Le syndrome de Chediak-Higashi : à propos d'un nouveau cas tunisien

Chediak-Higashi syndrome: a new Tunisian case report

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ABSTRACT

Chediak-Higashi syndrome (CHS) is a rare, autosomal recessive congenital immunodeficiency caused by mutations in CHS1, a gene encoding a putative lysosomal trafficking protein. It is typically characterized by infantile-onset hemophagocytic lymphohistiocytosis (HLH), which is lethal unless an allogeneic hematopoietic stem cell transplantation (HSCT) is performed.
Herein, we report the third Tunisian case of CHS in a 25-month-old boy who was referred to our pediatric unit for prolonged fever and abdominal distension. The diagnosis of a CHS in an accelerated phase was made on the basis of clinical characteristics, biological data, hair analysis, and identification of pathognomonic giant azurophilic granules in peripheral blood and bone marrow.

Key words : Chediak-Higashi syndrome, Hemophagocytic lymphohistiocytosis, giant azurophilic granules, accelerated phase.

RESUME

Le syndrome de Chediak-Higashi (CHS) est une maladie génétique rare de transmission autosomique récessive causée par des mutations dans le gène CHS1 (régulateur du trafic lysosomal). Elle est typiquement caractérisée par une lymphohistiocytose hémophagocytaire infantile (HLH), qui est mortelle à moins qu'une greffe allogénique de cellules souches hématopoïétiques (GCSH) ne soit réalisée.
Nous rapportons le troisième cas tunisien de CHS chez un garçon âgé de 25 mois qui a été référé à notre unité pédiatrique pour fièvre prolongée et distension abdominale. Le diagnostic d'un CHS en phase accélérée a été posé sur la base des caractéristiques cliniques, des données biologiques, de l'analyse capillaire et de l'identification de granules azurophiles géants pathognomoniques dans le sang périphérique et la moelle osseuse.

Mots Clés : syndrome de Chediak-Higashi, lymphohistiocytose hémophagocytaire, granules géants azurophiles, phase accélérée.

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare primitive immunodeficiency disease characterized by oculo-cutaneous albinism, frequent severe infections, bleeding diathesis, and late onset of neurologic deterioration. The accelerated phase of CHS, namely hemophagocytic lymphohistiocytosis (HLH) which develops in up to 85% of the cases, is fatal if not treated.
This disorder was first reported by Beguez Cesar, in 1943 [1]. Later, Chediak [2] and Higashi [3] emphasized the hematologic features that yielded to the association of the names of these two authors with the anomaly [4]. The disease is rare and fewer than 500 cases have been reported worldwide in

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the past 20 years [5]. In Tunisia, only two cases have been reported [6, 7].
Due to the rarity of the disease and to the clinical characteristics and hematological specificities, we report the third Tunisian case of CHS, which presented in an accelerated phase.

CASE REPORT

The patient is a male infant, born at term to consanguineous Tunisian parents, with a birth weight of 4000g. He might have had normal growth and psychomotor development up to the age of 25 months when he was admitted for a thirteen-day-long history of fever and abdominal distension. There was a prior history of acute gastroenteritis at the age of 9 months and respiratory-tract infections at the age of 11, 15 and 20 months. Otherwise, there was a family history of early deaths in cousins.
On examination, the patient was febrile, of average build, weighed 14 kg, and had gray hair and hypopigmentation of the skin (Figure 1).

