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Difficulties Diagnostic of Amegacaryocytic Thrombocytopenic Purpura in Developing Country: A Case Report

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Abstract: *Amegacaryocytic thrombocytopenic purpura (ATP) is a rare disease caractérise by severe thrombocytopenia. This thrombocytopenia is associated with a decrease or total absence of mégacaryocytes in the bone marrow. ATP may be constitutional linked to genetic anormalités, or acquired generally immunological. From the exact diagnosis dépend the management. Knowledge of its physiopathology requires very specialized examinassions, often difficulté réalisation in poor countries. From an observation in our départements, we discuss the problematic of the caractérisation of ATP in a country with limited ressources.*

Keywords: *Amegacaryocytosis, corticosteroids, immunotherapy, Purpura, Thrombocytopenia*

1. INTRODUCTION

Amegacaryocytic thrombocytopenic purpura (ATP) is a rare disease. It is characterized by a severe thrombocytopenia associated with a decrease or total absence of megakaryocytes in the bone marrow whereas granular and erythroid precursors are normal [1]. It can be constitutional, secondary to mutations of genes involved in megakaryocytopoiesis. The diagnosis is made most often in childhood [2]. The ATP can also be acquired. In this case, several factors are incriminated: viral infections, toxic, systemic diseases [1, 3]. Sometimes no etiology is found. The mechanism evoked is that of a dysregulation of the immune system [1]. Recognition of the physiopathological mechanism is essential to the diagnostic approach because of it depends appropriate care. We discuss the problematic characterization and management of ATP in a developing country through a case observed in our service.

2. CASE REPORT

A girl aged 6 years was hospitalized for gingivorragies and epitasis evolving intermittently for 1 month. She was transfused, two months before this episode, following a haemorrhage after the fall of a milk tooth. There was not family history of hemorrhagic diseases. The examination found petechiae and anemic syndrome (pallor, asthenia), without dysmorphism and without lymphadenopathy. The blood count revealed normocytic thrombocytopenia (platelets: 32G / l) and normocytic anemia (Hb: 5.1g / dl). The rest of the assessment was normal: leukocyte count, hemostasis, liver enzymes, creatinine clearance, viral serologies (hepatitis, HIV), sedimentation rate, abdominal ultrasound and chest X-ray. The diagnosis of immunologic thrombocytopenic purpura (ITP) has been discussed. Prednisone and erythrocyte concentrates were administered. After 6 weeks bleeding persisted despite a moderate increase of platelets (Figure 1). A milligram was performed. It showed a rich bone marrow with hyperplasia of the red line, a normal white line and absence of megakaryocytic (Figure 2). The diagnosis of ATP was retained. An associated thrombopathy has been discussed because of the persistence of hemorrhages despite an almost normal platelet count. Thrombopoietin assay, MPL gene analysis and platelet function studies could not be performed due to insufficient technical platform. The patient died after seven weeks of treatment with ciclosporin in a convulsive setting suggestive of cerebral hemorrhage.

