CASE REPORT

Severe Langerhans cell histiocytosis in an infant: haemophagocytic syndrome association

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SUMMARY

Langerhans cell histiocytosis (LCH) is a rare disease of unknown origin with a heterogeneous clinical presentation, varying from benign and self-limited to lethal. It is classified as single or multisystemic, according to the number of organs involved (one or at least two, respectively). Diagnosis can be challenging and is based on the histological and immunophenotypic examination of affected tissues. Secondary haemophagocytic lymphohistiocytosis is rarely reported in association with LCH and may impair its diagnosis. Some authors suggest that the coexistence of the two disorders is more than coincidental. We present a case of multisystem LCH in a 5-month-old infant, with all risk organs involved, in which severity and rapid progression reflect an association with haemophagocytic syndrome.

BACKGROUND

Histiocytosis encompasses a group of diverse disorders including dendritic-cell-related Langerhans cell histiocytosis (LCH), macrophage-related diseases (like haemophagocytic syndromes) and malignant disorders.

LCH is the most common histiocytic disorder in humans, with an estimated incidence of 8–9 cases per million/year.¹ The pathogenesis of LCH is unknown and proposed mechanisms include malignant transformation versus immune dysregulation. Clonality of LCH was described many years ago, but clonality does not necessarily mean malignancy.^{1–2} Recently, BRAF-V600E point mutations were present in a majority of LCH lesions and appear to have functional significance, but no clinical correlations have been established.³ The alternative hypothesis is that LCH is a reactive disease in the setting of immature dysregulation, leading to an aberrant reaction between Langerhans cells and T-lymphocytes, triggered by various stimuli, including viruses and malignancy.³

The clinical course may vary from self-limited and benign to a rapidly progressive and life-threatening disease.² LCH may be limited to one organ or system (single LCH) or it can involve two or more organs or systems (multisystem LCH). Multisystem LCH is generally more severe, especially when it includes risk organs (liver, spleen and bone marrow/haematological dysfunction).³ Life-threatening forms of LCH, previously referred to as Letterer-Siwe disease, typically present in infancy and have a high mortality rate (greater than 50% in children under 2 years), even with aggressive treatment.⁴ Typical findings include fever, hepatosplenomegaly, liver dysfunction and haematopoietic

failure with or without intestinal involvement.⁵ Gastrointestinal, thymus and mediastinal lymph nodes are rarely involved and associated with poor prognosis in cases reported in the literature.^{6–8} Definitive diagnosis of LCH is based on the identification of pathological CD207 positive and/or CD1a positive Langerhans cells in compromised tissue.⁵

Secondary haemophagocytic lymphohistiocytosis (HLH) is another type of histiocytic disorder rarely reported in association with LCH.^{9–11} According to a revision made in 2004 by the Histiocyte Society, diagnosis of HLH can be established if (I) there is a molecular diagnosis consistent with HLH or (II) there are at least five of the following eight criteria: fever; splenomegaly; bicytopenia (haemoglobin <9 g/dL, platelets <100×10⁹/L, neutrophils <10⁹/L); hypertriglyceridaemia and/or hypofibrinogenaemia; haemophagocytosis in bone marrow, spleen, lymph node or cerebrospinal fluid (CSF); low or absent natural killer (NK) cell activity; elevated ferritin (>500 µg/L); soluble CD25 above normal limits for age.¹² Favara *et al*⁹ reviewed 30 cases of LCH with different degrees of macrophage activation. There were only seven cases with fully developed haemophagocytic syndrome and an additional five with haemophagocytosis and some, but not all, diagnostic criteria. Most of these 12 cases were young children with high-risk LCH and poor prognosis, four of whom died. Another five cases published previously in the literature shared these clinical features, and two showed a relation with a known viral infection.

All the evidence suggests that the coexistence of these two diseases is likely to be more than coincidental. Pathophysiological mechanisms that explain such an association are yet to be determined.

The authors report a rare case of a 5-month-old infant with multisystem LCH, all risk organs, intestine and thymus involved, despite no skin or lytic bone lesions. The fulminant clinical course reflects not only a severe form of the disease itself, but also an association with secondary HLH. We highlight this association, as it may obscure primary diagnosis and delay the beginning of treatment.

CASE PRESENTATION

A 5-month-old African baby boy presented with unilateral cervical lymphadenitis, without fever or other symptoms associated.