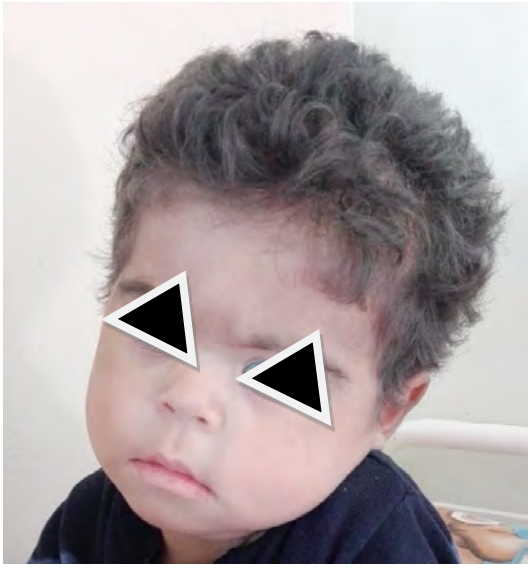

Figure 1 : Face of the patient. Note gray hair and hypo pigmentation of the skin

He was plaintive and asthenic. A mild pallor, a generalized edema, and bilateral cervical lymphadenopathies were also noted. Respiratory system examination revealed moderate respiratory distress with bilateral coarse crackles. The abdominal exam found soft non-tender enlarged liver and spleen (liver 10 cm and spleen 5 cm below the costal margin). The rest of her physical exam was unremarkable. Laboratory investigations showed elevated C-reactive protein (138 mg/L), hyponatremia (127mmol/L), high ferritin level (1463ng/mL), low fibrinogen level (0.49g/L), high level of serum lactate dehydrogenase (966UI/L), and hypertriglyceridemia (4mmol/L). The relevant hematological findings were anemia (hemoglobin 8.5g/dL), leucopenia at 2.98 x 109/L, neutropenia at 0.41x109/L, and thrombocytopenia (Platelet count 15 x 109/L). Liver function tests revealed an elevated liver enzyme (ALT 106U/L) and decreased prothrombin time (33%). Peripheral blood smear showed several abnormal giant granules in most leukocytes (Figure 2).

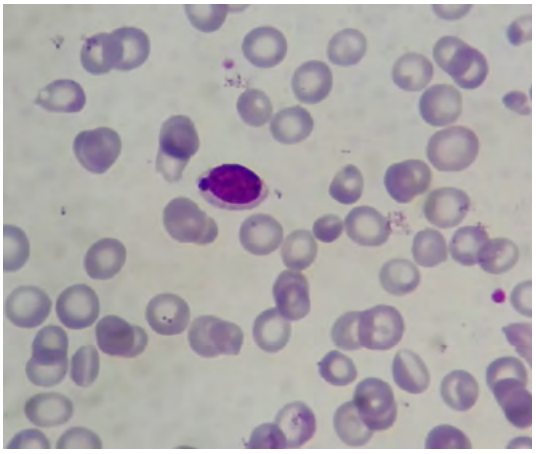

Figure 2 : Peripheral blood smear (Magnification Â100) showing several abnormal giant granule in a leukocyte, suggesting Chediak Higashi disease.

Bone marrow aspiration revealed prominent granules within the lymphocytes and myeloid cells (Figure 3).

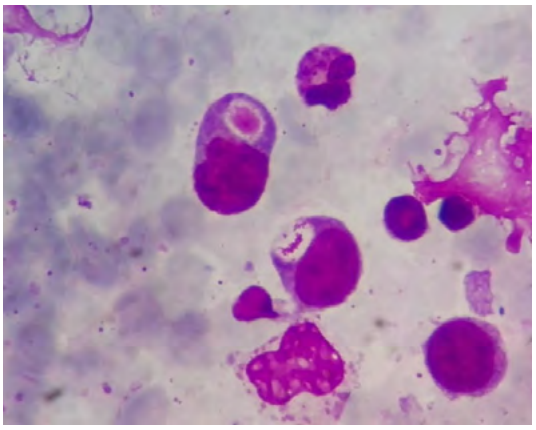

Figure 3 : Bone marrow aspiration (Magnification Â100) revealing prominent granules within promyelocytes suggesting Chediak-Higashi disease.

Phagocytosis of red blood cells and red-blood-cell precursors was also observed (Figure 4).

