CASE REPORT

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – A PRESENTATION OF ACCELERATED PHASE OF CHEDIAK HIGASHI SYNDROME; CASE REPORT AND CLINICOPATHOLOGICAL REVIEW

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Chediak Higashi syndrome (CHS), a rare form of autosomal recessive disorder has been reported globally in less than 500 cases over the past two decades. It clinically manifests as repeated episodes of infection, haemorrhagic sequelae, partial albinism, photosensitivity and late neurological signs (neuropathy, cognitive impairment etc). The pathognomonic morphological finding is the presence of abnormally large intra-cytoplasmic granules, particularly in leucocytes. Almost 85% of CHS cases advance into an accelerated phase, characterized by cytopenias and hemophagocytosis, leading to multi-organ failure. **Case presentation:** The child in the present case had consanguinity and a positive family history of recurrent infections. She had repeated episodes of bacterial infections. She also had a history of photosensitivity. CBC reported cytopenias. Peripheral smear showed neutrophils with characteristic large sized abnormal intra-cytoplasmic granules. Bone marrow biopsy was performed which also showed similar granules in leucocytes along with hemophagocytosis. Other clinical and biochemical markers also pointed towards hemophagocytic lymphohistiocytosis (HLH), thus patient was diagnosed as CHS in an accelerated phase. She received eight doses of chemotherapy but eventually expired. **Conclusion:** The definitive treatment is hematopoietic stem cell transplantation which improves the hematological and immune aspects of CHS but not the neurological. Steps should be taken for early diagnosis and to prevent advancement into the accelerated phase.

Keywords: Intra-cytoplasmic granulues, Photosensitivity, Albinism, chediak-higashi syndrome, Hemophagocytosis.

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INTRODUCTION

Chediak Higashi syndrome (CHS) was first reported in 1943 by Beguez Cesar[1] with the haematological features of the disease described in 1952 and 1954 by Chediak[2] and Higashi[3] respectively. It is a rare autosomal recessive disorder having characteristic features which include large abnormal cytoplasmic granules in neutrophils, partial albinism, photosensitivity, recurrent pyogenic infections, bleeding tendency and late onset neurological dysfunction. Fewer than 500 cases have been published on CHS in the last 20 years.[4]

Almost 85% of the cases of CHS patients advance into the accelerated phase termed as hemophagocytic lymphohistiocytosis which is characterized by fever, lymphadenopathy, hepatosplenomegaly, deranged liver enzymes, increased inflammatory markers such as ferritin, pancytopenia, bleeding and hemophagocytosis resulting in multi-organ dysfunction and eventual death if left untreated.[5,6] CHS still remains a rare disease with its characteristic findings in terms of presentation and laboratory parameters. We herein present a case of a female child who presented to us in advanced phase of the disease.

CASE PRESENTATION

A 6-years-old female patient, product of consanguineous marriage, was referred to our institute from another tertiary care center with complains of fever, cough, oral ulcers and abdominal distension for 2 months. There is history of recurrent tonsillitis as well for the last 2 years. The patient had a recent history of positive blood culture for Acinetobacter. The child also had a positive history of photosensitivity. On physical examination, the patient was febrile, thin and lean and had blonde hair with depigmented skin, as can be seen in Figure 1. The child was also having pallor, had cushingoid facies with generalized lymphadenopathy. The systemic examination revealed gross hepatosplenomegaly (liver four

fingers and spleen six fingers palpated below costal margin). The rest of the systems were unremarkable. The family history was found to be significant as an elder sibling had similar complains who had eventually succumbed to the disease at seven years of age, see Figure 2.

CBC reported pancytopenia. The peripheral smear showed giant azurophilic intra-cytoplasmic granules observed in neutrophils and lymphocytes, as can be seen in Figure 3A-3E. Bone marrow examination done for workup of cytopenias revealed bone marrow aspirate with giant azurophilic granules observed in all stages of myeloid maturation, monocytes as well as in lymphocytes. Occasional histiocytes with hemophagocytosis were also noted, as illustrated in Figure 4. The bone marrow trephine showed increased histiocytes which exhibited hemophagocytic activity. Other laboratory examination of the patient revealed hyperferritinemia (13912.5 ng/ml), hypertriglyceridemia (441 mg/dl), hypofibrinogenemia (90 mg/dl) and hyponatremia (125mEq/L). Abdominal ultrasound revealed hepatosplenomegaly.

