytomegalovirus. The family history was remarkable for chronic hepatitis C infection from intravenous drug abuse in the maternal grandmother.

The boy adapted well with an Apgar score of 9, 9 and 9 at 1, 5 and 10 minutes respectively. Birth weight, length and head circumference were within the 3rd and 50th centile. Due to active maternal hepatitis C infection, the baby was immediately bathed after birth, and the mother decided not to breastfeed her child. In the delivery room, multiple round red skin changes were noted (Fig. 1). They were a few millimeters in size, erosive, plane, moist and did not blanch on palpation. The skin lesions were distributed all over the body but sparing the hairy scalp, palms and soles. No abnormalities were detected in the genital area, the oral mucosa and nails.

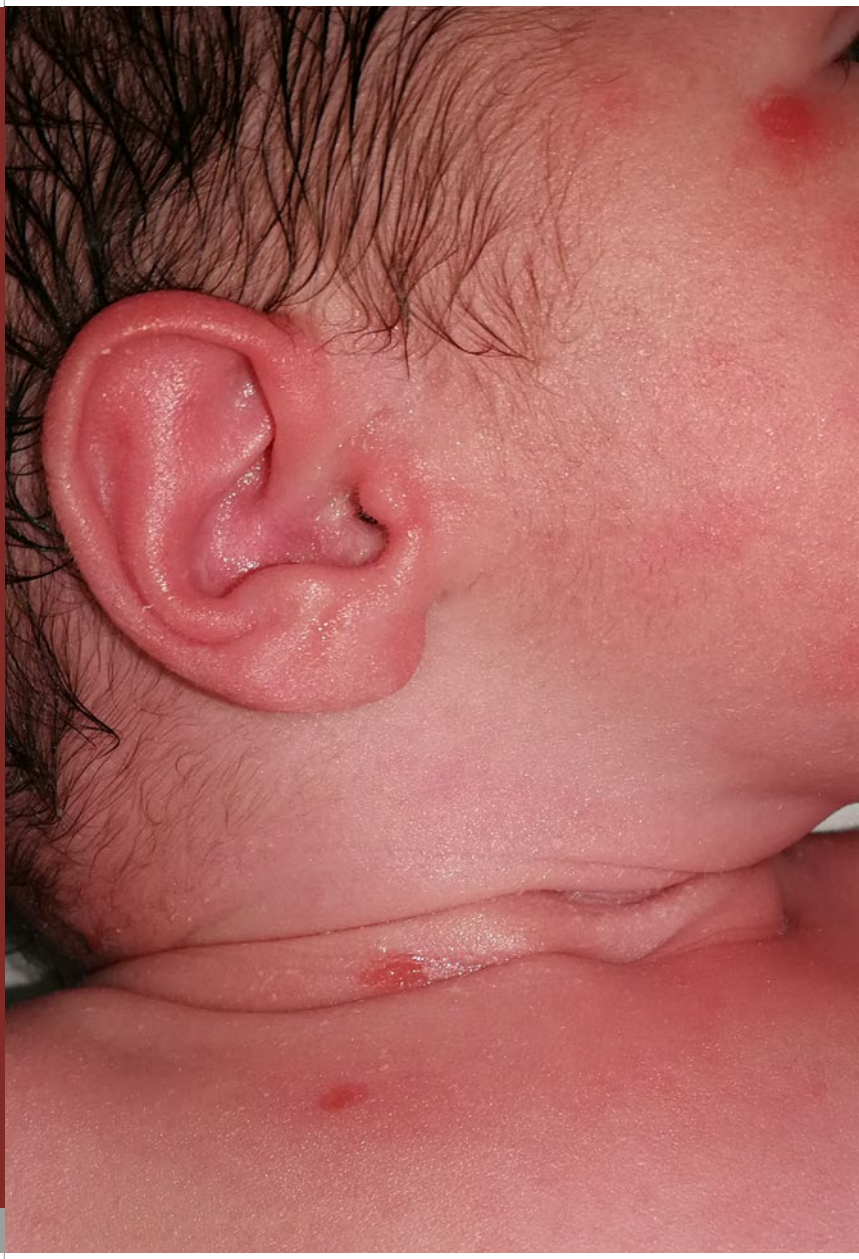

Fig. 1

In the delivery room, multiple red round skin lesions were noted.