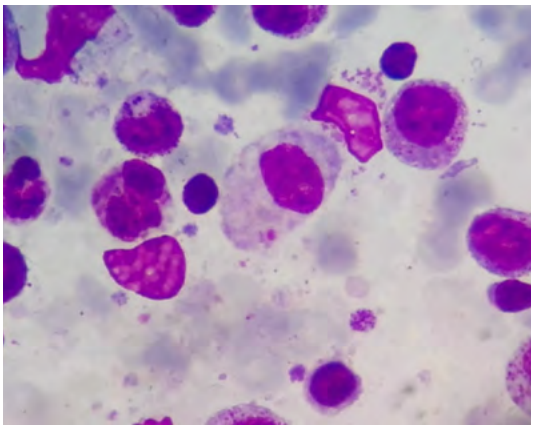

Figure 4 : Bone marrow aspiration (Magnification Â100) revealing hemophagocytosis.

Optical microscopy examination of the hair showed large melanin granules (Figure 5).

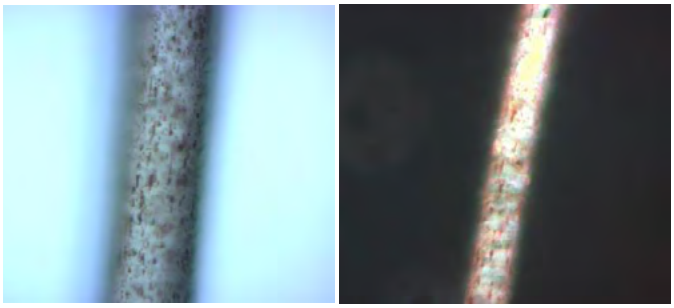

Figure 5 : Optical Microscopy examination of the hair shaft shows a typical pattern of evenly distributed regular melanin granules larger than those seen in normal hairs (hematoxylin-eosin, original magnification x 400).

Immune system investigation showed normal immunoglobulin levels, normal CD4, CD8, CD19, and natural killer cells counts, as well as a positive NBT test. However, chemotaxis of natural killer cells was not studied. The patient fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), with prolonged fever, splenomegaly, pancytopenia, high ferritin levels, low fibrinogen levels, hypertriglyceridemia, and hemophagocytosis. Thus, the diagnosis of CHS in an accelerated phase was made on the basis of clinical presentation (hypopigmentation, gray hair, and large melanin granules in microscopic hair examination) and hematological findings (giant azurophilic granules in leukocytes). Chest X-ray showed a mediastinal widening and opacities in bilateral lower zones. Chest and abdominal computed tomography showed cervical, thoracic, diffuse abdominal lymphadenopathies, and hepatosplenomegaly. The child was treated with ceftazidime, gentamicin, vancomycin, and fluconazole because of the neutropenic fever. He also received transfusions of platelets, fresh frozen plasma and packed red blood cells. Nevertheless, he did not receive granulocyte colony-stimulating factors since the drug was not available. During observation, the fever persisted. Blood, sputum, and urine cultures were negative for bacteria. Serologic tests for Leishmania, Brucella, Coxiella Burnetii, human immunodeficiency virus, viral hepatitis, EBV, CMV, and Parvovirus B19 were all negative. Polymerase chain reaction (PCR) was also negative for Pneumocystis jirovecii. The HLH 2004 protocol was begun with high-dose dexamethasone (10mg/m2), etoposide (150mg/m2/day for 3 days), and cyclosporin A (6mg/kg/day). After immune modulation, the fever subsided on day 6 after hospitalization; the general condition improved with regression of edema, cervical lymphadenopathy, and hepatosplenomegaly. The child was transferred to the bone marrow transplant center for HSCT. However, the parents refused the GCS after being informed about the percentage of success and the risks incurred by the patient. Thus, the child was maintained under the HLH 2004 protocol and returned to our service for additional cure treatment of VP16 and intravenous immunoglobulins every 2 to 3 weeks. The patient later was re-hospitalized in our pediatric unit at the age of three years for prolonged fever secondary to a mild Pneumocystis Jirovecii Pneumonia complicated by hemophagocytic lymphohistiocytosis syndrome. The treatment associated trimethoprim/sulfamethoxazole (TMP-SMX) administered at the dose of 100mg/Kg/day in intravenous route, intravenous immunoglobulins, etoposide and dexamethasone referring to the HLH-2004 protocol. The evolution was good enough to permit the discharge of the patient who had been in our hospital for over a month. The latest check-up of the boy, at the age of 5 years old, showed a normal psychomotor development, but also a moon face with telangiectasia, obesity and large hepatomegaly and splenomegaly. Actually, he receives regular perfusions of immunoglobulins and VP16 in addition to cyclosporine, prednisolone and oral antibioprophylaxie.

