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## WHAT'S YOUR DIAGNOSIS?

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### History

A five-month-old male infant, a product of a consanguineous marriage, presented with recurrent fever from the age of two weeks. He had developed abdominal distention and hepatosplenomegaly at two months of age.

On examination, the patient looked pale with grayish hair. The color of his skin was lighter than that of other family members. He had marked hepatosplenomegaly. Laboratory investigations were as follows: WBC  $2.1 \times 10^9/L$ ; Hgb 101 g/L; platelets  $4 \times 10^9/L$  (after packed

red blood cell and platelet transfusions); renal and hepatic functions were normal; serum ferritin was 2100  $\mu\text{g/L}$  (normal 22-322  $\mu\text{g/L}$ ); triglyceride was 6.3 mmol/L (normal 0.4-1.8 mmol/L); and cholesterol 2.8 mmol/L (normal 3.0-5.2 mmol/L).

1. What does the blood smear show?
2. What is the diagnosis?
3. What would you expect to see on fundoscopic examination?

## ANSWER TO WHAT'S YOUR DIAGNOSIS? (PREVIOUS PAGE)

**Diagnosis:** Chediak-Higashi syndrome (CHS).

**The differential diagnosis:** The differential diagnosis includes other genetic forms of partial albinism (e.g., Prader-Willi/Angelman syndromes, and Hermansky-Pudak syndrome), which can easily be differentiated by the absence of the giant granules in the granulocytes.<sup>1</sup> Both acute and chronic myelogenous leukemias may have giant cytoplasmic granules (pseudo-Chediak-Higashi granules) in blast cells.<sup>2</sup> Familial hemophagocytic lymphohistiocytosis, and the infection- and malignancy-associated hemophagocytic syndromes may all have clinical, laboratory, and pathologic findings similar to those observed in CHS.<sup>3-5</sup> X-linked lymphoproliferative disease may have hepatosplenomegaly and pancytopenia resembling the accelerated phase of CHS.<sup>5</sup>

**Discussion:** Chediak-Higashi syndrome (CHS) is a rare autosomal recessive syndrome that consists of increased susceptibility to bacterial infections, partial oculocutaneous albinism, and the presence of giant peroxidase-positive lysosomal granules in leukocytes and other granule-containing cells (including platelets, renal tubular cells, pneumocytes, gastric cells, hepatocytes, neuronal cells, and fibroblasts). Melanocytes contain giant melanosomes. The genetic defect at the molecular level remains unknown.<sup>3</sup>

Geographically, CHS has been reported to occur over a wide area with no racial predilection. It usually presents during the first decade, with a mean age at diagnosis of 5.85 years. The male to female ratio is 1:0.87. Of the reported cases, 48% were from children who were products of consanguineous marriages.<sup>6</sup> Most patients with CHS exhibit partial oculocutaneous albinism, which may be noticed only when compared with other family members. The hair color is usually light brown to blond, with a metallic silver-gray sheen noticeable in strong light. The skin is creamy white to slate gray and susceptible to severe sunburn. Iris pigment is present and photophobia and nystagmus may be present.<sup>1</sup> Abnormalities may include a variety of neurological symptoms, including cranial and peripheral neuropathies, progressive spinocerebellar degeneration and mental retardation.<sup>7</sup> Bleeding may occur as a result of thrombocytopenia (in the accelerated phase), platelets aggregation defect, and an increased bleeding time.<sup>6</sup>

The accelerated phase of CHS occurs during the first or second decade of life. It is characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia (due to hypersplenism), hyperferritinemia and hypertriglyceridemia (which are commonly associated with the general inflammatory condition, although the exact pathophysiological mechanism is not fully understood),<sup>5</sup> bleeding tendency, and diffuse mononuclear cell infiltrates of the reticuloendothelial system, with a picture of benign hemophagocytic lymphohistiocytosis.<sup>4</sup> The precise mechanisms involved are unidentified, although viral agents and/or immunologic mechanisms have been postulated to play a role. The outcome is uniformly fatal<sup>6</sup> unless bone marrow transplantation is performed.<sup>8</sup>

A variety of immune dysfunction has been described in patients with CHS. Neutropenia (moderate), and functional deficits of neutrophils (chemotaxis is markedly depressed, degranulation is delayed and incomplete, marked deficiency of antimicrobial proteins, such as cathepsin G, and decreased expression of Mo1 [CD11b/CD18]), monocytes (with decreased chemotaxis), and natural killer (NK) cells (with abnormal functions), have all been noted.<sup>2</sup>

The diagnosis of CHS can be ascertained by identifying characteristic phenotypic features, in addition to large cytoplasmic inclusions in all granular cells. Prenatal diagnosis can be made by finding giant granules in fetal blood neutrophils.<sup>2</sup> There is no reliable way of diagnosing the carrier state in CHS.

During the stable phase of CHS, treatment involves proper management of infection and supportive therapy. Ascorbic acid has been shown to improve *in vitro* phagocytosis and the clinical status in some studies, but not in others.<sup>3</sup>

The treatment of the accelerated phase is difficult. Corticosteroid, vincristine, and cyclophosphamide may slow the progression but are not able to arrest the disease.<sup>6</sup> Splenectomy may improve the clinical and hematological findings significantly.<sup>9</sup> Bone marrow transplantation from HLA-identical related donor is a curative treatment even when the accelerated phase has occurred, but the ocular and cutaneous albinism will not be corrected.<sup>8</sup>

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### References

1. King RA, Hearing VJ, et al. Albinism. In: Scriver CR, Beaudet AL, et al. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill, 1995:4353-92.
2. Curnutte JT. Disorders of granulocyte function and granulopoiesis. In: Nathan DG, Oski FA, editors. Hematology of infancy and childhood. Mexico: WB Saunders Company, 1993:904-77.
3. Barak Y, Nir E. Chediak-Higashi syndrome. Am J Pediatr Hematol Oncol 1987;9:42-55.
4. Rubin CM, Burke BA, McKenna RW, McClain KL, White JG, Nesbit ME Jr, Filipovich AH. The accelerated phase of Chediak-Higashi syndrome: an expression of the virus-associated hemophagocytic syndrome? Cancer 1985;56:524-30.
5. Henter JI, Arico M, Elinder G, Imashuku S, Janka G. Familial hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:417-33.
6. Blume RS, Wolf SM. The Chediak-Higashi syndrome: studies in four patients and review of the literature. Medicine 1972;51:247-80.
7. Sheramata W, Kott HS, Cyr DP. The Chediak-Higashi-Steinbrinck syndrome. Arch Neurol 1971;25:289-94.
8. Haddad E, Le Deist F, Blanche S, Benkerrou M, Rorhlich P, Vilmer E, et al. Treatment of Chediak-Higashi syndrome by allogenic bone marrow transplantation: report of 10 cases. Blood 1995;85:3328-33.
9. Harfi HA, Malik SA. Chediak-Higashi syndrome: clinical, hematological, and immunological improvement after splenectomy. Ann Allergy 1992;69:147-50.