

CASE REPORT

Chediak-Higashi syndrome: a case report

Jayarane S MBBS, MPath and Menaka N MPath, FRCPA

Haematology Unit, Department of Pathology, University of Malaya

Abstract

A 5-month-old Chinese male infant was referred to the University Hospital, Kuala Lumpur for persistent fever, generalised rash and abdominal distension. Clinically he was suspected to have haemophagocytic lymphohistiocytosis. Haematological findings including the presence of several abnormal giant granules in neutrophils and single large azurophilic granules in many lymphocytes and monocytes in the peripheral blood established the diagnosis of Chediak-Higashi syndrome. The patient responded to allogeneic bone marrow transplant. This paper discusses the characteristic features, clinical course and management of this rare disorder. We suggest that peripheral blood film examination for the abnormal giant granules in granulocytes is an essential investigation in all young children with frequent recurrent infections or who are suspected to have virus-associated haemophagocytic syndrome or familial haemophagocytic lymphohistiocytosis.

Key words: Chediak-Higashi syndrome, haemophagocytosis, accelerated phase.

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder of human, cattle, mink, mouse and other mammalian species.^{1,2} In humans it is characterized clinically by frequent pyogenic infections (usually skin, respiratory tract and mucous membrane), partial oculocutaneous albinism, nystagmus and photophobia. However the definitive diagnosis can only be made when the pathognomonic abnormal large granules are noted in the leucocytes and other granule-containing cells.² The susceptibility to recurrent infections may be explained by the defects noted in T-cell cytotoxicity and natural killer (NK) cell function as well as in chemotaxis^{3,4} and bactericidal activity⁵ of granulocytes and monocytes. CHS is now recognized as a disorder of generalized cellular dysfunction characterized by increased fusion of the cytoplasmic granules.¹

Other features of the disease include neutropenia, thrombocytopenia, recurrent unexplained fever and peripheral neuropathy.^{2,6} Children affected by CHS are at great risk of death from infection at any age, but they are particularly susceptible to infection during the accelerated phase which may occur in the first or second decade of life. This phase is characterized

by a diffuse lymphohistiocytic infiltration of the liver, spleen, lymph nodes, bone marrow and central nervous system, leading to persistent fever, hepatosplenomegaly, lymphadenopathy, abnormal liver function tests, pancytopenia, coagulation disorder, ataxia and seizures among others.⁷ Similar manifestations are noted in familial haemophagocytic lymphohistiocytosis⁸ and virus-associated haemophagocytic syndrome.^{9,10}

Modern antibiotics have reduced, but not fully eliminated death from bacterial infections. The only viable therapeutic intervention is an allogeneic bone marrow transplant¹¹ which by replacing the defective haemopoietic system helps to eliminate the susceptibility to bacterial infection and the progression of the disorder to the accelerated phase.

CASE REPORT

A 5-month-old Chinese male infant was referred to our hospital for persistent fever, generalised rash of one month duration and abdominal distension. The only past history of relevance was repeated treatment for upper respiratory tract infection and febrile episodes elsewhere. There was no history of consanguineous marriage. There are two unaffected older siblings; two

Address for correspondence and reprint requests: Dr. S.Jayarane, Haematology Unit, Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Email: jayarane@um.edu.my

girls aged 9 and 2 years.

On examination the infant appeared well nourished, was fair skinned (much lighter in colour than his other family members) with dark gray hair showing a silvery tint. He was noted to have bilateral horizontal nystagmus with a convergent squint. Generalised maculopapular rash was observed which resolved spontaneously during his hospital stay. There was no significant lymphadenopathy, however, hepatomegaly (7 cm below the right subcostal margin) and splenomegaly (10 cm below the left subcostal margin) were noted. The cardiovascular, respiratory and nervous systems were normal.

The relevant haematological findings on admission were a moderate anaemia (haemoglobin 84.8 g/L), mild leucopenia (white blood cell count $4.4 \times 10^9/L$), and a significant thrombocytopenia (platelet count $10 \times 10^9/L$). The coagulation screen showed a prolonged activated partial thromboplastin time of 47 seconds (27 – 38 seconds) and a thrombin time of 25 seconds (16 – 19 seconds). Other significant laboratory findings were a raised serum triglyceride level of 6.3 mmol/L, a grossly increased serum ferritin of 3,232.0 $\mu g/L$ and a low plasma fibrinogen of 1.9 g/L. Neutrophil phagocytic function was found to be low.

The striking feature in the peripheral blood film was the presence of several abnormal giant granules in the neutrophils (Figure 1) and single large azurophilic granules in many lymphocytes and in a few monocytes (Figure 2).

Bone marrow aspirate revealed normocellularity and adequate haemopoietic cells. Similar giant granules were noted in the granulocytes and in many of the intermediate precursors of the granulocytic series. These granules were strongly myeloperoxidase positive (Figure 3). Some mononuclear cells had vacuoles in the cytoplasm (Figure 4). Admixed amongst the haemopoietic cells were some lymphocytes and histiocytes, a few of which showed haemophagocytosis.

