Case study

Chediak-Higashi Syndrome: about a Case presenting the accelerated phase.

Abstract:

Chediak Higashi syndrome (CHS) is an autosomal recessive disorder, caused by biallelic mutations in the highly conserved *LYST* gene. It is characterized by partial oculocutaneous albinism and immunodeficiency. Approximately 500 cases reported worldwide. Here we report a case of a twelve years old girl, hospitalized in children's hospital of Rabat Morocco, who suffered from Chediak higashi syndrome presented in its accelerated phase, the diagnosis was made on the basis of clinical characteristics, hair analysis, and the presence of giant inclusions in peripheral blood smear and in the bone marrow. The only treatment reportedly leading to cure of CHS has been allogeneic hematopoietic stem cell transplantation. Without it, CHS is usually fatal before the age of 10 years because of "accelerated phase" HLH induced by infection. An early diagnosis can improve its prognosis by performing an allogeneic hematopoietic stem cell transplantation before reaching the accelerated phase.

Keywords: albinism; allogeneic hematopoietic stem cell transplantation; case report; chediak higashi syndrome; hemophagocytic lymphohistiocytosis; immunodeficiency;

Introduction:

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease that causes immunodeficiency, neurological dysfunction (including muscle weakness, ataxia, sensory loss, and nystagmus), oculocutaneous albinism, and a tendency to bleed as a consequence of impaired platelet function. [1,2].

The diagnosis is based on the presence of giant cytoplasmic granules in all granule-containing cells in peripheral blood and in the bone marrow.

Comment [s1]: Case report

Comment [s2]: Title can be modified as below: Chediak Higashi Syndrome, a case presenting in accelerated phase - A Case report

Comment [s3]: 500 cases **are** reported

The treatment of choice for CHS is bone marrow transplantation and should be proposed as soon as possible before the disease enters its accelerated phase [3].

Herein, we present a case of a twelve years old girl diagnosed with chediak-higashi syndrome presented in accelerated phase, hospitalized in the Division of Pediatric Immuno Allergology and Infectious Diseases in the children's hospital of Rabat Morocco.

Comment [s4]: performed

Comment [s5]: Chediak Higashi

Case report:

A twelve -years-old girl, born out of a first-degree consanguineous marriage, with a history of recurrent respiratory tract infection, a chronic otitis, treated for a pulmonary tuberculosis infection in 2018 and treated for a lymph node tuberculosis in 2022. Clinical examination showed palor, silvery gray hair with partial cutaneous albinism, moderate hepatosplenomegaly was noted on abdominal examination. The ophthalmologic examination revealed hypo pigmentation of fundus. The complete blood count showed low hemoglobin 6 g/dl, low platelet counts 87000/mm³ with neutropenia 300/mm³. The peripheral smear examination revealed giant block granules in the cytoplasm of the lymphocytes [figure 1].

Comment [s6]: Otitis media or externa needs to be mentioned

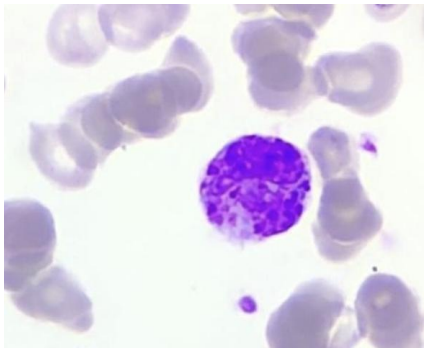

Figure 1: Peripheral smear showing cytoplasmic inclusion in the lymphocyte

The bone marrow examination showed giant eosinophilic granules and giant solitary block granules in the cytoplasm of lymphoid cells [figure 2].

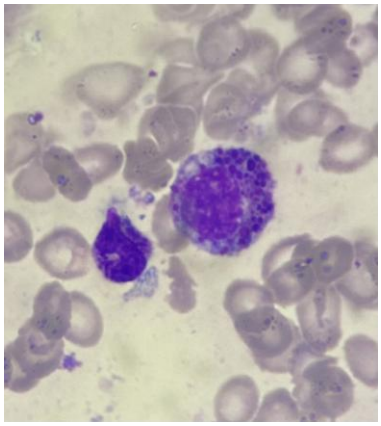

Figure 2: Bone marrow aspirate showing abnormal granulesin the precursor cells of leukocytes

Optical microscopy examination of the hair showed hypopigmented hair with melanin granules evenly distributed in the hair medulla compatible with chediak-higashi syndrome [Figure 3].

