Chediak-Higashi syndrome presenting in the accelerated phase

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Chediak-Higashi syndrome (CHS) is an extremely rare autosomal recessive disorder characterised by recurrent pyogenic infections, partial oculocutaneous albinism, and mild bleeding. The most reliable finding that helps in diagnosis is abnormally large granules in leukocytes and other granule-containing cells. Herein we report a case of CHS in a 3-month-old girl who presented to us in the accelerated phase of the disease. The case is reported because of the extreme rarity of CHS presenting in the accelerated phase at diagnosis.

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A 3-month-old female child, the third child born of a second-degree consanguineous marriage and developmentally normal with a normal birth history, presented to us with complaints of fever for 3 days. There was a history of hypopigmentation over the skin for the past month, with a history of recurrent respiratory tract infections. There was no family history of similar complaints.

Examination revealed an active, anthropometrically normal, febrile child with axillary lymphadenopathy and hepatosplenomegaly. The child had silvery hair with patchy areas of skin hypopigmentation over the face, trunk and limbs (Fig. 1). Other systems were normal.

Evaluation showed bicytopenia (low haemoglobin of 6.6 g/dL and platelets of 60 000/μL) with elevated serum triglyceride (323 mg/dL) and ferritin (2 734 ng/mL) – features suggestive of haemophagocytic lymphohistiocytosis (HLH). A familial or infectious cause was suspected. Blood and urine cultures were sterile. Toxoplasmosis, rubella, cytomegalovirus, herpes simplex and HIV (TORCH) screening was also negative. Ultrasonography of the abdomen revealed mild ascites. Radiographs of the chest and skull were normal.

Peripheral smear (Fig. 2) and bone-marrow aspirate (Fig. 3) showed characteristic giant cytoplasmic granules suggestive of Chediak-Higashi syndrome (CHS). Skin biopsy (Fig. 4) revealed irregularly placed giant melanosomes, consistent with CHS. Ophthalmic evaluation was normal. Ebstein-Barr virus work-up (IgG and IgM) was negative. CHS presenting with features of HLH

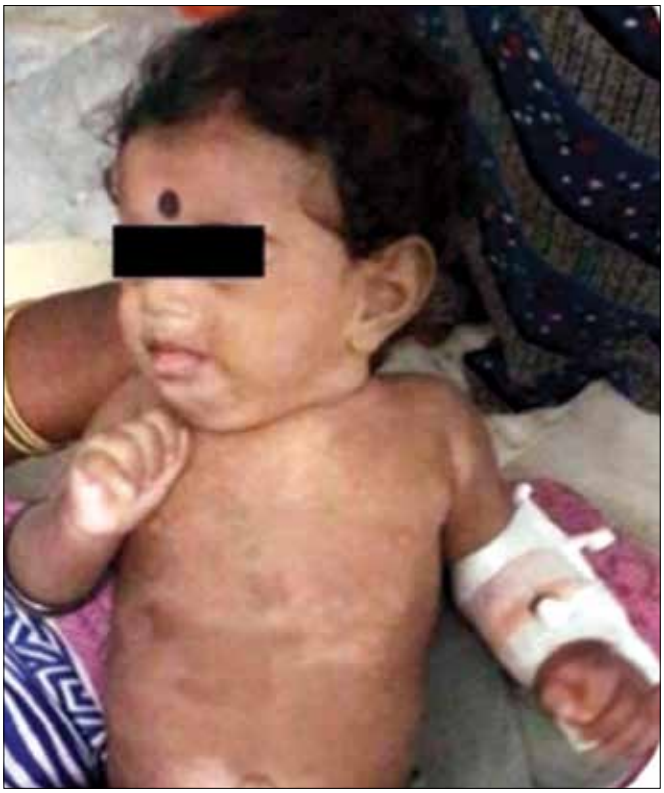

Fig. 1. Child presented with silvery hair and patchy areas of skin hypopigmentation.

