CASE REPORT

Chediak-Higashi syndrome in accelerated phase masquerading as severe acute malnutrition

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SUMMARY

A toddler presented with poor appetite, weight loss and frequent respiratory tract infections for the past 6 months, fever and increasing paleness for the past 2 months and bilateral pedal oedema for the past 1 month. Anthropometry confirmed severe acute malnutrition. Clinical and laboratory evaluation revealed that the child also had hypopigmented hair and skin, splenohepatomegaly, pancytopenia and hypoalbuminaemia. The coexistence of hypopigmentation and suspected low immunity prompted us to investigate the child's hair, peripheral blood smear and bone marrow. Hair under light microscopy showed evenly distributed, large melanin granules, suggestive of Chediak-Higashi syndrome (CHS). Peripheral blood smear and bone marrow aspirate examinations revealed abnormal large intracytoplasmic granules, which was diagnostic of CHS. The child's investigations revealed coexistent hemophagocytic lymphohistiocytosis, confirming the diagnosis of CHS in 'accelerated phase', which is fatal if not treated. The parents prematurely took the child home against medical advice, before definitive therapy could be instituted.

BACKGROUND

Severe acute malnutrition (SAM) affects nearly 19 million under-5-year-old children worldwide, most of whom live in southeast Asia and Africa.[1] Furthermore, more than 7% of all deaths in this age group are attributable to SAM.[1] It is well known that systemic illness such as pneumonia, measles and whooping cough can precipitate SAM in undernourished children. In countries where SAM is common, the physicians should be alert to recognise signs pointing to the coexistence of a rare but serious life-threatening systemic disease. Unlike SAM, Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease with fewer than 500 cases reported worldwide.[2] The 'accelerated phase' of CHS, namely hemophagocytic lymphohistiocytosis (HLH), develops in 50–85% of cases and is fatal if not treated.[2 3] CHS primarily presenting in 'accelerated phase' is rare.[2–4] To the best of our knowledge, this is the first report of a child with CHS primarily presenting in 'accelerated phase' with coexistent SAM.

CASE PRESENTATION

A toddler, born of a non-consanguineous marriage and belonging to lower socioeconomic class of society presented with poor appetite, weight loss and frequent respiratory infections for the past 6 months. The child had intermittent low-grade fever and increasing paleness for the past 2 months and pedal oedema for the past 1 month. On enquiry, the child was predominantly breast fed for the first 6 months of life, after which complimentary feeds were introduced. When the child was 9 months old, the mother conceived again. The mother continued to breast feed until the child was 1 year of age. Prior to the current illness, the child's total calorie intake was 2344 kJ/day (expected 4605 kJ/day) and protein intake was 8 g/day (expected 15 g/day).

On examination, the child was apathetic and irritable. Heart rate was 136 bpm, respiratory rate was 32 breaths/min and blood pressure was 90/60 mm Hg in the right upper arm. Child's weight was 6 kg, height 72 cm and head circumference was 42 cm, all three below the third percentile as per standard WHO growth charts. There was bilateral pedal oedema, and weight/height ratio was <−3 Z score below the median (as per WHO growth chart), and mid-upper arm circumference was 10 cm; all indicating SAM.[5 6] The child had severe pallor, angular stomatitis, cheilitis and buccal ulcers. However, the child did not have hypothermia, hypoglycaemia, dehydration or any skin changes associated with SAM.

A closer look revealed that there was more to the diagnosis than just SAM. The scalp hair was sparse, fine and uniformly silvery-brown with a metallic sheen (figure 1), but it was not easily pluckable, nor did it show the typical 'flag sign' as commonly seen in SAM. The child also had cutaneous albinism and was much fairer than other family members. Iris pigmentation was normal. There were hypopigmented macules over the back and multiple petechiae all over the body. Abdominal examination revealed splenohepatomegaly (spleen 6.5 cm and liver 3 cm below the costal margin) without evidence of ascites. Rest of the systemic examination was normal.

INVESTIGATIONS

Preliminary investigations revealed that the child had pancytopenia (haemoglobin 43 g/L, white cell count 3×10^9/L, absolute neutrophil count 0.72×10^9/L and platelets 20×10^9/L). Blood investigations revealed hypokalaemia (3.1 mmol/L), hypocalcaemia (1.75 mmol/L), hypoalbuminaemia (11.0 g/L) and deranged prothrombin time (patient's >110 s, control's 13.3 s, with International Normalised Ratio (INR) >13.16). Blood cultures were sterile. The coexistence of cutaneous albinism and suspected low immunity prompted us to investigate the hair, peripheral blood smear and bone marrow. Light microscopy