DISCUSSION :

Chediak-Higashi syndrome is a rare, inherited, complex, immune disorder that usually occurs in childhood. It is characterized by reduced pigment in the skin and eyes, immunodeficiency, and tendency to bruise and bleed easily. The disease is transmitted as an autosomal recessive genetic condition, without any higher risk for any particular ethnic or racial group. Fewer than 500 cases are recorded worldwide [8]. Patients with CHS are usually diagnosed during the first decade of life, since they suffer from recurrent precocious severe infections and bleeding. These symptoms when associated to a hypopigmentation of the hair, skin, and eyes often lead to the suspicion of the disease. Unfortunately, there was a delay in diagnosis in our patient although he had a history of death in early ages in the family, recurrent respiratory tract infections, and evident gray hair. The delay may be attributed to the ignorance of the classic signs of this rare disease. In reality, the degree of hypopigmentation varies and a speckled hyperpigmentation or dark skin may uncommonly be seen in more pigmented races, leading to the suspicion of other diseases with a consequent delay in diagnosis [9, 10]. Hair color may be blond, gray, or white, often with a distinguished silvery or metallic sheen. Iris hypopigmentation may be associated with photophobia and decreased visual acuity. Recurrent bacterial infections are troubling in most children with CHS. These infections are secondary to the abnormal functions of polymorphonuclear leukocytes. The most common sites of infection are the skin, respiratory tract, and mucous membranes. Staphylococcus and Streptococcus are the species most frequently isolated from these sites [11]. Patients with CHS also suffer from bruising and mild mucosal bleeding as a result of defective platelets. This