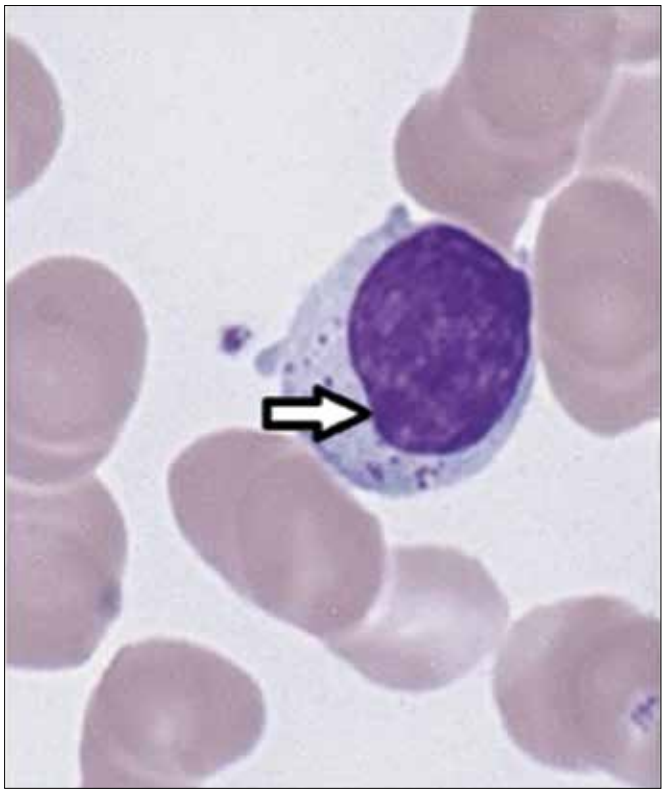

Fig. 2. Peripheral smear showing giant intracellular granules (arrow).

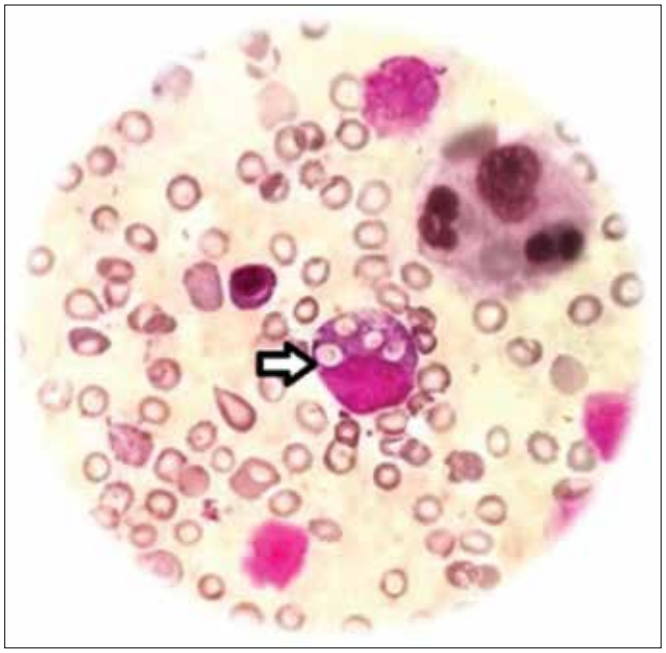

Fig. 3. Bone-marrow aspirate showing characteristic giant cytoplasmic granules (arrow).

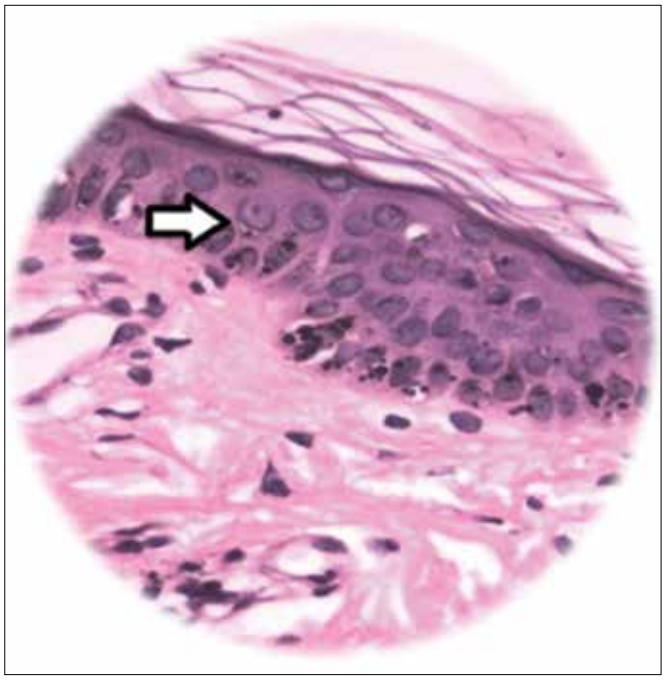

Fig. 4. Skin biopsy showing giant irregularly placed melanosomes (arrow).

was taken as the accelerated phase. Genetic testing for *CHS1/LYST* gene mutations is not available in India, and therefore this test could not be performed. T-cell subset levels were not done because of financial constraints.

The child was treated with intravenous piperacillin, tazobactam, and amikacin, which were later changed to meropenem and fluconazole owing to persistent high-grade fever spikes. Initiation of chemotherapy was planned as per the HLH 2004 protocol,[1] and a bone-marrow transplant was to be considered; however, the parents did not opt for any escalation of treatment and wanted to continue with the conservative management. The child was discharged at their request and succumbed to her illness 2 days after discharge.