Based on the clinical presentation, blood, bone marrow and other laboratory findings, the case was diagnosed as Chediak-Higashi syndrome (presence of blonde hair, hypopigmentation, recurrent infections and giant azurophilic granules in the leukocytes) in accelerated phase namely hemophagocytic lymphohistiocytosis (HLH).

The patient was treated with Etoposide (150 mg/m2) and corticosteroids (10 mg/m2) as per the HLH protocol 2004.[7] Although the protocol mentioned cyclosporin A and methotrexate (intrathecal administration) as part of the treatment, both drugs were not given due to increased incidence of toxic events and absence of neurological symptoms respectively. CSF examination done on day two of the treatment revealed lymphocytic pleocytosis. The patient was transfused with 2 units PRBCs on day four of chemotherapy for anaemia and her hyponatremia was corrected by infusion of hypertonic saline. She developed febrile neutropenia on day 14 of the treatment along with oral mucositis for which she was treated accordingly. The patient was COVID positive (via PCR) at the baseline and remained positive for a period of 24 days as a result of which she remained admitted in the COVID unit of our institute. During treatment, the patient suddenly became tachypneic for which she was kept on oxygen support provided via nasal prongs. On day 29 of chemotherapy, her blood culture reported growth of Acinetobacter which was treated with appropriate antibiotics. In total, patient received eight doses of Etoposide and showed clinical improvement which was also supported by her laboratory findings, as displayed in Figure-5 and 6. The patient was also referred for an immunologist review and counselled about the definitive treatment of the disease i.e. hematopoietic bone marrow transplantation (HSCT). However, the patient expired shortly after discharge due to sepsis.

DISCUSSION

The rarity of the Chediak-Higashi syndrome (CHS) has been proven in literature. A Japanese national survey reported the presence of the disease in only fifteen patients in a time period of 11 years which makes its incidence to be one to two patients annually.[8]

In CHS patients, age of onset has been reported to be approximately six years which was also the age of our patient. Moreover, patients usually expire within the first decade of life as was also observed in the present case in which the sibling of the patient expired at the age of seven years. Studies have reported the persistence and an increase in the severity of neurological symptoms in cases where patients survive into adolescence and adulthood.[9] The effect on the peripheral and central nervous system have been reported to result in peripheral neuropathy, ataxia, tremors and other gait disorders.[10–12]

The main symptoms of CHS are known to extend over a wide range. The presence of occulocutaneous albinism is due to aberrant melanosome fusion with melanocytes. The recurrent attacks of infections are attributed to the pathognomonic sign, i.e., giant azurophilic granules in neutrophils, lymphocytes and monocytes, which are dysfunctional in nature as they are incapable of release of appropriate granules in response to the bacterial or viral infections.[10,13] The infections are mostly pyogenic in nature which usually involve the respiratory system and/or skin as they are more susceptible to the opportunistic infections with commensal organisms with Staphylococcus aureus and Streptococcus as the most common causative organisms.[10,13] A considerably lower incidence of fungal and viral infections have been reported so far.[14] The defects in the cytotoxic CD8 positive T-lymphocytes, natural killer cells, granulocytic chemotactic and bactericidal ability make the patients more susceptible to repeated infectious attacks.[15]

Approximately 85% of the CHS patients have the tendency to advance into the accelerated phase and develop hemophagocytic lymphohistiocytosis (HLH). As per the guidelines

of Histiocytic Society published in 2004[7], it is diagnosed either by the presence of mutation in the LYST gene established through genetic analysis or the presence of atleast 5 features out of the following 8; 1) recurrent episodes of fever; 2) jaundice; 3) lymphadenopathy; 4) visceromegaly; 5) cytopenias of at least two cell lineages; 6) coagulation abnormalities; 7) reduced or absent NK-cell activity; 8) Increased CD25 levels; 9) elevated haemophagocytic activity in bone marrow or other tissues; 10) deranged laboratory markers such as hyperferrtinemia, hypertriglyceridemia and/or hypofibrinogenemia.[16] This advancement can be observed over a wide range of age spanning from the first year to second decade of life. The patients with accelerated phase of the disease are known to have a poor prognosis as the complications due to HLH can result in mortality.[14] The diagnosis in the current case was confirmed by the presence of fever, splenomegaly, hypofibrinogenemia, hyperferritinemia, hyperlipidaemia, anaemia, thrombocytopaenia, and haemophagocytosis.