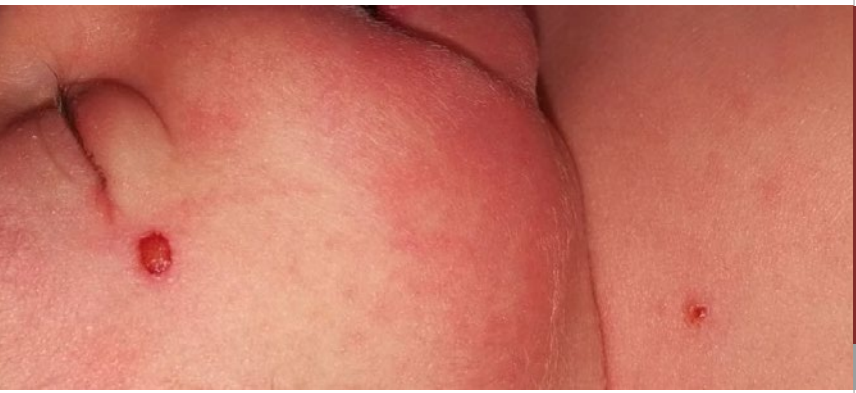

Fig. 2

On day 2 of life, most of the skin lesions had become encrusted.

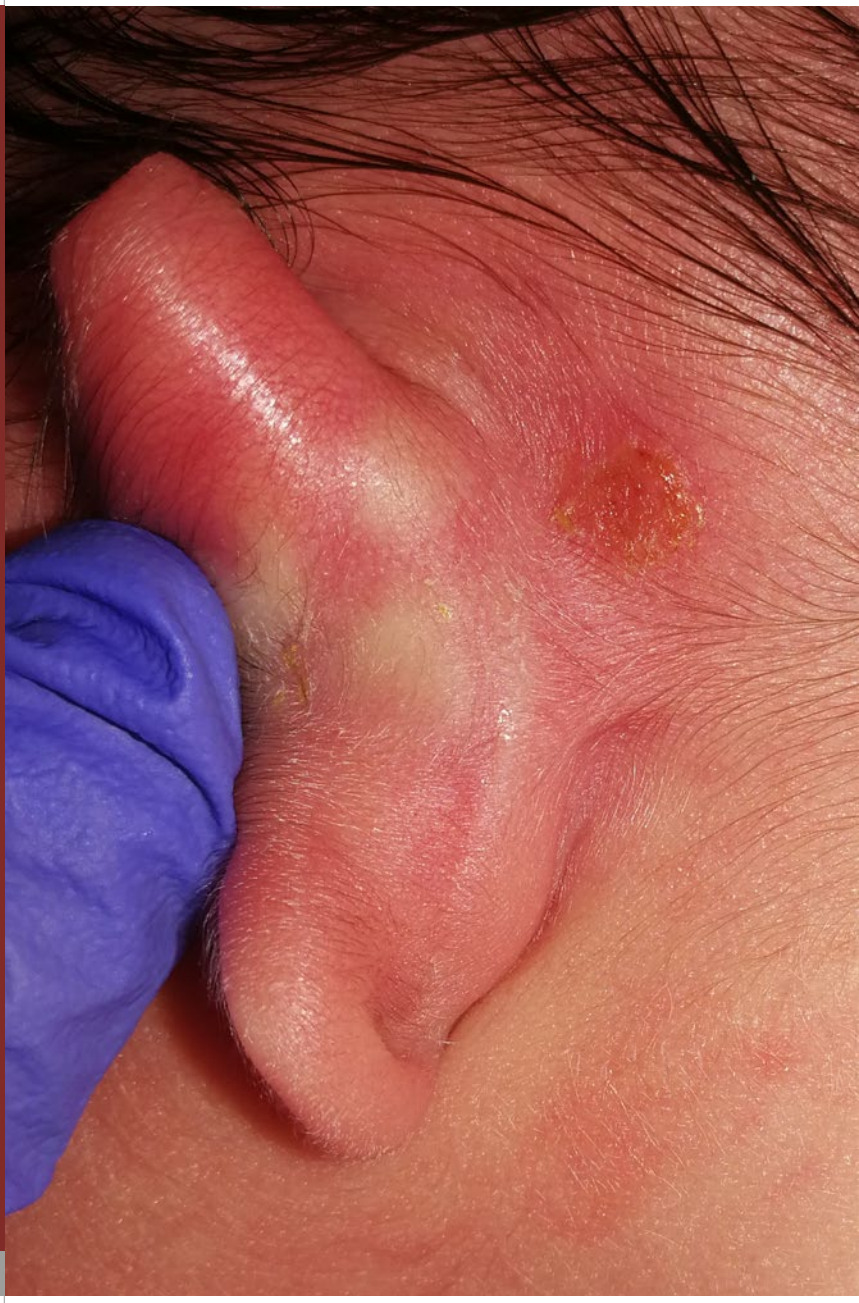

Fig. 3

Encrusted skin lesion behind the left ear.