Serology for Epstein Barr virus was positive for IgG but not for IgM. Parainfluenza virus 3 was isolated from tracheal secretions. Serology for Toxoplasma, Rubella, Cytomegalovirus, Dengue and Herpes was negative. Stool examination too was negative for rota virus, Salmonella and Shigella. Blood cultures proved to be negative.

Clinical course

During his hospital stay, the patient had one episode of croup which was attributed to the

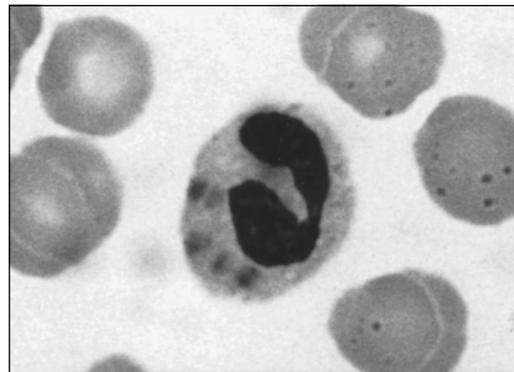


FIG. 1: Neutrophil with abnormal giant granules in the cytoplasm. MGG x 40

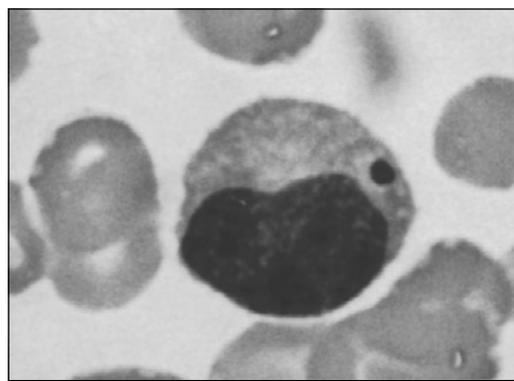


FIG. 2: Monocyte with a single large granule in cytoplasm. MGG x 40

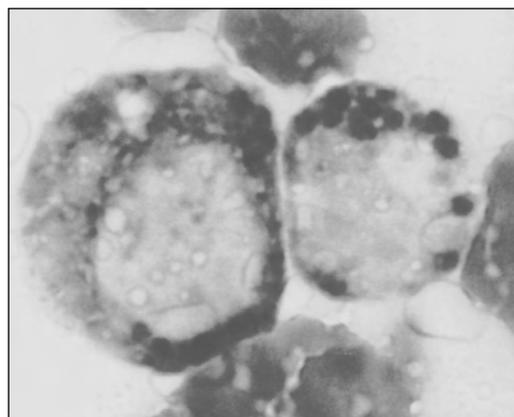


FIG. 3: Myelocytes with abnormal granules showing strong myeloperoxidase positivity. Peroxidase stain x 100

positive culture of Parainfluenza virus 3 from his tracheal secretions. His persistent fever was treated with various antibiotics. Since the patient was diagnosed to be in the accelerated phase at presentation, he was given dexamethasone and

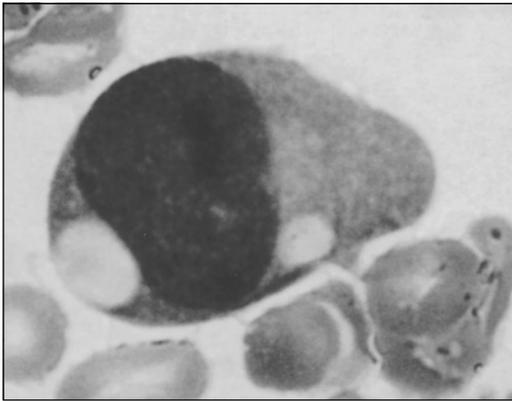


FIG. 4: Monocyte showing large vacuoles in the cytoplasm. MGG x 40

VP16 which caused only a partial shrinkage in the size of the liver and spleen. Subsequently an allogeneic bone marrow transplant was performed as a matched sibling donor was available. His post-transplant recovery was uneventful.

The peripheral blood smear two weeks post-transplant did not show the characteristic giant granules in the neutrophils. A sixty days post transplant bone marrow aspirate too did not show the typical giant granules in the myeloid cells. However it took more than six months for the triglycerides and fibrinogen levels to become normal. Serum ferritin levels were not repeated after bone marrow transplantation.