The differential diagnosis includes other genetic disorders presenting with oculocutaneous albinism like Griscelli syndrome and Hermansky-Pudlak syndrome, however they lack the giant granules as seen in Chediak Higashi Syndrome. Presence of similar giant granules resembling those seen in CHS may be seen in acute and chronic myeloid leukemia, also referred as pseudo-CHS anomaly.[17] The other diseases in differential diagnosis are Prader Willi and Angelman associated with hypopigmentation, but without ophthalmic albinism.

The evaluation of the clinical and laboratory findings of CHS patients by Roy *et al.*[18] and Farhoudi *et al.*[19] reported oculocutaneous albinism, blonde hair and repeated infections with advancement into accelerated phase observed in both studies. Our patient also presented in the accelerated phase. In a study by Nagai *et al.*[8] conducted in a cohort of fifteen patients, besides the development of HLH in 33% patients, one patient was reported to have a disease transformation into lymphoma. Lymphoma has been reported to be one of the most common associated malignancies with the accelerated form of the disease.[20]

The gold standard treatment for CHS remains hematopoietic stem cell transplantation (HSCT).[14] However, if the presentation occurs in accelerated phase, then the patient is treated with the protocol that is same as that given to patients with familial hemophagocytic lymphohistiocytosis, comprising of combination of etoposide, dexamethasone and cyclosporine A.[7] Once the patient enters the remission phase, which usually occurs in three-fourth of the patients, the immediate step is HSCT. The HSCT has however, failed to stop the progression of the neurological deficits despite a visible improvement in the haematological parameters.[10,13] Our patient had received eight doses of etoposide but without cyclosporine A due to the reported toxic events and was observed to be in the remission phase. She eventually expired after discharge due to infection related causes.