manifestation does not usually require treatment. CHS may present with neurologic dysfunction. In children, common physical findings include ataxia, tremors, cranial nerve palsies, low cognitive abilities, learning disabilities, seizures, and motor and sensory neuropathies. The 'accelerated phase' is the most life-threatening clinical feature of CHS. It affects 60 to 85% of CHS patients within the first decade. This condition oftetn occurs following exposure to Epstein-Barr virus (EBV), and as it was seen in our patient, it manifests by fever, lymphadenopathy, hepatosplenomegaly, cytopenia, liver dysfunction, hypertriglyceridemia, hyperferritinemia and lymphohistiocytic infiltration not only of the bone marrow but also of all organ systems. Most children with CHS showed recurrent infections before entering the accelerated phase, but primary presentation in the accelerated phase has also been reported [6, 12-15]. Clinical suspicion of CHS is confirmed by laboratory investigation, imaging data, and by histologic findings. Identification of giant granules, mainly in neutrophils, but also in lymphocytes and natural killer (NK) on peripheral blood smears is pathognomonic of CHS. Bone marrow aspirates demonstrate numerous large azurophilic or eosinophilic cytoplasmic inclusion bodies in cells of myeloid lineage that react strongly to peroxidase staining [16]. Microscopic examination of the hair is a contributing test for the diagnosis, since it can reveal clumped melanin granules, larger than those seen in normal hairs [17]. Immunodeficiency in CHS patients is related to a profound defect in the function of cytotoxic and NK cells [18]. In addition, defects of neutrophils [19] include ineffective granulopoiesis, moderate neutropenia, and delayed and incomplete degranulation associated with phagocytic, chemotactic, and bacterial killing defects. Immunoglobulin levels and complement are generally normal [20]. If the raised symptoms are suggestive of CHS, definite diagnosis is based on the molecular genetic testing. This genetic testing, unfortunately not done in our patient, allows ruling out the diagnosis of Griscelli syndrome type 2 and other syndromes that have similarities in clinical and biological signs [21]. To date, 63 CHS1/LYST mutations have been described with a reasonably straightforward genotype-phenotype correlation of the disease [9, 13, 22-24]. Prenatal diagnosis is confirmed by genetic testing in chorionic villous cells, amniotic fluid cells, or fetal blood leukocytes. Once the diagnosis is established, the management of CHS patients includes supportive management of disease derived complications, treatment of the "accelerated phase", and HSCT. The last one is the most effective treatment for hematologic and immune defects, albeit there is no evidence of efficacy in preventing progressive neurologic dysfunction [5, 25]. In reality, early disease identification is the key to appropriate and timely management. Since CHS patients are immuno-depressed, measures to prevent routine infections are crucial. They include education of the child and caregivers regarding effective hygiene, and meticulous attention to dental care. The duration of antimicrobial therapy to treat common infections should ideally be two to three times longer than standard recommendations [26]. While these patients can safely receive all killed or inactivated vaccines, live vaccines are contraindicated. Preventative measures for increased bleeding tendency include avoidance of drugs that interfere with platelet functions such as aspirin, and other non-steroidal anti-inflammatory agents, and careful dental hygiene which can minimize gingival bleeding in CHS patients. Desmopressin and antifibrinolytics agents are recommended after dental extraction or minor surgery to prevent bleeding [20, 27, 28]. Concerning the HLH, the management involves the use of immunosuppressive agents and a long-term strategy attempting to definitively correct the underlying genetic defect by allogeneic HSCT as early as possible. The HLH-2004 protocol recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine A [29]. Intrathecal therapy with methotrexate and prednisone is restricted to patients with evidence of central nervous system disease progression or in those with worsening or unimproved cerebrospinal fluid pleocytosis. The anti-CD52 monoclonal antibody alemtuzumab can be used as a second-line therapy for pre-transplantation treatment of HLH refractory to etoposide-based treatments [30, 31]. During the latter phase of management, maximal supportive care is recommended. It includes the use of presumptively appropriate broad-spectrum antibiotics until the culture results are available. Prophylactic cotrimoxazole, an oral antimycotic, an antiviral therapy, and intravenous immunoglobulins (0.5 g/kg) once every 4 weeks are also recommended [32]. G-CSF, blood transfusion, platelet transfusion, fresh frozen plasma, cryoprecipitates, and fibrinogen should be used as required [33]. Despite a rigorous management of HLH, the prognosis is poor. Thus, the only definite long-term therapy of CHS patients surviving HLH, even cases in the accelerated phase, remains allogeneic HSCT [34]. Nevertheless, it appears to be more effective, if performed prior to the accelerated phase in the early onset form of CHS, for prevention of life-threatening infections and HLH [27]. The overall survival of HSCT in CHS patients was 62% in a retrospective study. The mortality rate was of 58% in patients with active HLH at transplantation.

CONCLUSION :

Chediak-Higashi syndrome is a rare, unfortunately under-diagnosed, autosomal recessive disease. More than 50% of the patients have the 'childhood' form of the disorder, which is universally fatal without treatment. This form should be rapidly recognized in a child who has hair hypopigmentation and a history of recurrent or severe infections. A simple, quick, and non-invasive careful examina-

tion of a peripheral blood smear is primordial. Early treatment of children with CHS is of paramount importance. Thus, with a high degree of clinical suspicion, these patients should be immediately referred to a tertiary care center and treated by multidisciplinary teams. Young patients who develop HLH before transplantation should receive corticosteroids and etoposide-based regimens prior to inclusion in a transplantation protocol. In reality, the most effective treatment for the hematologic and immune defects in patients is HSCT, although there is no evidence of efficacy in delaying or preventing progressive neurologic dysfunction. Declaration of interest: the authors declare no conflict of interest.

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