Juvenile Xanthogranuloma and Acute Leukemia: A Case Report

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INTRODUCTION

Juvenile xanthogranuloma (JXG) is a benign disease of early childhood, affecting the skin, mucous membranes, eyes, and viscera. It is characterized by the presence of one or more yellowish, cutaneous papules or nodules which spontaneously regress.

The association between JXG and juvenile chronic myelomonocytic leukemia (JCML) has been well documented [1-14]. In this report we present a case demonstrating an uncommon association between JXG and acute lymphoblastic leukemia (ALL) and a comprehensive literature review.

CASE REPORT

ALL (FAB L1) was diagnosed in a 43-month-old boy, whose skin was remarkable for multiple papular lesions located primarily on the face and neck, noted at the age of 6 months. Histopathological examination at that time confirmed the diagnosis of JXG, demonstrating lipid-laden histiocytes infiltrating the dermis and polymuclear giant cells (commonly referred to as Touton cells).

He presented with a 2-week history of decreased activity and complaints of abdominal pain. Two days prior to admission he exhibited decreased ambulation and complained of leg pain. Additional pertinent history included: spontaneous epistaxis twice; appearance of areas of pinpoint-hemorrhage in the skin; intermittent temperature elevations to 40°C; and persistent cough.

The family history did not mention occurrence of neurofibromatosis type I (NFI), chromosomal disorders, or exposure to clastogens. Physical examination revealed a pale, listless boy in no acute distress. Examination of the skin was remarkable for the presence of petechiae, hematomas, and multiple red-yellow elevated skin lesions on the face, neck, and trunk (Fig. 1). No café au lait spots were found. Additional significant findings upon physical examination included: an enlarged liver palpated 5 cm below the right costal margin; an enlarged spleen was palpable 4 cm below the left costal margin, and profound, generalized lymphadenopathy.

Significant laboratory data included: hemoglobin, 2.7 mmol/l; platelet count, 12,000/mm³, and WBC, 7,100/mm³, with 29% blast cells. Serum cholesterol and triglyceride levels were normal. The bone marrow was hypercellular, with more than 98% blast cells of the lymphocytic type, FAB L1. The cerebrospinal fluid was free of leukemic cells. Immunological typing revealed a common ALL (CD10+, HLA-DR+). Chromosomal analysis of the leukemic cells revealed a normal karyotype, 46XY.

Treatment was started in accordance with the ALL-VII protocol of the Dutch Study Group Leukemia in children (DSGLC/SNWKL). The patient reacted promptly to therapy, without severe complications. He is currently receiving maintenance therapy, at the age of 4 years and 6 months. The skin lesions have decreased in number and size, but they have not yet resolved.

DISCUSSION

JXG was first described by McDonagh in 1912, who coined the term naevoxanthoendothelioma for this disorder.

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The differential diagnosis for JXG includes urticaria pigmentosa, Langerhans cell histiocytose, xanthoma, and dermatofibroma. Histological examination of the lesions demonstrates an infiltrate in the dermis and epidermis of histiocytic cells, often with foamy cytoplasm. The infiltrate contains Touton giant cells, eosinophilic leukocytes, lymphocytes, and mast cells [2,3,10]. Ladisch and Miller [13] classify this disorder as a localized transient form of histiocytosis. The histiocytes in this disorder are not OKT6 positive and do not contain Birbeck granulae, which is typical for langerhans cell histiocytosis.

The boy we described developed beside his JXG a common ALL. The annual incidence of leukemia is about 4.2 per 100,000 in children less than 15 years of age. It is therefore the most frequent malignant disease of childhood [14]. There is an increased incidence of leukemia in children with chromosomal disorders, e.g., trisomy 21, chromosomal breakage syndromes, and immune deficiency disorders [5,14,15]. In the light of this article concerning the relationship between JXG and leukemia, we must draw attention to the coincidence of leukemia, JXG, and NF [1–7,15–17]. In most of the cases, if not all, it concerns NF1 [18]. The other types of NF are much less common and in the literature no mention is made about such an association. This coincidence of NF and leukemia may be related to the fact that the EV12 mouse leukemia gene is located close to the NF1 gene on the short arm of chromosome 17 [19,20].

There is a striking difference in distribution of lymphocytic and nonlymphocytic leukemia in the group of patients with NF1 and leukemia. Bader and Miller [5] described 12 new patients and reviewed 17 previously reported cases from the literature, of patients with leukemia and NF1. They observed that the distribution in this group of lymphocytic and nonlymphocytic leukemia was 9:20, whereas in general this ratio is about 5:1 in childhood leukemia. Of the 29 case reports in the article of Bader and Miller [5], one child also had JXG. Morier et al. [3] cited 24 published cases in the literature, of patients with NF1, leukemia, and JXG in the period from 1954–1990.
Among these patients were 23 children with JCML and only one patient with ALL, described by Song et al. [16]. This article again demonstrates the remarkable distribution of JCML and ALL in this group of patients, distinct from the usual distribution in childhood leukemia.

In our experience of evaluating approximately 500 children with ALL we have never observed this combination of ALL and JXG before. The exact frequency of the coincidence of JXG and leukemia, with or without NF1, cannot be determined from the available literature data. It seems that JCML predominates in this group. Regarding the different age distribution of JXG, leukemia, and NF1, one possibility is that JXG has already disappeared at the time of diagnosis of leukemia or NF1. We doubt whether this would have produced severe underreporting of the association. However, to gain more thorough insight into the precise coincidence of JXG and leukemia, it is essential that in every new patient with childhood leukemia the past medical history includes also (pre)existing skin disorders.

In future cases of leukemia and NF1, appropriate specimens might be sent for laboratory study to determine if a mutation of the EV12 gene has occurred [19,20]. Concerning the relationship between JXG and NF1, the exact coincidence numbers cannot be determined either. Riccardi [18] states that the presence of JXG and café au lait spots in a patient may be sufficient to support the diagnosis of NF1. No predictive value can be assigned to this relationship whether or not leukemia will develop. That is why hematologic blood tests on a regular basis are not recommended [22].

REFERENCES