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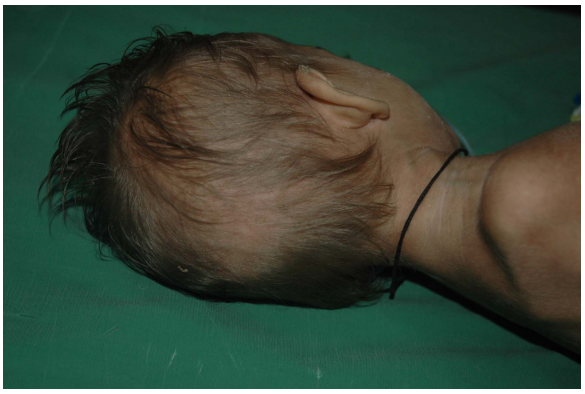

Figure 1 Posterior view of child's scalp showing sparse, fine and uniformly silvery-brown hair with a metallic sheen.

examination of the hair showed evenly distributed, regular melanin granules, larger than those seen in normal hairs (figure 2) which are typical of CHS.[3 7 8] Peripheral blood smear examination revealed pancytopenia along with occasional lymphocytes having coarse and large intracytoplasmic granules (figure 3A). Bone marrow aspirate examination revealed a normocellular marrow with erythroid hyperplasia and cells of the myeloid series showed large intracytoplasmic pink granules (figure 3B). Blast cells were absent in the peripheral blood smear and the bone marrow aspirate. The peripheral blood smear and the bone marrow picture confirmed the diagnosis of CHS.[3 9]

In view of fever, splenomegaly and pancytopenia, we suspected that the CHS was in 'accelerated phase' and investigated the serum triglyceride level and the natural killer (NK)-cell cytotoxicity. Serum triglyceride was raised (3.59 mmol/L, normal 0.30–1.41 mmol/L) and the NK-cell cytotoxicity was reduced confirming the diagnosis of HLH.[10–12]

DIFFERENTIAL DIAGNOSIS

- The presence of fever, splenohepatomegaly and pancytopenia made us consider the differentials of leukaemia, lymphoma, primary HLH or HIV-related secondary HLH.[10–12] Peripheral blood smear and bone marrow aspirate examinations ruled out malignancy. Our patient tested negative for HIV.
- The presence of hypopigmentation with frequent infections made us consider the differentials of CHS, namely Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2 and Elejalde syndrome.[3 13 14] The melanin granules in the patient's hair shafts were evenly distributed, regular, larger than those seen in normal hairs as in CHS; and is a feature lacking in the three differentials enlisted above.[7 8] Also, giant intracytoplasmic granules in the peripheral leucocytes and their bone marrow precursors are classically seen only in CHS.[3 9]

TREATMENT

On admission, the child was started on the recommended F-75 diet for SAM.[15] The child was also dewormed, given multivitamins and minerals along with parenteral broad-spectrum antibiotics.[15] Packed cell transfusions, fresh frozen plasmas and platelet transfusions were given. On the fifth day of hospitalisation, when a diagnosis of CHS in 'accelerated phase' was confirmed the parents were referred to the Medical and Social Work Department to obtain medications at concessional rates to begin the recommended chemoimmunotherapy regimen of etoposide, dexamethasone and cyclosporine A.[10–12] However, the parents took their child home against medical advice.

OUTCOME AND FOLLOW-UP

The patient is now deceased.

DISCUSSION

SAM is a major contributor to the under-5 mortality rate in developing countries.[1] A child is diagnosed as having SAM if his/her weight-for-height ratio is <−3 Z score below the median or mid-upper arm circumference is <11.5 cm or there is bilateral pedal oedema.[6] In India, over 8 million children are afflicted by SAM.[1] These children have mortality rates that are nine times higher than well-nourished children.[1]

CHS is a rare autosomal recessive immune deficiency disorder characterised by significant history of bacterial infections of the skin and respiratory tract, partial albinism, mild bleeding tendency and varying neurological problems.[2 3] CHS is caused by mutations in *LYST* (*lysosomal trafficking regulator*) gene located at chromosome 1q42.1-q42.2.[2 3] The *LYST* gene plays an important role in regulating lysosome size and trafficking.[2 3] *LYST* mutations result in abnormally large lysosomes which interfere with normal cell functions.[2 3] Enlarged lysosomes in immune system cells prevent them from responding appropriately to bacteria. Melanin gets trapped within the giant

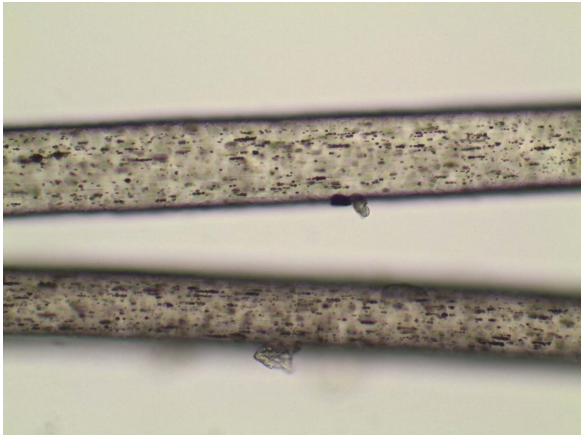

Figure 2 Hair under light microscopy showing evenly distributed, regular melanin granules, larger than those seen in normal hair.

