

Langerhans' Cell Histiocytosis

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CASE SUMMARY

History

A 4-month-old baby boy presented to clinic complained of 2-month history of recalcitrant rash. It started at the eyebrows, scalp, groin and legs. The lesions resolved initially with topical treatment but new lesions continued to develop and spread to arms, legs, torso, palms and soles. Private dermatologists diagnosed "eczema" and partial response was achieved with topical steroid and cefuroxime syrup. Many lesions healed with scarring but despite this initial response, new lesions never stopped developing. The rash was probably itchy, as the baby seemed irritated occasionally. There were no significant past medical or family illnesses. No family member was itchy.

Physical examination

There was a polymorphic eruption involving face (especially between the eyebrows), scalp, torso, groin, arms, legs, palms and soles (Figure 1). The eruption consisted of brownish hyperkeratotic papules and vesiculo-pustules at different stages of evolution. Some of the lesions were umbilicated and healed after crusting with varioliform atrophic hypopigmented scars (Figures 2 and 3). There were no burrow, purpura, nasal discharge or mucosal lesion. Physical examination was normal apart from few small cervical lymph nodes.

Differential diagnoses

These include seborrhoeic dermatitis, eczema herpeticum, post-chickenpox and impetiginized eczema, scabies, pustular dermatoses of infancy, early congenital syphilis, Langerhans' cell histiocytosis, and non-Langerhans' cell histiocytosis.

Investigations

Skin scraping for scabies was negative. Complete blood count, liver and renal function test, urine



Figure 1: Crusted brownish-red papules at scalp and face, most marked at glabella area



Figure 2: Polymorphic eruption involving the whole body. Some of the lesions were umbilicated and healed with varioliform atrophic hypopigmented scars



Figure 3: Lesions at different stages of evolution: brownish-red papules, followed by pustules then crusting and scarring. Lesions were most marked at acral sites

osmolality, anti-nuclear antibody, C3, C4, herpes culture, skin swab and VDRL were normal or negative.

Skin biopsy from right sole showed epidermal necrosis, neutrophilic infiltration & parakeratosis. At the papillary dermis there were aggregates of polygonal cells with eosinophilic cytoplasm and highly folded nucleus. Immuno-staining was positive for S-100 & CD1a. Electron microscopy showed classical Birbeck granules and laminated dense bodies seen in tumour cells.

Diagnosis

The features were diagnostic of Langerhans' cell histiocytosis (LCH). Staging investigations including chest radiography, skeletal survey, bone scan, abdominal

ultrasound, bone marrow biopsy, MRI brain and brainstem auditory evoked potential were all normal.

Management

Topical treatment

As topical nitrogen mustard is unavailable in Hong Kong, it has not been tried. The patient was given 1% hydrocortisone vioform and mometasone cream.

Chemotherapy

It was decided that an aggressive approach with chemotherapy should be given because of the following reasons: (1) The patient had disseminated skin disease with no ideal treatment and new lesions were developing.

(2) This age group was associated with high mortality.
(3) The patient could have very early Letterer-Siwe disease and the cutaneous lesions could precede full-blown systemic infiltration.

Combination chemotherapy with prednisolone, vincristine, cytarabine and co-trimoxazole (prophylaxis for pneumocystis carinii pneumonia) was given by paediatricians according to Egeler et al.¹

Progress

Lesion reduction was noted after two chemotherapy sessions, but it was impossible to distinguish whether it was due to spontaneous resolution or effects of chemotherapy. Long-term follow up is required to assess clinical response and detect for disease progression.

REVIEW ON LANGERHANS' CELL HISTIOCYTOSIS

Definition

Langerhans' cell histiocytosis (LCH) is a reactive condition of unknown cause characterized by proliferation of a distinct cell type that is S-100 and CD1a positive and contains cytoplasmic Birbeck granules.

Incidence

The annual incidence of LCH has been estimated at 0.5 per 100,000 children in USA and at 1 per 2 million children worldwide. The male to female ratio is 1.8:1.²

Aetiology

At present, the aetiology is unknown but most workers agree that it is a reactive rather than a neoplastic condition. This is based on its morphological appearance in histology and cases of spontaneous regression. Lahey et al.³ suggested that it could be due to altered immune response to viral infections (Human Herpes Virus Type 6).

