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Case Report

Disseminated juvenile xanthogranuloma secondary to chemotherapeutic treatment of acute lymphoblastic leukemia

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ABSTRACT

Juvenile xanthogranuloma is a benign, reactive, self-limiting disorder within the non-Langerhans cell histiocytosis group. It primarily affects infants and preschoolers, and occasionally in adults. Some cases report concurrent non-LCH and leukemia, with bone marrow being the second common pathology. We present a case of JXG with acute lymphoblastic leukemia in a 17-year-old male. Emphasizing the importance of considering the possibility of apparently disparate disorders in a patient, especially with unusual clinical findings.

Keywords: Juvenile xanthogranuloma, Acute lymphoblastic leukemia, Non-langerhans cells

INTRODUCTION

Juvenile xanthogranuloma (JXG) is a benign, reactive, self-limiting proliferative disorder corresponding to a group of non-Langerhans cell histiocytosis (non-LCH), predominantly occurring in infants, preschoolers, and occasionally in adults. Clinically, it is characterized by nodules of varying sizes located on the face, neck, and upper trunk.[1] There are reports of cases showing concurrent non-LCH and leukemia, with bone marrow involvement being the second common pathology. However, few cases initially diagnose leukemia followed by non-LCH presentation.[2-5] We present a case of multiple JXG with acute lymphoblastic leukemia in a 17-year-old male.

CASE REPORT

A 17 years old male resident of San Luis Potosí, Mexico, presented to the Dermatology service with a disseminated dermatosis involving the head, trunk, upper and lower extremities. Characterized by multiple nodular, molluscoid formations of varying sizes with mild light brown hyperpigmentation, some clustering together (Figure 1). Dark brown nodules of irregular shape, poorly demarcated with a tendency to coalesce, were observed on the face and anterior neck (Figure 2). As a relevant history, he was diagnosed with acute lymphoblastic leukemia 6 months before the appearance of the lesions and received chemotherapy treatment as shown in (Table 1). One month after the induction phase of chemotherapy, he reported the onset of the mentioned dermatosis. Diagnostic approach included histopathological study of a nodular formation on the face, revealing epidermis with basket-weave stratum corneum, flattening of rete ridges, and basal cell hyperpigmentation. In the superficial to deep reticular dermis, a diffuse nodular cellular infiltrate was observed (Figure 3), primarily composed of histiocytes with large basophilic nuclei, granular chromatin, and abundant cytoplasm. Some histiocytes appeared multivacuolated (foamy) with interspersed

Touton-type multinucleated giant cells, along with predominantly eosinophilic infiltrate (Figure 4).

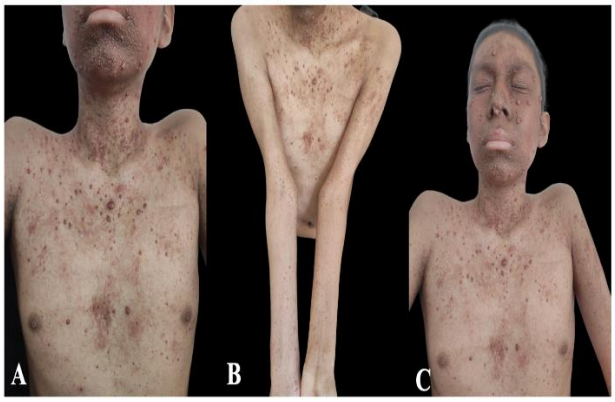

Figure 1 (A-C): Dermatosis involving the head, trunk, upper and lower extremities. Characterized by multiple nodular, molluscoid formations of varying sizes with mild light brown hyperpigmentation, some clustering together.

