

Case Report

Clinicopathological aspects of Chediak-Higashi syndrome in the accelerated phase

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ABSTRACT

This report describes clinical and laboratory features of a case of Chediak-Higashi syndrome that presented in the accelerated phase of the disorder. This female infant presented with a fever, marked neutropenia, large cytoplasmic granules in leukocytes and a constellation of features that suggested a virus-associated hemophagocytic syndrome. The clinical course was marked by limited response to the therapeutic agents that included ascorbate, cytotoxic agents and granulocyte colony-stimulating factor.

Keywords: Chediak-Higashi syndrome, accelerated phase, virus-associated hemophagocytic syndrome.

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Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized clinically by recurrent infections, neutropenia, partial oculocutaneous albinism, and bleeding diatheses with variable neuropathy.^{1,2} The pathogenesis is probably due to defects in vesicle formation, fusion and mobilisation.¹ This results in formation of pathognomonic giant cytoplasmic granules in various cells, typically seen in blood and marrow leukocytes, and skin melanocytes.^{1,3} Chediak-Higashi syndrome is usually a disorder of infancy and childhood. Most cases experience an accelerated phase with overwhelming infection leading to a high incidence of mortality by the first decade.^{1,2} The disease has also been reported in adults with a relatively milder expression in some cases.^{4,5} The human lysosomal trafficking regulator (LYST) gene, which maps to chromosome 1q42, has been identified as the homologue of the beige LYST gene, present in the animal model of the disease: beige mice. In a recent study, heterogeneous mutations in LYST all of which

lead to a truncated LYST-protein, have been identified in CHS.⁶ Molecular heterogeneity may explain atypical clinical presentations of the disease. Despite current advances in our understanding of the disorder, therapy for patients in the accelerated phase remains problematic. The present report, highlights certain diagnostic and treatment related aspects of this unusual condition.

Case Report. A 2-month-old Syrian baby, presented with fever, poor feeding and excessive crying. She had experienced a full term normal delivery at the hospital with a birth-weight of 2.575kg and was the product of a consanguineous marriage between first cousins. There were no neonatal problems and she was on breast and formula feeds. At the time of presentation, the baby showed normal for age development, but was febrile and markedly pale. She was reported to be noticeably fairer than other family members. Moderate

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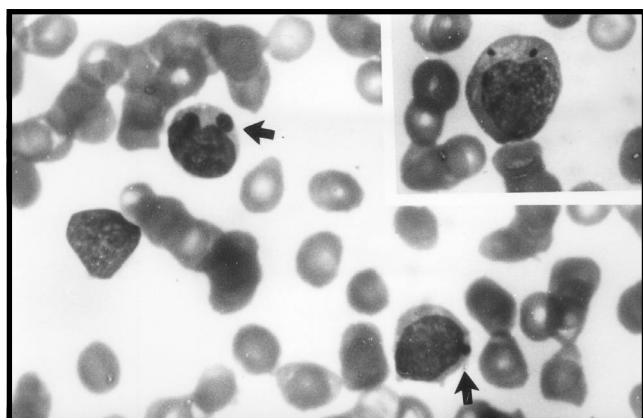


Figure 1 - Lymphocytes with abnormally large cytoplasmic granules in Chediak-Higashi syndrome. Inset shows a lymphocyte with 2 cytoplasmic inclusions. Wright stain, magnification x 1000.

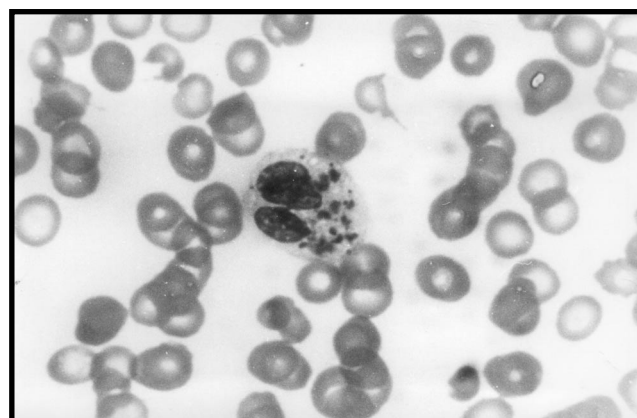


Figure 2 - Giant cytoplasmic granules in a polymorphonuclear neutrophil. Wright stain, magnification x 1000.

hepatosplenomegaly was observed. There was no jaundice or lymphadenopathy. Skiagram of the chest was normal. Initial laboratory investigations revealed lymphocytosis with neutropenia and sterile blood, stool and urine cultures. Peripheral blood lymphocytes showed cytoplasmic inclusions suggesting CHS. She was then referred to Salmaniya Medical Complex for further management.

Physical examination confirmed the previous observations. In addition, light-colored hair with a silvery sheen, photophobia and severe oral candidiasis were observed. Examination of the eyes showed bilateral transilluminant iris, orange-red reflex and retinal hypopigmentation. Laboratory tests revealed albumin 27 g/l, globulin 37 g/l, total bilirubin 23 $\mu\text{mol/l}$ (direct 14 $\mu\text{mol/l}$), alanine transferase (ALT) 181 u/l, γ -glutamyl transferase (GGT) 224 u/l, alkaline phosphatase 338 u/l, hyperlipidemia (cholesterol 6.3 mmol/l, triglyceride 8.4 mmol/l). Serological tests showed: cytomegalovirus antibody Immunoglobulin (Ig) G (+), IgM (-); Epstein-Barr virus antibodies to early antigen (EA): IgG weak (+), IgM (-) and Epstein-Barr virus nuclear antigen (EBNA): IgG, strongly positive. All bacteriological cultures were negative. Blood counts showed hemoglobin 9.4 g/dl, hematocrit 0.28 l/l, platelets $2 \times 10^9/l$, leukocytes $8.7 \times 10^9/l$ and a differential of polymorphs 2%, lymphocytes 90% with 21% atypical lymphocytes, and monocytes 8%. Lymphocytes showed prominent cytoplasmic inclusions, which were usually single, round or elliptical and azurophilic structures (**Figure 1**). Rare lymphocytes showed 2 or 3 smaller inclusions. Polymorphs also showed the abnormally large inclusion-like granules characteristic of CHS (**Figure 2**). These granules showed positive reaction for myeloperoxidase.