Clinical features

LCH presents with a very wide clinical spectrum and runs a variable course. Its manifestations range from isolated self-healing lesions to generalized and fatal destructive disease of tissue.² Four subtypes of LCH have

been described as follows:

- 1) Letterer-Siwe disease
- 2) Hand-Schüller-Christian disease
- 3) Eosinophilic granuloma
- 4) Hashimoto-Pritzker disease (congenital self-healing histiocytosis)

Letterer-Siwe disease (LSD)

This is the acute, disseminated multi-systemic form of LCH and typically runs a rapid and fatal course. One third of cases occur in the first 6 months of life and the remaining two third before the age of 2 years. Rarely, congenital cases and adult cases were reported. Cutaneous manifestations include crops of "rose-yellow" papules at scalp & torso with or without crusting. Scaling, ulceration, vesicles, pustules and purpura may occur. Lesions may merge and mimic seborrhoeic dermatitis. Mucosal lesion is rare. *Cutaneous manifestations may be the earliest sign of Letterer-Siwe disease.* Systemic manifestations include fever, pulmonary lesions (50%), hepatosplenomegaly, lymphadenopathy (25-75%), osteolytic lesions (60%), chronic otitis media and haemopoietic involvement.

Hand-Schüller-Christian disease

This is the chronic, progressive multi-focal form of LCH. Patients usually present between 2-6 years (70%) and 91% occurs before 30 years. Clinical manifestations include osteolytic lesions (80%), diabetes insipidus (50%), exophthalmus (10-30%) and mucocutaneous lesions (30%).

Eosinophilic Granuloma

This is the localized and benign form of LCH. Patients present usually between 5 to 30 years old (70%) with insidious onset. Lesions occur in bones (cranium > ribs > spine > long bones) and patient may present with fractures or otitis media. Muco-cutaneous lesions are rare.

Hashimoto-Pritzker disease (HPD) (congenital self-healing LCH)

Since its first description in 1973, 34 cases of Hashimoto-Pritzker disease were reported. This is the congenital self-healing form of LCH. The prognosis is excellent with rapid spontaneous regression. Longaker et al.⁴ described four diagnostic criteria as follows:

- 1) Congenital/neonatal skin lesions with generalized papules, vesicles, or nodules resemble healing chickenpox. Palms and soles may be involved;
- 2) Healthy infant with no systemic involvement;

- 3) Langerhans' cell histiocytic infiltrate;
- 4) Spontaneous involution of lesions in weeks and months.

Hashimoto-Pritzker disease or early Letterer-Siwe disease both fitted the clinical picture of this patient. However, histology did not help to distinguish the two entities. The former has been described to be more likely if there were nodular infiltrate of Langerhans' cell with dermal necrosis or if there were fewer cells (10-30%) with Birbeck granules and more cells with laminated dense bodies at electron microscopy.⁴

Diagnosis

Diagnosis is confirmed by skin biopsy, which identifies the typical LCH cell by S-100, CD1a & CD-4 molecules expressions. It can be distinguished from normal Langerhans' cells by positive staining to placental alkaline phosphatase, peanut agglutinin and interferon- γ receptor. At electron microscopy, Birbeck granules are seen in 50% of histiocytes. Three histological patterns are described including proliferative (early stages), granulomatous (chronic stages) and xanthomatous (especially Hashimoto-Pritzker disease).

Treatment

Single system disease

For skin, topical 20% nitrogen mustard was described to be helpful but this is no longer available in Hong Kong and United States.^{5,6} Other treatment described in isolated case reports included topical and oral PUVA, CO₂ laser, thalidomide and isotretinoin.

For bone, surgery (excision or curettage) and steroid injections with and without radiotherapy are the treatment of choice. Mono-chemotherapy with vinblastine, etoposide or methylprednisolone considered if multi-focal lesions are present.

Multiple system disease

Chemotherapy is the mainstay of treatment. Agents used include: vinblastine, etoposide, methylprednisolone, vincristine, doxorubicin, chlorambucil and cyclophosphamide.

Prognosis

This depends on age at diagnosis and the degree of

organ involvement and dysfunction. Mortality in those presented before 2 years old with disseminated disease was 37% compared with 16% in those presented after 2 years.⁷ Causes of death include pulmonary involvement, bone marrow involvement and infection. Poor prognostic signs include jaundice, anaemia, thrombocytopenia, signs of hepatic failure, nail involvement and purpura. In Hashimoto-Pritzker disease, lesions are usually self-limiting in weeks to months. Esterly et al. recommended conservative treatment only.⁸ However, spontaneous resolution did not preclude relapse. Longaker et al described recurrence in two out of four cases, with cutaneous relapse at 3 months in one case and bony relapse at 6 months in another.⁴ A case was reported with resolution of multiple skin lesions at birth but later developed diabetes insipidus after 4 years.⁸ Long-term follow-up is therefore essential.

Learning points:

Langerhans' cell histiocytosis must be ruled out in children presenting with recalcitrant seborrhoeic dermatitis.

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