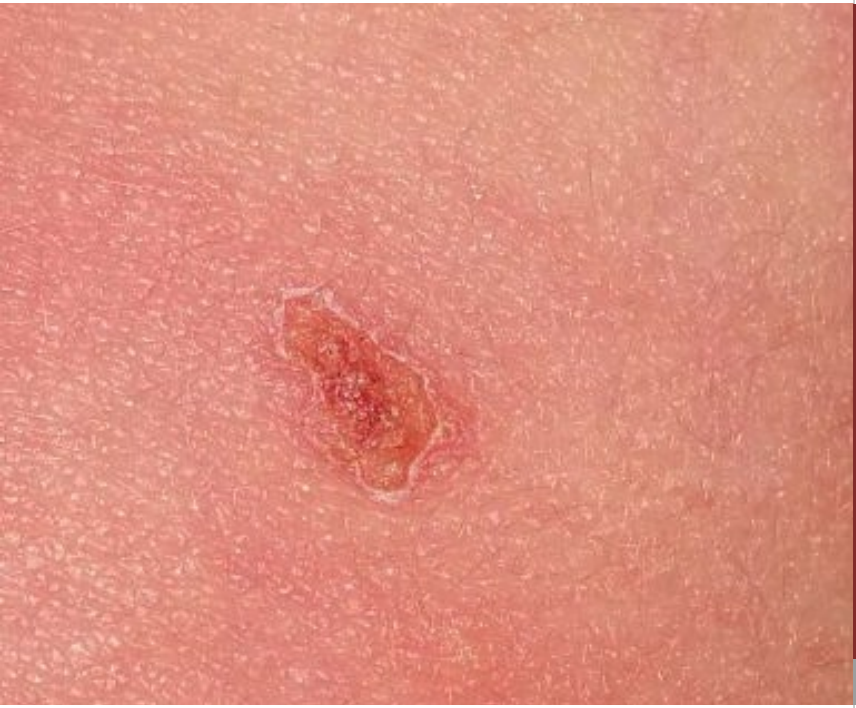

Fig. 4

Close-up view of encrusted skin lesion.

On the second day of life, the baby's skin was dry and treated with a cream containing glycerin and petroleum jelly. Most of the skin lesions had become encrusted (Fig. 2 – 4). Nikolsky's sign was negative.

The skin changes were not felt to be related to hepatitis C infection. The differential diagnosis focused on congenital epidermolytic ichthyosis and Langerhans cell histiocytosis. Culture of a skin swab grew Staphylococcus epidermidis as part of the normal human skin flora. Virology swabs were negative for herpes simplex virus 1 and 2. Complete blood count, kidney and liver function tests were within normal limits (except for a slightly elevated LDH with a value of 1043 U/l and a reference range for newborns < 780 U/l) (2, 3).

Ultrasound examination of the abdominal organs showed no abnormalities. A skin biopsy of the skin lesion shown on Fig. 4 was obtained. Histological examination showed a crusted epidermis and a bandlike dense infiltrate of epithelioid round cells in the upper dermis with pronounced epidermotropism. Admixed to the infiltrate, there were some eosinophils. On immunohistochemistry, the epithelioid cells expressed S100, CD1a and langerin, which are typical markers for Langerhans cell histiocytosis (4). Therefore, histological and immunohistological analysis confirmed the diagnosis of Langerhans cell histiocytosis (Fig. 5, 6). Furthermore, the subgroup Hashimoto-Pritzker, also called congenital self-healing

reticulohistiocytosis, was suspected because the diagnosis was made directly after birth and there was no evidence for further organ involvement.

After discharge from the postnatal ward, the baby had regular follow-up visits in the Oncology Department of the Children's Hospital. The oncologist decided not to obtain additional imaging studies since regular abdominal ultrasound examinations and a chest x-ray did not suggest further organ involvement and the baby did well.

Two months after birth, all skin lesions except a small lesion behind the left ear had disappeared. An observation-only strategy was chosen within the international trial LCH-IV (EudraCT Nr. 2011-001699-20). For the next five years, follow-up visits every 6 months are planned, and the local pediatrician is sensitized to early sings of relapse or further organ involvement of Langerhans cell histiocytosis.