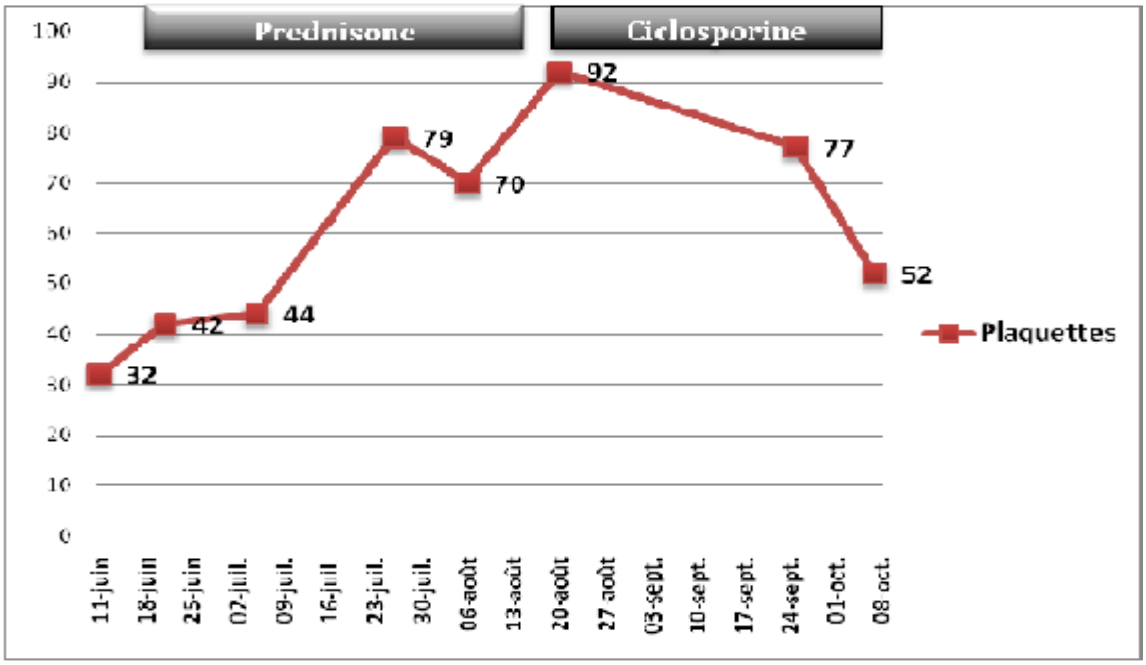

Figure1: *Evolution of the number of platelets under immunosuppressive treatments.*

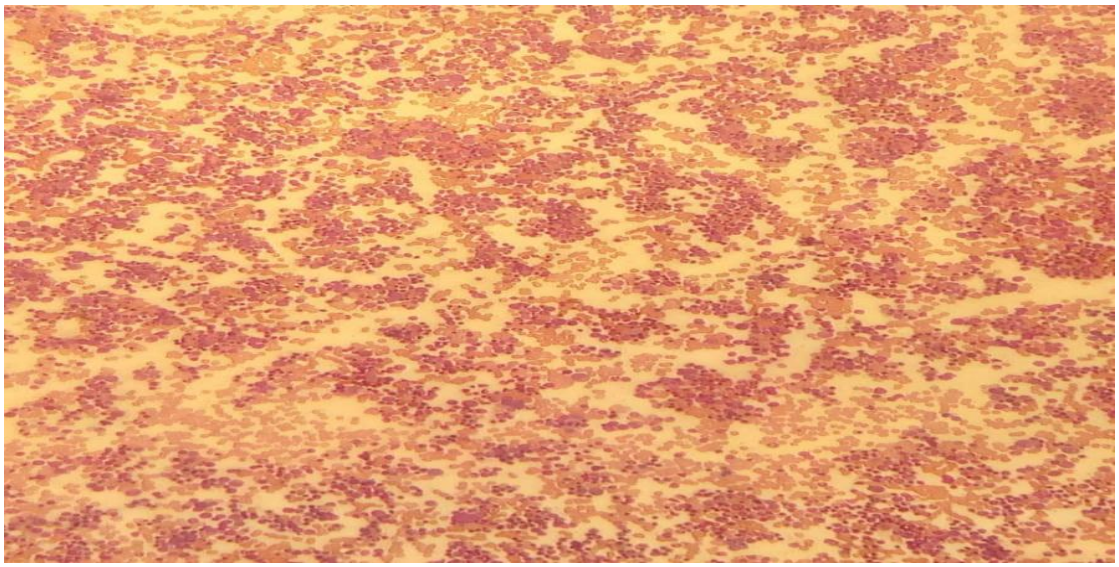

Figure2: *bone marrow with hyperplasia of the red line and absence of megakaryocytic (low magnification x 10)*

3. Discussion

The exact prevalence of ATP is unknown, the available literature being summarized as case reports. Many ATP are probably mislabeled as ITP [1]. This is indeed the main differential diagnosis of ATP and also the first cause of thrombocytopenia isolated from the child [4]. But unlike ATP, the examination of bone marrow found megacaryocytes in normal or increased numbers [5].

