

Chediak-Higashi syndrome: case report in afro-descendant individual

Síndrome de Chédiak-Higashi: relato de caso em indivíduo afrodescendente

Judde Lacerda Andrade Carlos¹; Márcio Vasconcelos Oliveira²; Claudio Lima Souza²

ABSTRACT

This is a Chediak-Higashi Syndrome (CHS) case report in afro-descendant individual, male, 3 months old, born from consanguineous union. On admission he had fever for a month, unresolved pneumonia, and hepatosplenomegaly. He evolved to bacterial sepsis, septic shock, and death. CHS presents quantitative and morphological and hematological changes. Abnormal leukocyte inclusions are the pathognomonic finding of the disease; its recognition and differentiation from other leukocyte inclusions is essential for diagnosis and institution of therapy. Early diagnosis of CHS increases the life expectancy of the individual and provides appropriate therapeutic approach for patients affected by the disease.

Key words: Chediak-Higashi syndrome; immunodeficiency; afro-descendant; diagnosis.

INTRODUCTION

Chediak-Higashi Syndrome (CHS) is a primary immunodeficiency with autosomal recessive heritage, more common in the presence of inbreeding, and very rare in black⁽⁵⁾. CHS is the result of a series of genetic changes, and the main one is the mutation in the *LYST* gene^(3, 7), which provides irregular clustering of lysosomes, affecting hematopoietic cells, renal tubular cells, neurons, Schwann cells, melanocytes, and fibroblasts⁽²⁵⁾. This condition leads to several complications, such as prolonged and recurrent infections, due to phagocytes primary dysfunction, tendency to bleeding, progressive neurological involvement, lymphoproliferative syndrome, and oculocutaneous albinism^(7, 8, 10, 11, 24). In leukocytes, there is a formation of giant azurophilic granules, that are organized in a linear fashion, similar to rosary beads, and are pathognomonic feature of the disease^(5, 12, 18, 24). This study was performed with the family consent, by signing the Informed Consent form and approved by the Research Ethics Committee on Human Beings from the Instituto Multidisciplinar

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CASE REPORT

Male, 3 months old, afro-descendant, first-born of consanguineous marriage, was admitted to Emergency Room at General Hospital, come from smaller city agreed by *Sistema Único de Saúde* ([SUS] – Brazilian National Health System). The main complain was fever for one month. Physical examination revealed hepatomegaly and splenomegaly, 8 to 10 cm from the respective costal margins.

On admission, he was diagnosed with pulmonary infection, although he was in antimicrobial treatment, as prior medical prescription. During hospitalization, with antibiotics and supportive care, the patient had recovered infection, but remains hospitalized due to persistent neutropenia and need of investigation for diagnosis of the underlying condition. Throughout the

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1. Pharmacist.

2. PhD in Public Health and Epidemiology at Universidade Federal de Minas Gerais (UFMG); assistant professor II at Instituto Multidisciplinar em Saúde at Universidade Federal da Bahia (IMS-UFBA).

hospitalization period, patient presented neutropenia (mean $494/\text{mm}^3$) (**Figure 1**), thrombocytopenia (mean $13,477/\text{mm}^3$), and elevated C-reactive protein (CRP) (mean 54.79 mg/l), besides low prothrombin activity (international normalized ratio [INR] = 1.64), and elevated aspartate aminotransferase (AST) (mean 130.4 U/l).

Patient had increased serum levels of total bilirubin serum levels = 3.06 mg/dl and direct fraction = 2.1 mg/dl , due to infectious cholestasis and coagulopathy, and persistent thrombocytopenia, mean = $13,477/\text{mm}^3$, and reduced prothrombin activity, mean = 61.3%, (INR = 1.36), consistent with infectious cholestasis and worsening of the infectious process^(3, 17, 25).

On the fifth day of hospitalization (DOH), the CBC showed abnormal leukocytes granules in patient's peripheral blood smear, stained by Wright method (**Figure 2**). In this case report, inclusions were described as intracytoplasmic giant granules in all neutrophil-lineages, suggesting CHS investigation.