He was the first child of non-consanguineous and healthy parents. There was a history of single umbilical artery and prenatal mild bilateral hydro-nephrosis, confirmed in postnatal ultrasound and followed by a paediatric nephrologist. He was a

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full-term baby, appropriate for gestational age, exclusively breastfed until the age of 4 months, when solid food was started. He had normal growth and development, and had been immunised as per schedule. He had mild atopic eczema.

Physical examination on admission was described as normal, except for the referred cervical lymphadenitis. The patient was started on intravenous amoxicillin and clavulanic acid. Five days later, he was submitted to surgical drainage and clindamycin was added. Methicillin-sensitive *Staphylococcus aureus* was isolated from abscess fluid and he achieved significant clinical improvement. Blood culture was positive to *Staphylococcus hominis* (probable skin contamination). Meanwhile, at day 3, spleen enlargement was noticed approximately 3 cm below the left costal margin.

At day 13 the patient developed fever every 8 h, with vomiting and diarrhoea, hepatomegaly and increase of splenomegaly (5 cm below the left costal margin). He was transferred to a tertiary hospital on day 15 for investigation. On admission he was afebrile, pale and tachycardic, with normal blood pressure. He presented tachypnoea, with 100% oxygen saturation in room air. A systolic murmur was heard, with normal breath sounds. The liver was enlarged 4 cm below the right costal margin and spleen was enlarged up to the left iliac fossa. He maintained left cervical lymphadenitis (3 cm in diameter) and small bilateral cervical lymph nodes, maximum of 1 cm in diameter, without active drainage.

INVESTIGATIONS

Lab results showed normocytic anaemia (minimum haemoglobin of 5.0 g/dL), with 6.6% ($138 \times 10^9/L$) reticulocytes. The patient had normal white cell count ($11.76 \times 10^9/L$, neutrophils 27.9%, lymphocytes 56%, monocytes 4.2%, stimulated lymphocytes 7.4%) and mild thrombocytopenia (platelets $105 \times 10^9/L$). Peripheral blood smear revealed anisopoikilocytosis and stimulated lymphocytes. C reactive protein (CRP) was 2.38 mg/dL and sedimentation rate 3 mm/h.

Creatinine, blood urea nitrogen, blood electrolytes and screening coagulation tests were normal. Aspartate aminotransferase was mildly elevated (54 U/L), but alanine aminotransferase (32 U/L) and ferritin (169.6 ng/mL) were within the normal range.

Coombs test was negative; haemoglobin chromatography and glucose-6-phosphate dehydrogenase levels were normal. Immunoglobulins and lymphocyte subsets in blood were normal.

The patient had immunity for cytomegalovirus; the other viral serologies (HIV, parvovirus, Epstein-Barr virus and herpes simplex virus) were negative (IgG and IgM).

TREATMENT

The patient received a red blood cell transfusion and maintained therapy with amoxicillin, clavulanic acid and clindamycin.

OUTCOME AND FOLLOW-UP

During the next 3 days after being transferred, the patient's clinical condition continued to deteriorate. He maintained fever with irritability and gradual increase of respiratory effort. Cervical lymph node enlargement and generalised petechial rash were noticed. Lab studies revealed pancytopenia (minimum of 5.4 g/dL haemoglobin, $0.54 \times 10^9/L$ neutrophils and $5 \times 10^9/L$ platelets), hypofibrinogenemia (101 mg/dL) and hypoalbuminaemia (2 g/dL). Ferritin (400 ng/mL), triglycerides (235 mg/dL), aspartate aminotransferase (maximum 154 U/L), D-dimers ($3.07 \mu\text{g/mL}$) and lactate dehydrogenase (2135 U/L) were elevated, with normal sodium, coagulation and bilirubin tests. Maximum CRP was 6.1 mg/dL.

Chest X-ray showed mediastinum enlargement by thymus. Ultrasound revealed mild pericardial effusion and a small quantity of ascitic fluid. Bone marrow biopsy was normal, without evidence of haemophagocytosis or *Leishmania* spp.

On day 4 after admission the patient was transferred to the paediatric intensive care unit for increased respiratory distress. During intubation he developed significant pulmonary haemorrhage and bradycardia, with recovery after resuscitation manoeuvres. He received red blood cell and platelet transfusions and started treatment with intravenous immunoglobulin and dexamethasone, considering the hypothesis of secondary HLH of unknown aetiology. He died 8 h after being admitted in the intensive care unit.

