ACUTE LYMPHOBLASTIC LEUKEMIA WITH MARKED EOSINOPHILIA : TWO CASE REPORTS

LEUCEMIE AIGUE LYMPHOBLASTIQUE AVEC HYPEREOSINOPHILIE : A PROPOS DE DEUX CAS

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Abstract

Leukemias are considered among the most common childhood malignancies. Rarely, patients with acute lymphoblastic leukemia (ALL) may have eosinophilia. In recent years, discrete reports and case studies have generated considerable interest in the field of "acute leukemia with eosinophilia". We present two cases of eosinophilia in association with ALL with brief review of literature. These two cases highlight the importance of considering ALL as one of the causes of eosinophilia. Immediate diagnosis and intensive therapy are necessary due to the worsened prognosis of ALL presenting as eosinophilia.

Key – words : Hyperosinophilia ; Acute lymphoblastic leukemia ;T(5,14) ; Eosinophilic infiltration**.**

Résumé

Les leucémies constituent l'une des principaux cancers pédiatriques. Dans de rares cas, les patients atteints de leucémie aiguë lymphoblastique (LAL) peuvent présenter une hyperéosinophilie. Ces dernières années, des rapports et des études de cas ont suscité un intérêt considérable dans le domaine de la "leucémie aiguë avec hyperéosinophilie". Nous présentons ainsi deux cas de LAL associées à une hyperéosinophilie, avec une brève revue de la littérature. Ces deux cas soulignent l'importance de considérer la LAL comme l'une des étiologies d'hyperéosinophilie. Un diagnostic immédiat et une thérapie intensive sont nécessaires en raison du pronostic aggravé decette entité.

Mots - clés : Hyperéosinophilie ; Leucémie aigue lymphoblastique ; T(5,14) ; Infiltration éosinophilique.

ملخص

تعتبر اللوكيميا من أكثر الأورام الخبيثة شيوعًا في مرحلة الطفولة. نادرا، المرضى الذين يعانون من سرطان الدم الليمفاوي الحاد يكون لديهم فرط الحمضات. في السنوات الأخيرة، أثارت التقارير المنفصلة ودراسات الحالة اهتمامًا كبيرًا في مجل اللوكيميا الحادة مع فرط الحمضات". نقدم حالتين من فرط الحمضات بالاشتراك مع سرطان الدم الليمفاوي الحاد مع مراجعة موجزة للأدبيات. تسلط هاتان الحالتان الضوء على أهمية اعتبار سرطان الدم الليمفاوي الحاد أحد أسباب فرط الحمضات. التشخيص الفوري والعلاج المكثف ضروريان بسبب سوء تشخيص هذا الكيان

الكلمات المفاتيح: فرط الحمضات ; سرطان الدم الليمفاوي الحاد ; ت(5،14) ; تسلل الحمضات.

INTRODUCTION

Hypereosinophilia can be caused by many malignant diseases , but rarely (in less than 1%) by acute lymphoblastic leukemia (ALL) [1,2]. This association presents a distinct entity. Patients with this association that presents a distinct entity may develop non-specific symptoms such as intermittent low-grade fever, fatigue and also signs caused by eosinophilia, including the infiltration of different body organs and systems [3]. This diagnosis becomes challenging when only eosinophilia is present in the peripheral blood with no circulating blasts. Its occurrence seems to be associated with poor prognosis, both in children [4] and adults [5]. Cytogenetic abnormalities, such as t(5;14), are often encountered with this subtype of leukemia [6]. It is important to be aware of this un common initial presentation of ALL in order to avoid a delay of diagnosis and treatment. We report two pediatric cases of ALL diagnosed with this rare presentation, admitted at our institution at the same period, raising the question of a possible common etiology.