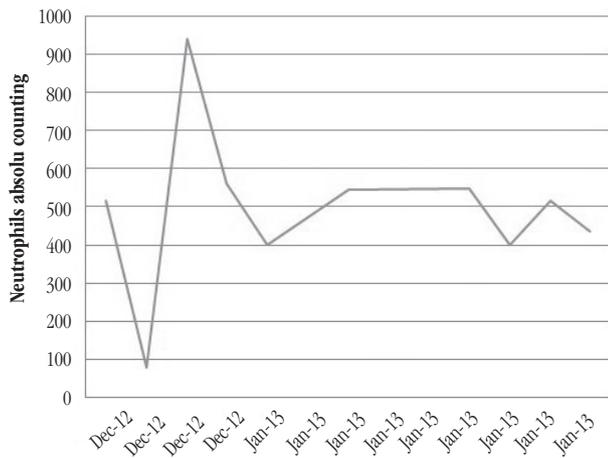


FIGURE 1 – Severe neutropenia in patient with CHS in the presence of infection
CHS: Chediak-Higashi syndrome.

On the 34th day of hospitalization, he showed fever peek, facial swelling, diarrhea, abdominal distension, and tachypnea. On the 36th day of hospitalization, he was transferred to Intensive Care Unit (ICU), where new antimicrobial therapeutic was implemented, including broad-spectrum drugs (meropenem) and measures of supportive therapy.

Two blood cultures and one catheter tip culture were performed during hospitalization. The result of first blood culture was positive, and *Staphylococcus epidermidis* was isolated, which presents high potential to produce biofilm, especially in immunocompromised patients. After establishing the treatment, new blood and catheter tip cultures were performed, and both results were negative.

On the 41st day of hospitalization, he presented another fever peek, abdominal distension, and diarrhea. And, despite the imposition of necessary support measures, there were worsening of general condition with severe tachypnea and hypotension, which culminated in cardiac arrest and death in the 45th day of hospitalization. The cause of death was reported as sepsis caused by CHS complication.

DISCUSSION

It is a rare disease, with 200 cases described in the literature⁽¹⁵⁾, and it is especially rare in black people⁽⁵⁾. During our search in the U.S. National Library of Medicine (PUBMED) baseline, in March 2014, we found seven cases of CHS diagnosis in black children. CHS diagnosis may be difficult, since characteristic clinical and laboratorial findings are not well defined, or are not properly reported by laboratorians or well interpreted by the prescribing physician.

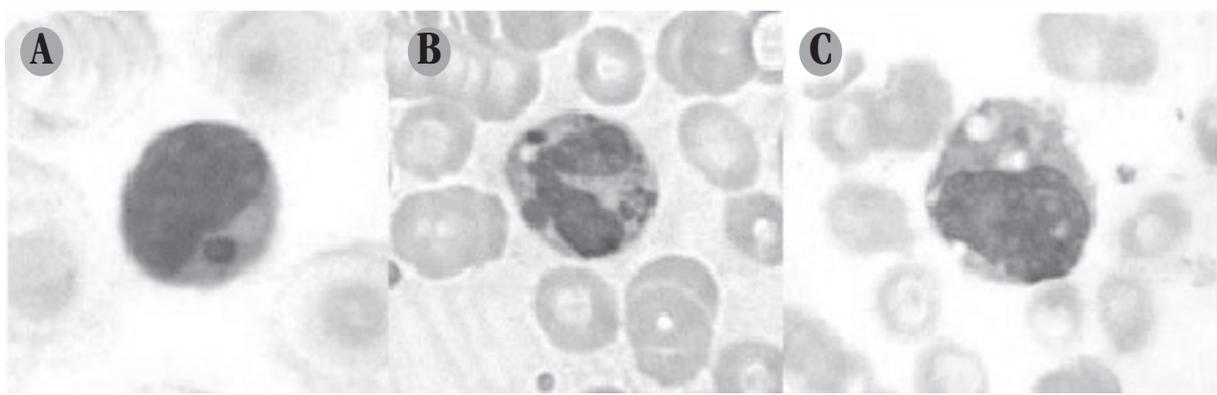


FIGURE 2 – Photomicrograph of peripheral blood smear of CHS patient
Single giant azurophilic granules in lymphocyte (2A), multiple giant azurophilic granules in neutrophil (2B) and monocyte (2C) (Wright, 100×).
CHS: Chediak-Higashi syndrome.

