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A Rare Syndrome in Pediatric Patients: Chediak-Higashi - Case Report

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1. Abstract

Chediak-Higashi syndrome is a rare autosomal recessive immunodeficiency associated with congenital mutations in the lysosomal trafficking regulator gene (CHS1/LYST). Usually the diagnosis is established by examination of the peripheral smear, which reveals pathognomonic giant cytoplasmic granules in leukocytes (neutrophils) and platelets. The giant abnormal granule-containing are also found in other cells: melanocytes, central and peripheral nerve tissue, fibroblast and hair that characterize the clinical aspects. The positive diagnosis of CHS implies clinical signs: pigment dilution of skin, hair and eyes; immunodeficiency; congenital and transient neutropenia; neurologic symptoms or neurodegeneration. The certain diagnosis can be established based on the presence of abnormally large granules in leukocytes, melanocytes, fibroblasts, nervous tissue and hair. Molecular genetic testing can also be done to detect variants of LYST gene. The prognosis is reserved, and most patients die around the age of 10. The only curative option is the hematopoietic stem cell transplantation (HSCT). Patients should undergo this treatment as the diagnosis has been made. CHS is a rare, genetic disease with high mortality and morbidity. It is very important that these patients be cared for by a multidisciplinary team. Also, patients should be trained in the risk of infection.

2. Introduction

Chediak-Higashi syndrome (CHS) represents a rare, congenital, autosomal recessive disease, which was first described in 1943, by Beguez-Cesar. Later, the pathophysiology of the syndrome was discovered, the involvement of the maldistribution of myeloperoxidase in the granules of the neutrophils. These contributions were made by Chediak in 1952 and Higashi in 1954 [1, 2]. Currently, scientific research shows that CHS is caused by mutations in the lysosomal trafficking regulator gene (CHS1/LYST), located on chromosome 1[3]. This defect leads to decreased phagocytosis

and predisposition to recurrent bacterial infection. The pathognomonic histological sign consists in the presence of large intracellular granules in: leukocytes (neutrophils), platelets, melanocytes, central and peripheral nerve tissue, fibroblast and hair [4]. The molecular phenotype dictates the severity of the disease. Often patients show signs of a severe phenotype and die in the first decade of life. In 10%–15% of patients, the disease has a milder clinical course [5]. As for the epidemiology of the disease, there are over 500 cases reported worldwide, with an incidence of 1/1,000,000 cases [6]. The onset of the disease is typically before the age of five. Clinically, CHS's aspects are suggestive of the immunodeficiency characterized by recurrent pyogenic infections, progressive neurologic abnormalities (neuropathy, ataxia, stroke, coma), partial oculocutaneous albinism, hemophagocytic histiocytosis and also,thrombocytopenia (platelets are deficient in dense bodies resulting in a storage pool deficiency and mild bleeding diathesis, with easy bleeding and epistaxis) [7]. Management of CHS is quite challenging because of the development of the accelerated phases secondary to the frequent acute infections caused by the cellular immunodeficiency. The only curative option is the hematopoietic stem cell transplantation (HSCT). Patients should undergo this treatment as the diagnosis has been made. Unfortunately, oculocutaneous albinism has no treatment. On the other hand, irreversibile neurologic deficits may develop [8].

3. Case Presentation

One of our most relevant clinical cases is that of a patient of a 14 months old male, who was referred to "Grigore Alexandrescu" Children's Emergency Hospital, in July 2021. The reasons for hospitalization included: fever (maximum temperature was 39.1 ° C), diarrheal stools and loss of apetite. The onset of symptoms started 7 days before admission in our clinic. As we mentioned, these patients suffer from recurrent infections; as for our case, he presented recurrent fever for 2 months, and was treated with Isoniazide ½ cp/day, for the last 2 months. He is neuropsychomotor normal, and developed properly according to the age stages.

At admission, clinical examination revealed: a weight of 10kg (percentile 25-50 CDC); afebrile, mediocre general condition; pale, hypopigmented skin, without eruptive elements, with bruising on the right flank, discreetly lazy abdominal skin fold; congenital strabismus; wrinkled facies, symmetrical; hyperemic pharynx; normal adipose connective tissue represented globally; impalpable superficial ganglion system; respiratory and cardio-vascular systems showed no pathologic signs, digestive and urinary system showed no pathological signs; splenomegaly; conscious, no signs of meningeal irritation, psycho-motor agitation.

We performed several laboratory tests and paraclinical examinations, which revealed anemia and thrombocytopenia: hemoglobin = 7.1g/dl; hematocrit = 22.6%; platelets = 82*10^9/L; ANC = 570/mm3. The evolution of biological parameters of blood count varied during the 3 weeks, with high values of leukocytes, and very low values of platelets. On the other hand, inflammatory syndrome was evidenced, as follows: ESR 30 mm/h (NV=7-12 mm/h) and CRP 7.87 mg/dl (NV=0-0.5 mg/dl). Chest radiography, performed at admission, showed periolar and bilateral infrahilar alveolar infiltrate (Figure 1A). In evolution, repeat this examination, 2 weeks later, revealed discrete bilateral infrahilar interstitial accentuation (Figure 1B). Abdominal ultrasound evidenced splenomegaly: spleen 38/121/115 mm (tr / ap / cc), diffuse inhomogeneous through numerous small irregular hypoechoic areas; maximum periportal lymphadenopathy 11 / 7.5 mm (Figure 2). The bone marrow aspirate showed presence of pathognomonic giant cytoplasmic granules in leukocytes (neutrophils) and platelets (Figure 3). Thus, a positive diagnosis of SCH was established. In our case the Lyst gene was negative, but the microscopic examination of the hair reveal clumped melanin granules that confirm the diagnosis of CHS. Currently, the patient is being evaluated for the possibility of a bone marrow transplant.