CASE 1

A 2-and-a-half-year-old child presented with asthenia, dyspnea and fever, for 2 weeks. Pallor, diffuse petechiae, lymphadenopathy and hepatosplenomegaly were noticed on examination. Neurological signs were absent. Oxygen saturation was 92%. Blood examination showed leukocytosis (99.5 x109/l) with marked eosinophilia (83.7%) and rare blasts (1%), anemia (Hb 8g/dL) and thrombocytopenia (55 x 109/L) (figure 1). Bone marrow examination showed hypercellularity with 51% blasts and eosinophilia (38%) (figure2). Blasts were CD19+CD34+cCD79a+ in flow cytometry with positivity of PAX5, tdt, bcl2 and CD34, CD20 in immunochemistry.
Cytogenetic analysis showed a hyperdiploid karyotype:57,XY,+X ,+4 ,+6 ,+8,+10,+11,+15,+18, +21,+21,+22 [3],/46,XY[29]. The main molecular leukemic rearrangements including: BCR-ABL, CBF-MYH11, FIP1L1-PDGFRA were negative. Computed tomography scan showed bilateral ground-glass areas, no pleural effusions suggestive of pulmonary-pneumocystis or eosinophilic-pneumonia. The patient went into remission after induction chemotherapy which was conducted according to EORTC protocol.

CASE 2

A8-year-old child presented with fever and multiple cervical lymphadenopathies for the past 3 months. On examination, he had bilateral cervical and inguinal lymphadenopathy.
No hepatosplenomegaly was found. Lymph node's biopsy and immunochemistry concluded to B lymphoblastic lymphoma. Blood examination revealed eosinophilia (4.68 10^9/l) and lymphopenia (0.75 10^9/l) and no peripheral blasts. Bone marrow examination revealed a blastic infiltration with excess of eosinophilia, with a flow cytometry in favour to BIII ALL. Cytogenetics revealed a complexkaryotype:57~60,XY,+X[17],dup(1q)[2],inv(2),del(3q)[3],+3[4],+4,+5,+6,+8,+10,+11[9],+14[10]+15[14],add(16q)[12],+16[10],+17,+18,+21x2,+mar1[8],+mar2[4]+dmin[2]cp[20]/46,XY[5].FIP1-like-1-platelet-derived growth factor receptor-a (FIP1L1-PDGFRa) fusion, as well as BCR-abl rearrangement, were not detected on fluorescence in situ hybridization. Chemotherapy was initiated according To EORTC protocol. To date, the patient is incomplete remission, no further increased eosinophil counts have been documented.

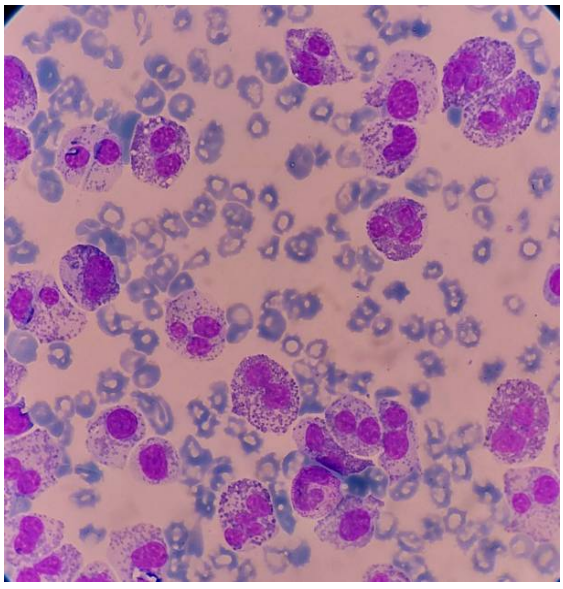

Figure 1: Peripheral blood smear showing marked eosinophils

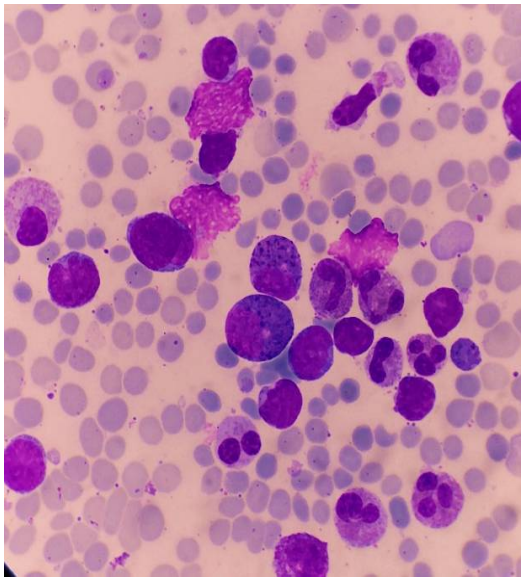

Figure 2: Smear of bone marrow aspiration. Presence of the eosinophils (thick arrow) and lymphoblasts (thin arrow).