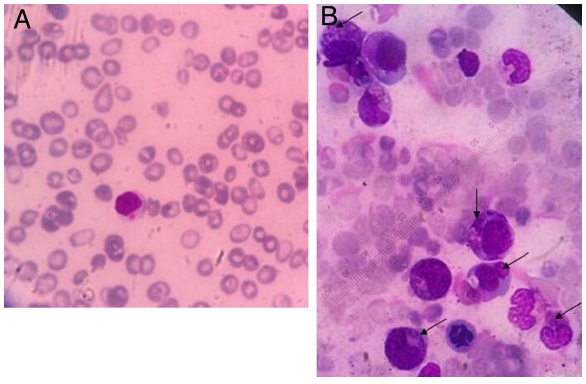

Figure 3 (A) Peripheral blood smear showing pink intracytoplasmic giant granules within a lymphocyte (Giemsa stain). (B) Bone marrow aspirate showing purple intracytoplasmic giant granules in the neutrophils and its precursor cells (marked with arrows; Giemsa stain).

melanosomes (which are related to lysosomes). Abnormal lysosome-like structures in platelets underlie the mild coagulation defects. Similarly, abnormal lysosomes in nerve cells probably cause the neurological problems associated with this disease.[2 3]

CHS is a potentially lethal disorder characterised by diverse clinical manifestations.[2 3] CHS should be suspected in a child who has partial albinism and history of recurrent or severe infections.[2 3] CHS patients show varying degrees of hypopigmentation of the skin, eyes and hair; and easy bruising and mucosal bleeding.[2 3] A small percentage of people with CHS have a milder form of the condition that appears later in life. People with the adult form of the disorder have less noticeable changes in pigmentation and are less likely to have recurrent, severe infections. They do, however, have a significant risk of developing progressive neurological problems, for example, peripheral neuropathy, ataxia, tremors and decline in intellectual functioning.[3]

Children with CHS should be treated prophylactically with antibiotics.[2 3] This is effective in controlling recurrent infections but does not prevent the other complications of CHS, for example, bleeding, onset of the 'accelerated phase' or neurological problems.[2 3]

Simple, quick and non-invasive tests like examining the patient's hair under light microscopy and a careful peripheral blood smear examination can easily clinch the diagnosis of CHS.[3 7–9] However, the challenge lies in suspecting the disorder in the first place.[2] In our patient, molecular study for mutations in *LYST* gene could not be carried out for lack of availability.

Patients who do not succumb early to infections subsequently develop the 'accelerated phase' or HLH, a lymphoproliferative infiltration of the bone marrow and reticuloendothelial system which is a serious and potentially fatal complication of CHS.[2 3] The diagnosis of HLH is established by fulfilling five of the following eight criteria: (1) fever, (2) splenomegaly, (3) cytopenias (affecting ≥2 of 3 lineages in the peripheral blood), (4) hypertriglyceridaemia and/or hypofibrinogenaemia, (5) hemophagocytosis in bone marrow, spleen or lymph nodes without evidence of malignancy, (6) hyperferritinaemia (≥500 μg/L), (7) low or absent NK-cell cytotoxicity and (8) soluble CD25 (ie, soluble IL-2 receptor) ≥2400 U/mL.[10–12]

Hematopoietic stem cell transplantation (HSCT) is the curative treatment for CHS.[3 10–12] The outcome is most favourable when HSCT is instituted early in the course of the illness.[3 10–12] Also, HSCT should be performed only after coexistent HLH is ruled out.[3 10–12]

In summary, we present a case of CHS primarily presenting in 'accelerated phase' and masquerading as SAM. We have hypothesised that the combined effects of an inadequate diet, recurrent infections due to CHS and, eventually the CHS going into an 'accelerated phase' precipitated the SAM.

Learning points

- High clinical suspicion is paramount to diagnose Chediak-Higashi syndrome (CHS).
- Simple and non-invasive tests like examination of hair under light microscopy and peripheral blood smear help to confirm diagnosis of CHS.
- Presence of hypopigmented skin, splenohepatomegaly and cytopenias in a child with SAM should alert the physician towards the possibility of a serious coexistent immune deficiency disorder, namely CHS in 'accelerated phase'.
- CHS in 'accelerated phase' is a fatal condition if untreated.

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