In general, patients with CHS seek health service due to recurrent infections in early, and the disease is diagnosed when they are about 5 years old^(1, 5). This period depends on disease presentation and severity. In this case, the clinical presentation was early identified, with pulmonary infection, not responsive to first-line antibiotics, and persistent fever. Increased susceptibility to infections comes from phagocyte primary dysfunction, which keeps its ability to phagocytosis of pathogens; but digestion is not effective due to lysosomal deficiency^(7, 8, 10, 11, 24).

Patients suffering from this disease have an average life expectancy of 10 years, if hematological symptoms of the disease are not treated^(1, 5). In case reported, the patient progressed quickly and unsatisfactorily, with recurrent infections caused by resistant microorganisms likely enough, due to his stay in the nosocomial environment. Although cultures kept negative results, patient presented persistently increased levels of CRP, indicative finding of inflammatory or infectious process, consistent with the case, considering the related immunodeficiency, that does not change the systemic inflammatory response against the pathogen, but it strongly affects phagocytic activity^(4, 10, 11, 13).

Hematological dysfunction in CHS causes important changes in CBC, such as qualitative/morphological and quantitative abnormalities^(5, 12, 18, 24). Neutropenia persistente is observed by increasing apoptosis, throughout hospitalization, evolving to febrile neutropenia. On the fifth day of hospitalization, it was observed giant azurophilic lysosomal granules in the neutrophils and other leukocytes cytoplasm^(2, 4, 10, 11).

Establishing a diagnosis, goes through a suitable description of inclusions in CBC report, so that there is an accurate investigation and diagnostic differentiation from other hypotheses, such as Hermansky-Pudlak Syndrome (HPS), and Griscelli syndrome, which exhibit symptoms similar to CHS, differing only in regards to granular leukocytes^(9, 14).

CHS lysosomal granules may be easily differentiated from typical toxic granulation of severe infectious processes (**Figure 3**), which represent benign response, helping neutrophil phagocytosis, and they are markers of infection severity⁽¹³⁾. These granules are present during the process, and cease in stimulus absence. CHS lysosomal granules are not restricted to neutrophils (Figure 2B), they may be present in lymphocytes (Figure 2A) and monocytes (Figure 2C), in addition, they are larger and rougher, and are present in all stages of disease, with or without symptomatology^(12, 13, 16). Other inclusions that may get confused with CHS are Alder Reilly inclusions, which are more common in individuals with Tay-Sachs disease and mucopolysaccharidosis, which present azurophilic variable in size and shape from spherical to ellipsoid, that may

hide nucleus cell^(16, 22). May-Hegglin Anomaly is another condition that presents leukocytes inclusions, in which the spindle granules are similar to Döhle bodies, which are typically peripheral, bright blue basophils, and irregular contour⁽¹⁶⁾.