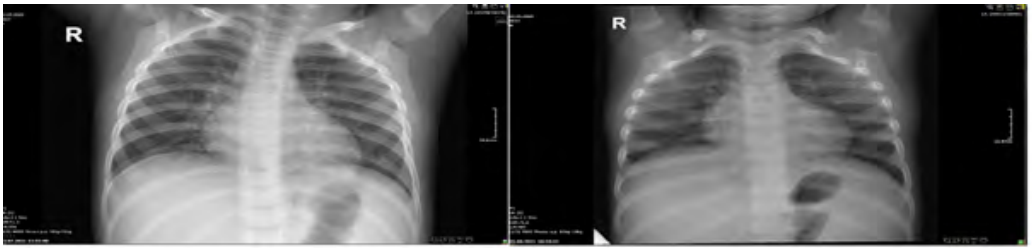

Figure 1A and 1B: Chest radiography, performed at admission.

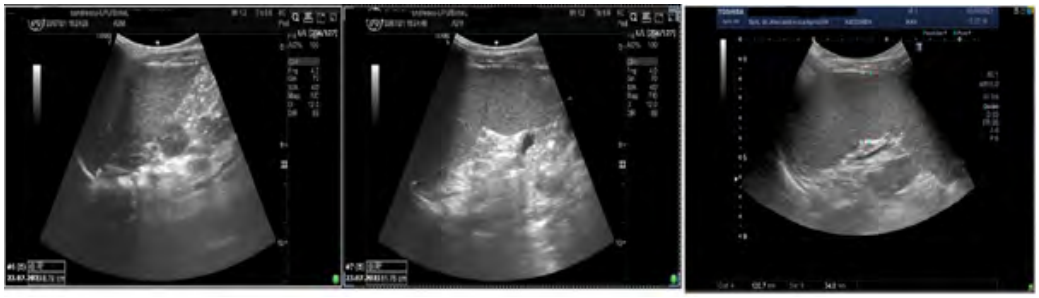

Figure 2: Abdominal ultrasound, performed at admission.

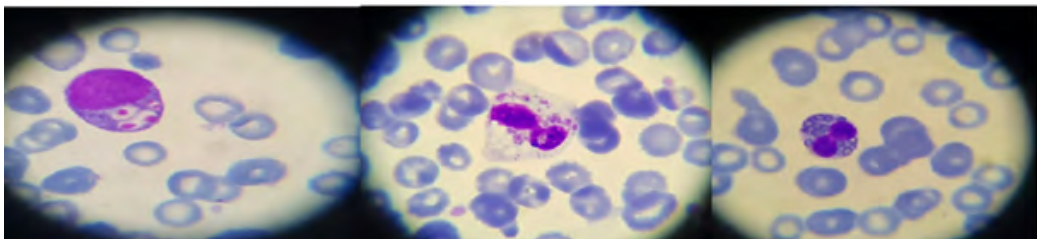

Figure 3: Bone marrow aspirate (neutophils) with abnormal large intracytoplasmic granules.

4. Discussion

CHS is a very rare syndrome, the exact prevalence is not known worldwide. All age groups are affected, and there is no predilection for race. Clinical manifestations may vary, and the severity of the syndrome is associated with molecular and cellular phenotype. Hypopigmentation of the skin, hair and eyes, is almost every time present. However, the degree of pigments is different for every child. The silvery appearance of hair is frequently seen. Also, visual acuity may be affected: nystagmus, photophobia, increasing red reflex [7]. Our patient hypo pigmented skin and bone marrow and peripheral blood smears showed giant granules in leukocyte. Hair examination under light microscope showed clumped melanin granules

Most common, mortality of CHS come from immunodeficiency with predominantly bacterial infections. Locations of infectious include: respiratory tract, mucous membranes or skin. As for the severity, it varies between superficial pyoderma and deep abscesses and ulcerations. The etiology involved may be: Staphylococcus aureus. Streptococcus Pyogenes and Pneumococcus species [7]. Because of the thrombopathy these pediatric patients may develop abnormal bleeding, or bruising. Other characteristics of the clinical picture are: periodontal disease, oral ulcerations or gingivitis. Not so frequent, enterocolitis was reported [9-11].

Management of CHS is a challenge. Potentially curative treatment is represented by allogeneic hematopoietic stem cell transplantation (HSCT), but with an increased morbidity and mortality rates secondary to the conditioning therapy. Unfortunately, it does not have an effect on progressive neurologic deterioration. It is preferable to be done as soon as we establish the diagnosis. If the form of the disease is severe and accelerated phase is present, the progressive disease includes the diagnosis of secondary HLH treatment and include: dexamethasone, cyclosporine A, and etoposide, in accordance with HLH protocol [12-14].

The CHS prognosis is reserved. The vast majority die in the first decade of life, due to infections or the development of an acute form of the disease from which emerges an accelerated phase. Therefore, an early positive diagnosis with a quick therapeutic intervention is essential for increasing the survival rate.

5. Conclusion

CHS is a rare, genetic disease with high mortality and morbidity. It is very important that these patients be cared for by a multidisciplinary team. Most patients die before de age of 10, and have a low quality of life. As for our pediatric patient, despite the negative genetic test, all diagnostic criteria were meet: pathognomonic giant cytoplasmic granules in leukocytes (neutrophils) and platelets, persistent pancytopenia, recurrent infections (including EBV) and cutaneous albinism. Bone marrow transplantation before the accelerated phase is the only curable therapy, and an early diagnosis is required.

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