Comment [s7]: Chediak-Higashi

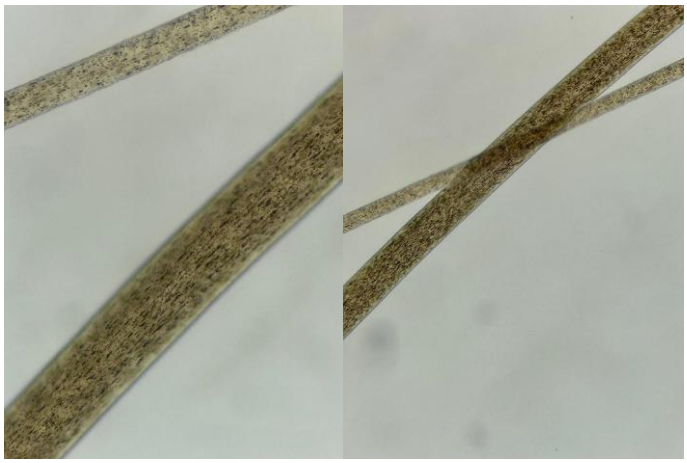

Figure 3: Microscopic examination of the hair shaft shows a typical pattern of evenly distributed, regular melaningranules larger than those seen in normal hairs.

Based on the clinical presentation, hematological findings and microscopic examination of the hair a diagnosis chediak higashi syndrome was made.

We recommended bone marrow transplantation to our patient, her older brother had an HLA-identical marrow, however, weeks before the procedure the child presented fever and asthenia laboratory investigations showed: hemoglobin 5.6 g/dL, neutropenia 800/mm³, and thrombocytopenia (Platelet count 9000/mm³) high ferritin levels (10823 ng/mL), low fibrinogen levels (1.4 g/L), and hypertriglyceridemia (5 g/L).The patient fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis, serology of Epstein–Barr virus was positive with a viral load of 252269 UI/ml, she received intravenous methylprednisolone (20 mg/kg/day for 3 days) then high doses of intravenous gamma globulin (1 g/kg per day for 2 days), a prompt blood transfusion and perfusions of Rituximab (375mg/m²/week) for four weeks. We obtain remission for three weeks, then she presented a second hemophagocytic lymphohistiocytosis and we decided to put her on a combination therapy that consists of etoposide, dexamethasone, and cyclosporine. The patient didn't respond to this therapy, she passed away a month later by a septic shock.

Comment [s8]: infusion

Comment [s9]: obtained

Discussion:

Chediak–Higashi syndrome (CHS) was first described by Beguez Cesar, a Cuban pediatrician, in 1943 [4]. Initially characterized by neutropenia and abnormal granules in leucocytes, the syndrome was further delineated in 1948 by Steinbrinck's description of a second case [5]. In 1952, Chediak reported the hematologic characteristics of the disorder [6] and, in 1953, Higashi emphasized the "monstrous" peroxidase-containing granules within patients' cells [7]. CHS is caused by mutations in a single gene characterized in 1996 as the *LYST* gene (lysozyme trafficking regulator) localized to 1q42–43 [8]. Approximately 500 cases reported worldwide, in a nationwide survey in Japan, 15 patients were diagnosed during a period of 11 years (2000–2010), indicating that one or two patients with CHS were diagnosed each year [9].

Comment [s10]: ;

Clinically characterized by oculocutaneous albinism, easy bruising, abnormal functions of the natural killer cells, and recurrent pyogenic infections , patients may develop neurological symptoms such as ataxia and neuropathies which could be a predominant feature in the atypical forms of the disease [10], in our case the diagnosis was suspected based on clinical particularity the oculocutaneous albinism , the grey hair and the recurrency of infections. The diagnosis is based on the presence of abnormally large intracytoplasmic granules, especially in white blood cells and bone marrow, as the case of our patient, molecular genetic

testing also can be done to detect the biallelic variants in the *LYST* gene [10], however it was not available in our hospital.

The majority (85%) of patients with CHS develop hemophagocytic lymphohistiocytosis (HLH) which define the accelerated phase of the disease, characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, neurological abnormalities.[11]

The only cure is an allogeneic hematopoietic stem cell transplantation (HSCT). Therefore, HSCT should be done as soon as the diagnosis is established, and before the development of the accelerated phase. If signs of accelerated phase are evident, then hemophagocytosis should be brought into a stage of remission before HSCT. [10]Without HSCT, CHS is usually fatal before the age of 10 years because of "accelerated phase" HLH induced by infection [12].

The guidelines for the treatment of the accelerated phase are the same as that for familial hemophagocytic lymphohistiocytosis and include combination therapy of dexamethasone, cyclosporine A, and etoposide. [10]

The most common cause of death in patients with Chediak Higashi syndrome results from recurrent infections or the development of an accelerated phase where there is lymphoproliferation into major organs. 80% of deaths occur in the first decade of life, and those who survive into adulthood develop progressive neurological symptoms [10]. Our patient had the same course as the cases previously described in literature, our patient presented in the accelerated phase, we couldn't perform an HSCT, although she received the combination therapy of dexamethasone cyclosporine A and etoposide she didn't get into remission and passed away by a septic chock.

Comment [s11]: The definitive treatment is

Comment [s12]: Dexamethasone

Comment [s13]: Cyclosporine A

Comment [s14]: Etoposide

Conclusion:

In conclusion, Chediak higashi syndrome is a rare disease that should be suspected in the presence of an oculocutaneous albinism, an early diagnosis can improve it's prognosis by performing an allogeneic hematopoietic stem cell transplantation before reaching the accelerated phase.

References :

Comment [s15]: All references should be in one format - need to adjust into Vancouver style as initial references are in that style

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