DISCUSSION

Chediak Higashi syndrome (CHS) is a rare autosomal recessive disorder of lysosomal granule-containing cells with clinical features prominently involving the haematologic and neurologic systems. Majority of the patients enter an accelerated phase characterized by lymphohistiocytic infiltration in many organs leading to haemophagocytosis, pancytopenia and coagulation disorders. The accelerated phase may occur shortly after birth or several years later which, left untreated, proves to be invariably fatal. The use of etoposide (VP-16) combined with steroids and intrathecal methotrexate though resulted in remissions, such remissions were transient only. Subsequent relapses have been noted to become increasingly resistant to conventional therapy, with death occurring due to haemorrhage and/or infection.¹¹ Those patients who survive into young adulthood, develop a progressive sensorimotor peripheral neuropathy which leads them to become wheel-

chair bound and they eventually die of infective complications in their thirties.¹² Uyama et al after extensive review, have suggested that there may be two distinct clinical forms: (i) the well recognized childhood type with the characteristic marked susceptibility to infection, leading to early death from overwhelming infection or an accelerated lymphohistiocytic proliferative phase, and (ii) the rarer adult form where neurological defects mimicking parkinsonism, dementia, or spinocerebellar degeneration and peripheral neuropathy dominates with a lack of severe susceptibility to infection.¹³ Sung et al's autopsy findings lend some credence to this school of thought.¹⁴ They have shown three types of pathological changes, (i) lymphohistiocytic cellular infiltrates in many organs which appeared to occur late in the course of the disease since it was observed in the older patients only, (ii) degenerative changes in the axons and myelin sheaths, the intensity of which paralleled the severity of infiltrates, and (iii) abnormal intracytoplasmic inclusions in a variety of neurons including nerve cells, astrocytes, satellite cells of the dorsal spinal ganglia and schwann cells; interestingly these were found in all ages (both young and older individuals) and were thought to be altered lipofuscin granules, since their presence did not seem to interfere with the function or survival of the cells.

Typically patients with CHS present at an early age with recurrent bacterial infections, especially with *Staphylococcus aureus* and beta haemolytic streptococcus, partial ocular and cutaneous albinism, easy bruising due to platelet dysfunction and severe periodontal disease.^{15,16} The diagnosis is made by observing the characteristic defective giant granules in the leucocytes in the peripheral blood film. The susceptibility to infections may be explained by defects observed in T-cell cytotoxicity and the NK cell activity as well as in impaired chemotaxis and bactericidal capacity of the granulocytes and monocytes.¹⁷

In normal neutrophils, two distinct types of granules, primary (azurophilic) and secondary (specific) are present. The azurophilic granule, formed in promyelocytes is a typical lysosome containing acid hydrolases whereas the specific granule formed in myelocytes differs from the typical lysosome in that it contains enzymes which act best in alkaline pH. Since the latter is active in phagocytosis as well, it too can be considered as a lysosome. Myeloperoxidase is restricted to the azurophilic granules. Lysosomes

are membrane-limited organelles that contain a variety of acid hydrolases. These structures are present in most cells and their function is related to intracellular digestion which includes the hydrolysis of extracellular material and under certain circumstances, hydrolysis of intracellular contents. Primary lysosomes may fuse with cytoplasmic vacuoles or phagosomes, forming secondary lysosomes that contain partially or completely digested materials.¹⁸

In Chediak-Higashi syndrome, the large granules within the neutrophils result from abnormal fusion of primary (azurophilic) granules with secondary (specific) granules.^{19,20} The fusion of the giant granules with phagosomes is delayed, contributing to the impaired immunity.^{5,15} Almost all cells of a CHS patient show some aspect of the abnormal and dysmorphic lysosomes, storage granules, or related vesicular structures. For example, the melanosomes of melanocytes are oversized and delivery to the keratinocytes in the hair follicles is partly impaired. When examined microscopically, the hair shafts have a mixture of giant melanosomes alternating with small regions devoid of these pigment granules. This leads to the macroscopic impression of hair that is lighter than expected from parental colouration and has an irregular grayish-silver particulate sheen. The same defect in melanocytes results in partial ocular albinism with light sensitivity. There may be reduced dense bodies in platelets, which may explain the easy bruising and prolonged bleeding time found in some CHS patients.¹²

Treatment options for CHS patients are limited. Previously, the mainstay of treatment has been mainly symptomatic with antibiotics and Vitamin C²¹ for bacterial infections and blood product replacement for bleeding complications. Subsequently when accelerated phase occurs, etoposide (VP-16), steroids and intrathecal methotrexate have been tried. Only recently has allogeneic bone marrow transplantation become a viable option for these patients. However, though transplantation has been shown to correct the haematologic and immunologic complications of CHS thus halting the inevitable grim prognosis, it has not been shown to reverse or prevent further neurological deficit.¹² This is probably because once the degenerative changes in the axons and myelin sheaths occur in the course of the disease, it cannot be reversed, they being permanent cells with no regenerative capacity.¹⁴

Since the diagnosis of CHS depends on the recognition of the characteristic abnormal giant granules present in the granulocytes in a peripheral blood film, we suggest that this is an essential investigation in all young children who are seen for frequent recurrent infections or who are suspected to have virus-associated haemophagocytic syndrome or familial haemophagocytic lymphohistiocytosis. It is important to offer allogeneic bone marrow transplant at an early stage of the disease since the prognosis is uniformly fatal once the disease progresses to the accelerated phase.

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