Discussion

CHS is a rare disease that follows an autosomal recessive pattern of inheritance. Less than 500 cases have been reported worldwide. The first case in India was diagnosed in 1982.[2]

Genetic studies suggest a mutation in the lysosomal trafficking regulator (*CHS1/LYST*) gene located at 1q42, resulting in abnormal organellar protein trafficking and aberrant fusion of vesicles, further resulting in a failure to transport lysosomes to the appropriate site of action.[3] Altered lysosomes/granules are found in all cell types in CHS, and are the hallmark of the disease.

CHS can be suspected on presentation of partial oculocutaneous albinism with a history of recurrent infections.[3] *Staphylococcus aureus* is the predominant cause while *Streptococcus pyogenes* and *Pneumococcus* spp. are the other common infectious organisms. Most of the cases also present with leukopenia, thrombocytopenia and coagulopathy. Photosensitivity has been reported in many cases. Differential diagnosis includes Hermansky-Pudlak syndrome and Griscelli syndrome.[4,5] Hermansky-Pudlak syndrome, an autosomal recessive disorder, is characterised by partial oculocutaneous albinism and a platelet storage pool deficiency. Griscelli syndrome is another autosomal recessive disorder that is characterised by similar partial oculocutaneous albinism with immunodeficiency, which is attributed to a mutation in one of three intracellular trafficking genes.

Defective neutrophil chemotaxis, degranulation and bactericidal activity could be the reason for recurrent infections. Pathological aggregation and uneven distribution of melanosomes play a role in hypopigmentation. The degree of hypopigmentation varies. The hair can be light blonde, grey or white with a metallic sheen. In darkly pigmented races, hypopigmentation is appreciated more in sun-exposed areas. Iris and retinal pigmentation is also reduced; light-coloured eyes are seen. Impaired platelet aggregation may contribute to the mild bleeding diathesis found in some cases. The mild coagulation defect in such cases can result in easy bruising and abnormal bleeding, especially noted in mucosal tissue.

Diagnosis can be made with a simple peripheral smear for the classic giant azurophilic granules, which are peroxidase-positive, in all granule-containing cells including the peripheral blood and bone marrow.[6] Giant melanosomes can be seen on skin melanocytes. Genetic testing for *CHS1/LYST* gene mutations can confirm the diagnosis. This gene is large with most mutations being unique, and therefore identifying the exact mutation is a challenge. Prenatal diagnosis is made by amniocentesis or chorionic villus sampling for enlarged lysosomes – this helps in early diagnosis and treatment before the accelerated phase.[7]

There are two phases in the progress of the disease: a stable or chronic phase; and a progressive or accelerated phase. The stable phase is characterised by recurrent infections. This phase can be managed with appropriate use of antibiotics or antifungal agents with adequate hygiene. About 10% of patients survive early childhood despite serious infections, but develop severe, debilitating neurological manifestations such as mental retardation, peripheral neuropathy and seizures in adolescence and early adulthood.

The accelerated phase may occur soon after birth, as in our case, or years later, and is usually fatal unless intervention occurs rapidly. It mimics a lymphoma-like scenario and is considered a form of familial HLH.[8] Epstein-Barr virus and a lack of natural killer cell function has been implicated in the accelerated phase.[9] There is lymphohistiocytic infiltration of virtually all organs with more profound immune deficiency. Affected individuals present with fever, increased hepatosplenomegaly and lymphadenopathy, with worsening pancytopenia and bleeding.[10] Other presentations can include unexplained hepatosplenomegaly and unexplained neurological abnormalities, especially in an older child, in the form of ataxia, tremors, muscle weakness, sensory loss, cranial nerve

palsies, progressive intellectual decline and seizures. Movement disorders, such as Parkinson's disease and dementia can also occur.

The accelerated phase is treated with chemotherapy as per the HLH 2004 protocol. Haematopoietic stem cell transplant is the ultimate treatment for the immunological and haematological manifestations of CHS.[11,12] However, it has no effect on the neurological symptoms and oculocutaneous albinism.

Successful transplantation depends on having an HLA-identical donor. HLA-non-identical transplant remains an experimental approach. There has been a report of successful bone-marrow transplantation in a 2-year-old male with CHS in the accelerated phase with hereditary elliptocytosis, the boy being clinically well post transplant.[13]

Most patients with CHS die in their first decade if a stem-cell transplant is not done, although patients have been reported as old as 27 years.[14] In a study of 35 children with CHS, the 5-year prognosis post transplantation was 62%. Prognosis is better if the transplant is done before the onset of the accelerated phase. Atypical presentation of CHS can include subtle or absent oculocutaneous albinism, insignificant or less frequent infections, subtle bleeding manifestations and progressive neurological findings that are highly variable and nonspecific.[15]

A carefully examined peripheral smear can clinch the diagnosis. Early detection facilitates early bone-marrow transplant, which is the only curative approach for CHS.

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