DISCUSSION

Hypereosinophilia is defined by a count of eosinophils>500 , graded as mild (500-1500/uL), moderate (1500-5000 /uL) or severe (>5000/uL)[1,7]. Hematological diseases constitute the third most common cause of hypereosinophilia after allergic and parasitic diseases. In fact, hypereosinophilia a well-defined hematologic malignancy like myeloproliferative neoplasms, hodgkin's lymphoma, primary cutaneous T-cell lymphoma and solid tumors (colon cancer, ovarian carcinoma etc.). However, significant eosinophiliais a rare finding in ALL and the incidence is less than 1% [8]. It was first reported by Spitzer in 1973 [9]. The median age at diagnosis is 10 years with a male predominance and the majority of cases are B-cell ALL[10]. Eosinophilia usually precedes the diagnosis of ALL by 1 to 9 months and rapidly resolves with remission, but tends to accompany relapse [11].Its reoccurrence remains uncertain whether it is due to leukemia or to an associated infection.

Clinically, several clinical manifestations associated with the eosinophilia in filtration may occur in addition to non-specific symptoms such as fever and fatigue.

In a case series of 35 patients with this association, pneumonia or pulmonary infiltrates were reported in 51%, and chest pain was present in 20% [12].

The pulmonary infiltrates found in our first patient might be related to eosinophilia. In addition, a significantly increased risk of cardiac and vascular thrombosis exists in patients bearing this association [13]. In fact, congestive heart failure represents the main cause of mortality [13,14].

The pathophysiology of hypereosinophilia with ALL is not well established. Eosinophilia may result from excessive release of eosinophilic cytokines by neoplastic cells and T-helper cells (IL-5, IL-3, GM-CSF...) or from clonal development subsequent to a variety of cytogenetic abnormalities [1]. Nevertheless, concerning the development of hypereosinophilia in patients with ALL, it probably appears to be the consequence of a mixture of clonal and reactive processes [15].

A variety of genetic abnormalities in hematological malignancies have been documented in association with eosinophilia. However, the common finale cascade leads to the formation of fusion genes leading to constitutive stimulation of tyrosine kinases (commonly PDGFRA, PDGFRB, and FGFR1) responsible for eosinophilic proliferation [1]. In 2008, WHO has created a new entity entitled "Myeloid and lymphoid tumors with eosinophilia and abnormalities of PDGFRA, PDGFRB, and FGFR1" given the importance of the coexistence of eosinophilia in hematological malignancies.

The most prevalent cytogenetic findings concern chromosomes 5 and 14, t(5;14) (q31;q32) and chromosome 5 deletion, del(5)(q15q33).In fact, chromosome 5 carries IL-3 gene, whoseover-expression induces increased eosinophil production. In the two patients reported here, no particular chromosomal abnormalities were observed. However, a hyperdiploidy was found in both patients.

The prognosis for ALL with hypereosinophilia is significantly worse than for ALL alone, with a median survival of 7.5 months. In comparison to standard definition of ALL, congestive heart failure is the main cause of increased mortality in patients with ALL and hypereosinophilia [14]. With the limitations of a short follow-up, our two patients are in hematological complete remission.

CONCLUSION

The two cases presented strengthen the fact that ALL is one of the possible causes of persistent hypereosinophilia. Therefore, we suggest that hematologists should be aware of this unusual presentation of ALL within the context of a correct differential diagnosis of persistent peripheral eosinophilia, particularly in the absence of lymphoblasts in peripheral blood. Thus, an appropriate investigation, including bone marrow aspirate, is necessary.

Finally, this unique ALL form presents additional morbidity and mortality related to hypereosinophilia, such as cardiac failure, peripheral neuropathy and thromboembolic phenomena.

Follow-up should therefore include careful monitoring of secondary complications.

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