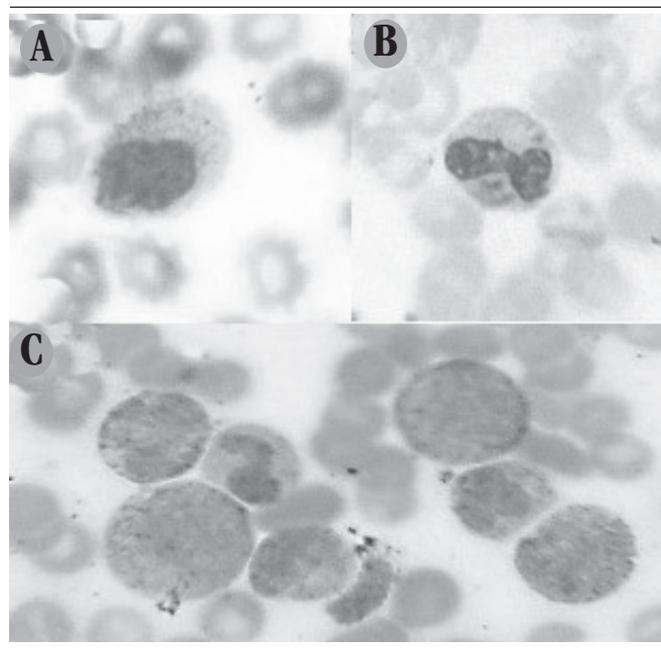


FIGURE 3 – Photomicrograph of peripheral blood smear Toxic granulation in neutrophils cytoplasm (3A and 3B) and normal azurophilic granules in immature granulocytic precursors (3C) (Wright, 100 \times).

Platelets in CHS are also altered and have less ability to aggregate due to adenosine diphosphate and serotonin deficiency, resulting from Delta-storage pool deficiency, that influences the quantity and content of dense-granules in megakaryocytes and platelets, and may result in thrombocytopenia^(7, 23), exacerbated in septic processes, consistent to patient outcome.

CHS course with periods of acceleration and chronicity of the disease. The accelerated phase is a complication with obscure and usually fatal prognosis, which must be avoided^(1, 3, 11, 18).

Changes in hepatic markers may be directly related to the disease, or as the result of frequent infections. At this phase, activated T CD8 lymphocytes and macrophages infiltrate viscera in several organs, especially the highly perfused ones, leading to increase in transaminase and decrease in liver activity, also contributing to decrease in prothrombin activity^(1, 3, 17).

The treatment considered curative for CHS is bone marrow transplantation (BNT)^(6, 12, 19, 20), which should occur in the stable of disease, although some authors assert that BNT is healing only for the hematological symptoms of disease^(6, 21), showing no interference in other symptoms, such as neurological and cutaneous.

CHS early and correctly diagnosis is especially important, due to complications during clinical course of disease, and its need for appropriate therapy. It is noteworthy that since CHS is a rare disorder, it may affect patients of different ages and ethnicities, including afro-descendant, as the case reported, and impose different degrees of immunodeficiency⁽³⁾.

The accurate description of the CHS abnormal giant azurophilic granules, that are peroxidase-positive, is decisive for diagnosis. This fact requires clinical analyst to improve knowledge and skills necessary to differentiate leukocytes abnormalities, since

cytomorphological diagnosis is essential in the disease differential diagnosis process.

This report is of particular relevance since it presents CHS occurrence in an afro-descendant individual. As the occurrence is rare in this race, cytomorphologic differentiation with correct statement of characteristic leukocyte inclusions, and laboratory findings associated with the disease, may contribute decisively, together with clinical findings, to differential diagnosis and subsequent better clinical management.

RESUMO

Trata-se de relato de caso de síndrome de Chediak-Higashi (SCH) em indivíduo afrodescendente, sexo masculino, 3 meses de idade, filho de união consanguínea. Apresentava na admissão febre há um mês, pneumonia não resolvida e hepatoesplenomegalia. Evoluiu para sepse bacteriana, choque séptico e óbito. A SCH apresenta alterações hematológicas, morfológicas e quantitativas. As inclusões leucocitárias anormais constituem achado patognomônico da doença e seu reconhecimento e sua distinção de outras inclusões leucocitárias é fundamental para diagnóstico e instituição da terapêutica. O diagnóstico precoce da SCH aumenta a expectativa de vida do indivíduo e proporciona abordagem terapêutica adequada aos pacientes acometidos pela doença.

Unitermos: Chediak-Higashi; imunodeficiência; afrodescendente; diagnóstico.

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MAILING ADDRESS

Claudio Lima Souza

Universidade Federal da Bahia; Instituto Multidisciplinar em Saúde; Campus Anísio Teixeira; Rua Rio de Contas, 58, Quadra 17, Lote 58; Candeias; CEP: 45.029-094; Vitória da Conquista-BA, Brazil; Phone: +55 (77) 3429-2709/9954-0509; e-mail: claudio.lima@ufba.br