The histopathological examination of autopsy collected samples revealed diffuse infiltration of lymph nodes, thymus, spleen, liver, gastrointestinal tract and lungs (the latter aggravated with diffuse alveolar damage) by oval cells with scant cytoplasm, and oval and grooved nuclei, some with complex foldings. These cells were CD1a positive. In the spleen and lymph nodes an increased number of macrophages were also observed, with haemophagocytosis. The diagnosis was multisystem LCH, with associated haemophagocytic syndrome.

DISCUSSION

Diagnosis of LCH may be challenging mainly because of its wide range of clinical manifestations and organ involvement. It can present rarely as an acute, fulminant and disseminated disease. Systemic involvement must be considered even in apparently limited forms. More severe presentations with involvement of risk organs occur in children under 2 years of age. Non-risk organs appear to be related with poor prognosis. The gastrointestinal tract, although rarely affected (estimated incidence of less than 1%), is associated with 59% of mortality within 18 months of diagnosis.⁸ Thymus and mediastinal lymph nodes involvement is probably underdiagnosed, with no more than 50 cases reported to date, also associated with life-threatening disease.⁶

Our young patient had a very severe form of LCH, with multisystemic involvement, including all risk organs and also thymus, mediastinal nodes and gastrointestinal tract. The most lethal forms of LCH reported in the literature are related to Letterer-Siwe disease, which was included in the previous classification of LCH. Letterer-Siwe presented in those under 2 years of age as an acute and disseminated disease, with systemic and cutaneous involvement. The few reported cases describe recurrent pyoderma-like lesions, and vesicopustular and purpuric eruptions resembling seborrheic dermatitis.¹³ Our patient had an earlier diagnosis of mild atopic eczema, but without any rash or cutaneous alterations at the time of disease presentation.

Despite the severity of LCH itself, we believe that such a fulminant clinical deterioration was caused by a secondary form of HLH. To our knowledge, there are no previous reports in the medical literature of such a fulminant clinical course, with death occurring within 2 weeks of presentation. This fast clinical deterioration prevented a prompt diagnosis in vivo. Early on we considered haemophagocytic lymphohistiocytosis as a possible diagnosis, but the patient only met four criteria (fever, splenomegaly, bicytopenia, hypofibrinogenemia), as ferritin was not high enough and there was no haemophagocytosis in the bone marrow. We did not have time for other diagnostic studies such as NK cell function or soluble CD25. Without definitive diagnosis of HLH, targeted therapy was not initiated due to the risk of sepsis with immunosuppressive drugs. Post-mortem histopathological examination identified CD1a positive LCH and

haemophagocytosis in spleen and lymph nodes, which constitutes the fifth criteria for HLH.

This rare association of LCH and HLH has been described in the literature and seems more frequent in younger children with multisystem disease. Manifestations of macrophage activation may be serious enough to mask the primary disorder and impair diagnosis and management,⁹ as seen in our case. Even when LCH is already known, some authors suggest that the laboratory profile of macrophage activation should be routinely investigated, especially in multisystemic disease.

The pathogenic mechanism of this probably underdiagnosed association is still to be determined. Both are disorders of immune regulation, in which T cells and related cytokines seem to play an important role, eventually linking the two. One proposed explanation is that LCH can predispose some patients to macrophage activation in response to a variety of stimuli, including viral infection. This agrees with our case and with other reported in the literature.⁹ In fact, after a period of clinical improvement, the patient developed fever, vomiting and diarrhoea, with increase of splenomegaly. It is possible that a concurrent viral infection could serve as a trigger to the development of HLH. We could not, however, identify any viral agent as blood tests were negative for acute infection, and rotavirus or adenovirus screen in faeces was not performed. Further investigation is needed to highlight the pathogenic mechanisms involved and the eventual role of concurrent viral infection.

Learning points

- ▶ Langerhans cell histiocytosis (LCH) is a rare dendritic cell-related histiocytic disorder that can be lethal.
- ▶ Secondary HLH is another histiocytic disorder that can occur in association with LCH. It appears to be more frequent in multisystemic disease occurring at a younger age.
- ▶ Definitive diagnosis may be challenging. We should look for macrophage activation in patients with evidence of multisystem LCH or hyperacute clinical deterioration.

Definitive diagnosis of HLH and LCH coexistence is difficult and implies an invasive approach. Clinical deterioration demands urgent management and further investigation is needed to highlight the pathogenic mechanisms involved. This understanding would certainly help to prevent and optimise effective treatment in such a life-threatening condition.

Competing interests None.

Patient consent Obtained.

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