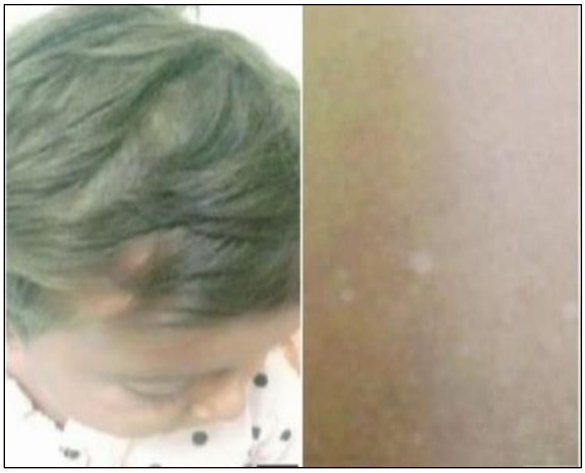

Figure-1

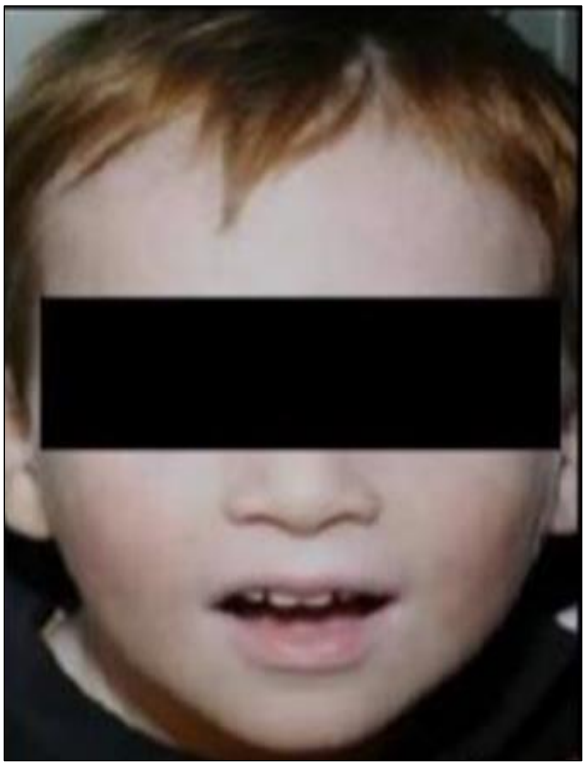

Figure-2

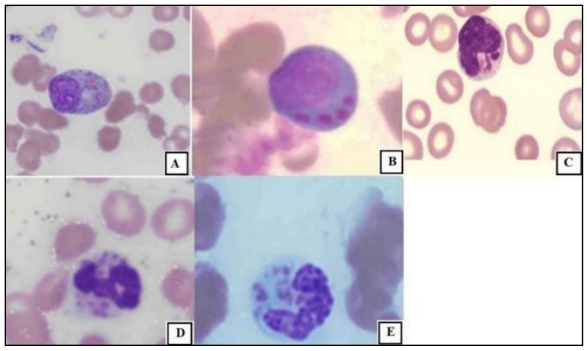

Figure-3

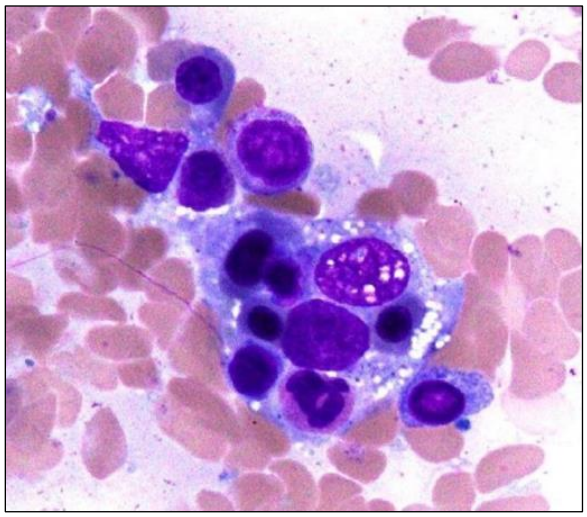

Figure-4:

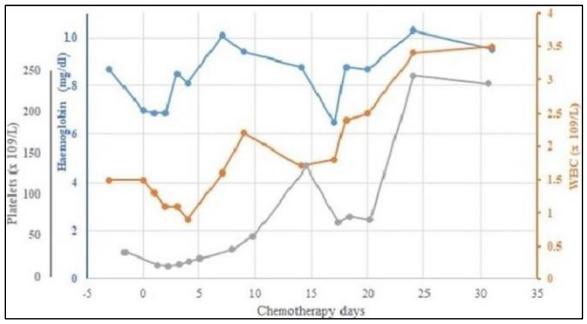

Figure-5

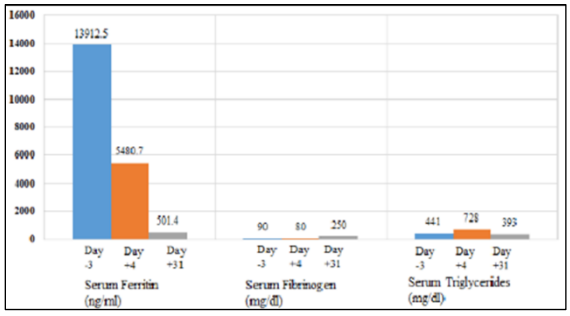

Figure-6

CONCLUSION

Chediak Higashi syndrome, a rare disease, has clinical presentation and laboratory findings that spans over a large spectrum and carry adverse prognosis, if the patient presents in the accelerated phase. HSCT remains as the only curative treatment for haematological and immunological disorders. There is a strong need to strive for early diagnosis, which is based on specific clinical and examination findings as well as laboratory parameters, resulting in transplantation at an early stage of the disease and younger age of the patient prior to the advancement of the disease into the accelerated phase.

Declarations:

Informed consent: taken from the patient's parents and saved. Consent for publication: taken from the patient's parents and saved. All authors also approve for submission and publication of the manuscript. Competing interests/conflict of interest: none to declare. Funding disclosure: none to declare.

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