The bone marrow aspirate showed poor cellularity. The majority of cells were lymphomononuclears and

macrophages, some of which, showed hemophagocytosis. The marrow trephine biopsy also showed markedly reduced myeloid and erythroid cells and few megakaryocytes. Marked proliferation of macrophages and increased numbers of lymphocytes were observed. These features suggested a hemophagocytic syndrome accompanying the accelerated phase of CHS. During the next few days hemoglobin and leukocyte counts showed progressive reduction. Treatment with antibiotics and amphotericin B along with packed red cells and platelet support produced little improvement. She was then administered granulocyte colony-stimulating factor (G-CSF) 12 $\mu\text{g/kg}$ daily, along with ascorbic acid 20mg/kg, methylprednisolone 10 mg/kg and acyclovir 15 mg/kg. After 6 days of therapy, her clinical condition improved, she became febrile and total leukocyte count reached normal levels although neutropenia persisted. This phase lasted a week, following which fever recurred.

As further administration of G-CSF produced little improvement, it was stopped after a total duration of 2 weeks. Combination chemotherapy consisting of vincristine 0.24 mg (day one) and cyclophosphamide 95 mg (days one and 2) administered on alternate weeks and prednisolone 2 mg/kg daily was tried. Two cycles of this combination produced a temporary clinical remission with normalized blood counts except for persistent neutropenia. After the 3rd cycle the patient was discharged on request with instruction to return for the 4th chemotherapy cycle. A week later the baby was readmitted with high spiking fever. She was found to have urinary tract infection with enterobacter and gastroenteritis. Despite supportive therapy the clinical and lab parameters took a downturn. Preterminally, she developed a bleeding diathesis with epistaxis, and blood culture was positive for staphylococcus

epidermidis resistant to penicillin. The patient died a few days later aged 5 months.

Discussion. Cases of CHS usually present in infancy or childhood with recurrent bacterial infections. Progression to the accelerated phase generally occurs by the first or 2nd decade of life and is probably due to a viral infection.⁷ The present case was unique due to the extremely early age of presentation in the accelerated phase. The other characteristic features of CHS, partial oculocutaneous albinism and giant inclusion like granules in leukocytes were present. Since neutropenia was profound, giant granules in the lymphocytes provided the first clue to the diagnosis.

The clinicopathological features of the accelerated phase of CHS as seen in this case: an acute febrile illness, hepatosplenomegaly, pancytopenia with marked lymphohistiocytic infiltration of the marrow and resistance to therapy, are similar to those described by Rubin et al.⁸ These occur in the absence of bacterial sepsis,⁹ may be related to viral infection and simulates the virus-associated hemophagocytic syndrome (VAHS).^{8,10} Lack of natural-killer (NK) cells in CHS⁹ may predispose these cases to viral infection. In the present case, in the absence of IgM antibodies, the role of cytomegalovirus or Epstein-Barr virus or both, could not be proved as the IgG antibodies may have been passively derived from the mother. However, the possibility of a congenital viral infection cannot be excluded. The other features of typical VAHS were present: fever, hepatosplenomegaly, cytopenias, hemophagocytosis, abnormal liver-function tests and hyperlipidemia.¹¹ Neurological abnormalities are variably seen in CHS¹ and were not present in this case, possibly due to the extremely early presentation.

Therapy of CHS in the accelerated phase remains an unresolved issue and the outlook for these cases remains dismal. Antibiotics, antifungal and antiviral agents were used in this case without benefit. Ascorbate administration has resulted in improvement in a minority of cases,¹² but was not successful in this case. There have been few trials with G-CSF in these cases and we did not find any reference related to the use of this agent in the accelerated phase. Baldus et al reported normalization of leukocyte counts following G-CSF treatment of a 27-year-old lady with CHS.⁴ Though infection episodes appeared to be controlled, neurological manifestations in their case deteriorated. In our case, there was a brief and partial response of clinical symptoms and leukocyte counts to G-CSF. Immunosuppressive therapy with glucocorticoids or vincristine or both, has been used in the past, but without any clear-cut benefit.^{2,8} The response in this case too was of short duration. Bone marrow

transplantation, which offers the only possibility of cure, is ideally performed before the onset of the accelerated phase.⁷ Consanguinity, documented in this case, is not uncommonly associated in the families of CHS.⁷ Screening of the parents showed normal blood counts. Interestingly, examination of the father's blood smear showed large cytoplasmic granules in some lymphocytes.

In conclusion, the accelerated phase of CHS is probably caused by an overwhelming viral infection that leads to clinicopathological features of a typical hemophagocytic syndrome. The use of agents such as G-CSF to counteract neutropenia and cytotoxic chemotherapy appear to be of limited benefit in this condition.

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