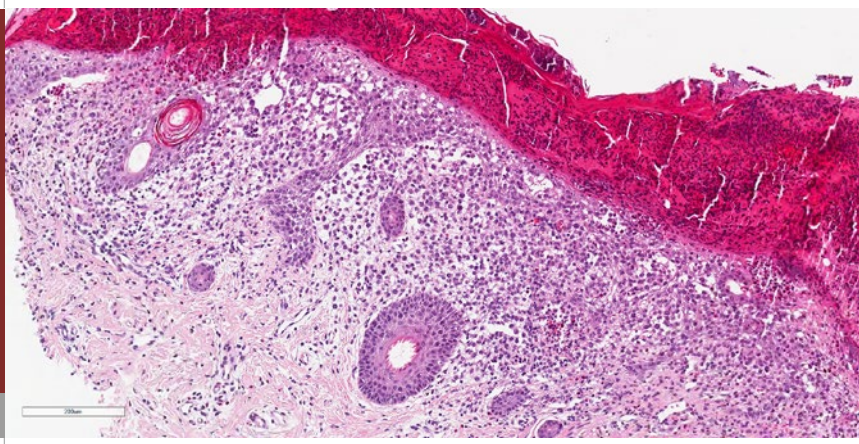

Fig. 5

Biopsy of the skin lesion shown in Fig. 4: crusted epidermis, bandlike dense infiltrate of epitheloid round cells in the upper dermis with some eosinophils admixed to the infiltrate (H&E staining).

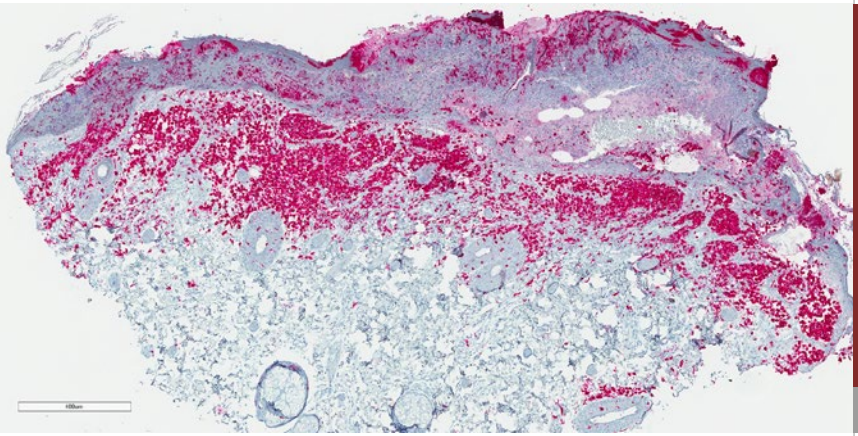

Fig. 6

Immune histochemistry: epitheloid cells expressing langerin.

DISCUSSION

Newborns can show a variety of skin changes. Most of them are benign and transient, and malignancies are very rare (5). Langerhans cell histiocytosis is a rare disease with an estimated annual incidence of 1 to 2 cases per million adults and 2 to 9 cases per million children (6 – 8). It is a very heterogeneous condition, which can first present between birth and adulthood, can affect one or several organ systems and can manifest in one or multiple episodes (6). Its etiology is unknown, and the disease is characterized by a clonal expansion of myeloid dendritic Langerhans cells, which differ from the skin Langerhans cells (4). A skin biopsy is needed for diagnosis (9).

Due to the heterogeneity of Langerhans cell histiocytosis, making a diagnosis it is not trivial (6, 9). In the presented case, congenital epidermolytic ichthyosis was a differential diagnosis. Congenital epidermolytic ichthyosis usually presents at birth with fragile skin, blistering and erythroderma (10). Over time, hyperkeratosis is more prominent with yellow-brownish hyperkeratotic plaques (10). Many other differential diagnoses to Langerhans cell histiocytosis are described in the literature. The main differential diagnoses occurring in neonates are listed in Tables 1 and 2 in more detail. In addition, other very rare conditions in neonates are mentioned in the literature, namely incontinentia pigmenti, neonatal disseminated hemangiomatosis, congenital leukemia, dermoid cyst, pilomatricoma, congenital Spitz nevus, infantile myofibromatosis,

congenital fibrosarcoma, erythropoiesis dermica, congenital vasculitis and cutaneous lymphoma (11 – 13).

Langerhans cell histiocytosis most often presents in children below the age of 5 years (7). Bones and the skin are the most frequently involved organs (15, 16). Half of the cases, often very young children, present with multi-organ disease (9, 17, 18). The disease is heterogeneous not only regarding the type of organs involved («low-risk» organs including skin, bones, lymph nodes and the pituitary vs. «high-risk» organs including the hematopoietic system, liver, spleen and lungs) but also regarding the number of affected organ systems («single-system» vs. «multi-system» disease) (8, 9). Management strongly varies according to whether high-risk organs are affected and whether multi-system disease is present (6, 8, 9). It reaches from observation only or curettage of selected single bone lesions (with or without intralesional steroid injection) to systemic chemotherapy with cytostatic drugs (i.e. with various combinations of drugs such as vinblastine, mercaptopurine, cytarabine, methotrexate, cladribine, and indomethacin) (6, 8, 19).