In children the diagnosis of constitutional ATP should be considered in the context of all chronic thrombocytopenia, especially in case of suspected autoimmune thrombocytopenia and resistant to usually effective treatments such as immunoglobulins or corticosteroids [6]. Constitutional thrombocytopenia (CT) is a group of diseases characterized by a lack of bone marrow production secondary to mutations in genes involved in megakaryocytic differentiation. They are rare and heterogeneous entities classified according to several criteria: the platelet size, the syndromic or isolated nature of thrombocytopenia, the genetic anomaly or the mode of transmission [4, 6]. Thrombocytopenia can be distinguished schematically by megakaryocytosis, dysmegakaryocytosis and thrombocytopenia with normal megakaryocytic lineage. Family history and early onset of hemorrhagic symptomatology in early childhood are strong

arguments to discuss [2,6]. However, their absence is not enough to eliminate them.

Congenital megakaryocytosis, the most commonly reported entity, is an autosomal recessive disorder which may explain the lack of a family history. It results from mutations in the c-Mpl gene located on chromosome 1 and encoding the thrombopoietin (TPO) receptor, a cytokine essential for megakaryocytic differentiation and proliferation (4,6). These mutations are responsible for the production of a non-functional receptor and the absence of any residual activity in the most severe forms. There is a lack of megakaryocytic differentiation, despite a high plasma TPO level. The production of megakaryocytic colonies in culture is absent in the presence of TPO and all hematopoietic progenitors are globally decreased [7]. In two-thirds of cases, there is no associated morphological abnormality. Three clinical forms are identifiable, depending on the type of mutation. Type II is associated with transient increases in platelet counts to nearly normal values during the first year of life. Thrombocytopenia worsens at 3 to 6 years of age or later. In this group, there are partially functional receptors for the c-Mpl gene. The average number of platelets is generally from 35 G / l to 132 G / l [7]. This description is similar to the clinical picture of our patient. However, congenital amegakaryocytosis is not accompanied by thrombopathy. The severity of the haemorrhagic syndrome is correlated with that of thrombocytopenia [6].

This led us to mention secondly familial thrombocytopenia and susceptibility to leukemias by mutation of the aML gene located on chromosome 21. These mutations lead to CBFα transcription factor abnormalities responsible for thrombocytopenia / thrombopathy by default of megakaryocytopoiesis. The majority of cases are autosomal dominant but de novo forms are possible. The hemorrhagic symptomatology is variable and thrombocytopenia is moderate (30 to 150 g / L) as observed in our patient [4, 6]. CT diagnosis involves explorations such as molecular biology, in vitro megakaryocytic progenitor culture and platelet function studies, performed only by specialized laboratories. They are not practiced in our country and this has limited our etiological inquiry. It is important to look for a TC because their evolution is dominated by the risk of developing aplastic anemia or acute leukemia, leading to these children performing an early hematopoietic stem cell transplant, the only curative treatment to date [7].

We also mentioned for this child an acquired ATP although it is rarely reported in children [8]. The etiological factors implicated in its occurrence are essentially viral infections, drug or environmental toxicants such as benzene or systemic diseases such as lupus [1, 3, 9]. But most often, it is idiopathic and can precede the appearance of a hematological malignancy or an aplastic aplasia [1,10]. The mechanism most often mentioned is that of a dysregulation of the immune system [1]. The search for etiology has been limited in our context by the impossibility of searching for certain incriminated viruses such as non-B and C hepatitis, cytomegalovirus or parvovirus. Several treatments are used with more or less success in acquired ATP: immunosuppressants (immunoglobulins, corticosteroids, cyclophosphamide, ciclosporin alone or in combination with anti-lymphocyte serum), androgens, splenectomy and bone marrow transplantation [1, 11]. The efficacy of ciclosporin monotherapy has been reported in children [8]. The response is usually delayed with a normalization of the platelet count after 3 to 6 months of treatment [12].

4. CONCLUSION

Isolated thrombocytopenia in children is not always an ITP. It is important to mention the hypothesis of central thrombocytopenia or even constitutional thrombocytopenia even in the absence of an evocative history. The etiological diagnosis of ATP allows appropriate management and monitoring of patients. In our context it is made difficult by the insufficiency of the technical platform which does not allow the realization of specialized examinations in particular the study of the karyotype, the molecular biology and the study of the platelet functions.

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