Patients with skin-limited Langerhans cell histiocytosis have an excellent prognosis with a disease-free survival around 90 % and a long-term survival around 100 %; in contrast, in patients with multi-organ involvement reactivation is common (more than 50 %), and long-term survival varies between 20 % and 90 % (6, 9, 20).

In neonates, there is a harmless and rare form of Langerhans cell histiocytosis called Hashimoto-Pritzker or congenital self-healing reticulohistiocytosis. It presents with isolated skin involvement which resolves without any treatment within a few months (12). Nevertheless, the patients require careful complete organ screening to exclude involvement of other organs since in about 40 % of affected neonates multi-organ disease can be detected (17, 21). Even in the absence of initial multiorgan involvement, close follow-up is required as progression to systemic disease is possible (17, 22). Accordingly, the harmless Hashimoto-Pritzker form can only be diagnosed retrospectively.

See also: COTM 06/2001:
A newborn with a papulonodular rash at birth.

Disease entity	Presentation	Course of disease	Severity	Diagnostics
Erythema toxicum neonatorum	1 to > 100 macules (1 – 3 cm) with a central vesicle (1 – 4 mm) or pustule, spares palms and soles	Transient rash, self-limiting, recovery within 3 – 7 days without any residual	Benign, physiological, 50 % of term newborns	**Wright stain:** numerous eosinophils
Pustular melanosis	Flaccid, superficial, fragile pustules (1 – 3 mm), no erythema, on whole non-hairy body including palms and soles	Pustules rupture and form brown crust, heals with brown pigmented macules which can persist for 3 months	Idiopathic, neonate appears well	**Wright stain:** predominance of neutrophils with occasional eosinophils
Infantile acropustulosis	Sterile vesiculopustules, mainly on palms and soles	Tiny, red papules evolve into vesicles and then pustules over 24 hours, excoriation results in erosions and then crusts, heals with post-inflammatory hyperpigmentation, each crop lasts for 7 – 14 days, recurrent at intervals of 2 – 4 weeks	Intensely itchy, gradually less severe until the disease disappears within 2 years of onset	**Smear:** predominance of eosinophils and later neutrophils **Histopathology:** circumscribed aggregations of subcorneal or intraepidermal neutrophils with scanty lymphohistiocytic infiltrates in the papillary dermis
Eosinophilic pustular folliculitis	Crops of pruritic annular or polycyclic plaques, composed of coalescing sterile papulopustules, on seborrheic areas of the scalp, face, trunk, and extremities	Evolving through crusted phase of 5 – 10 days, heals with hyperpigmented macules without scaring	Absence of systemic symptoms, recurrent every 2 – 8 weeks, resolves spontaneously between 4 and 36 months	**Wright stain:** abundant eosinophils **Histopathology:** perifollicular inflammatory infiltrates in dermis, composed mainly of eosinophils, neutrophils and mononuclear cells, hair follicles show spongiotic degeneration of the outer root sheath with necrotic center

Table 1. Differential diagnoses of Langerhans cell histiocytosis in neonates: *non-infectious* pustular dermatoses (12, 14).

Disease entity	Presentation	Course of disease	Severity	Diagnostics
Perinatal listeria monocytogenes	Grey-white maculopapules with vesicles or pustules		Usually associated with septicemia or meningitis	Routine culture of CSF can detect organism
Congenital candidiasis	Discrete pustular lesions with erythema, distributed over face, chest, trunk, palms and soles		Mostly self-limiting, can disseminate	Identification of organism in skin scraping and culture
Herpes simplex infection	Vesicles and pustules (2 – 4 mm) in clusters with erythema, possible shallow mucosal ulcerations with inflammation		Encephalitis and disseminated disease is possible and associated with high mortality	Viral culture can detect organism Tzanck smear: presence of multinucleated giant cells
Neonatal varicella	Clear fluid-filled vesicles	Later pustular and then scab, new crops appear for about 3 – 4 days, continuing up to 7 days	Severe disseminated varicella is possible	Tzanck smear, serology and immunofluorescence microscopy are diagnostic options

Table 2. Differential diagnoses of Langerhans cell histiocytosis in neonates: *infectious* pustular dermatoses (12, 14).

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