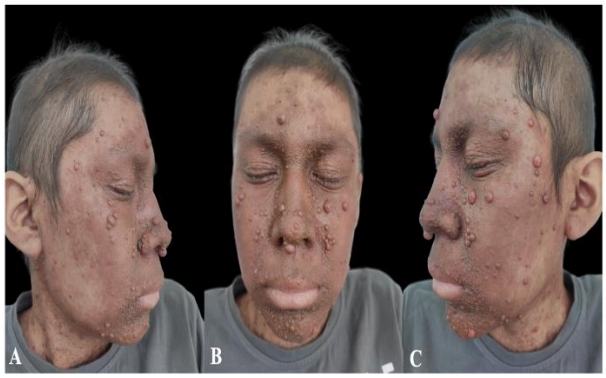

Figure 2 (A-C): Dermatosis of the face and anterior neck with dark brown nodules of irregular shape, poorly demarcated with a tendency to coalesce.

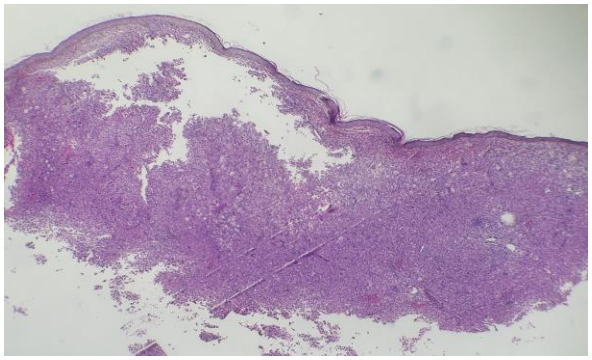

Figure 3: Epidermis with basket-weave stratum corneum, flattening of interpapillary processes, and basal cell hyperpigmentation (HE,4X).

Immunostaining for CD68 showed diffuse cytoplasmic granular positivity in proliferating cells, while S100 immunostaining was negative (Figure 5). PAS and Gomori Grocott stains revealed no evidence of fungal structures. Based on histopathological findings, a diagnosis of juvenile xanthogranuloma was established in a patient with acute lymphoblastic leukemia.

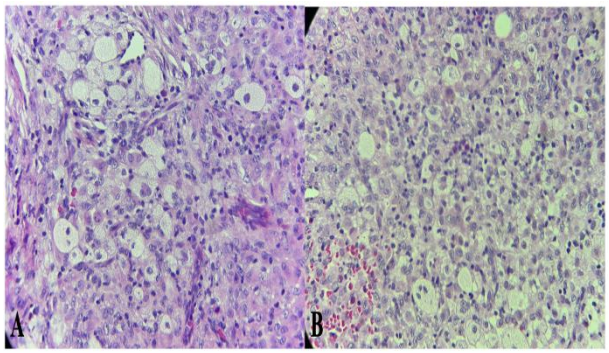

Figure 4 (A and B): Diffuse nodular cellular infiltrate composed of histiocytes with large basophilic nuclei, granular chromatin, and abundant cytoplasm. Some histiocytes appeared multivacuolated (foamy) with interspersed Touton-type multinucleated giant cells, along with predominantly eosinophilic infiltrate (HE, A 60X, B40X).

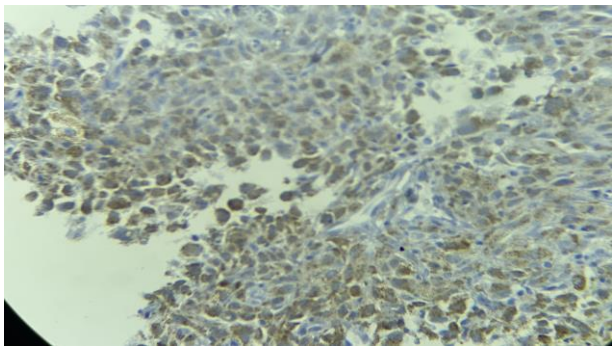

Figure 5: Immunostaining for CD68 (anti-CD68) shows diffuse cytoplasmic granular positivity in proliferating cells (60X).

Table 1: Patient chemotherapy treatment.

Drugs	Dosage
Prednisone	60 mg/m^2
Vincristine	4 doses of 1.5 mg/m^2
Daunorrubicine	2 doses of 30 mg/m^2
L-asparaginase	9 doses of 10000 UI
Cyclophosphamide	1gr/m^2
Cytarabine	3 doses of 75mg/m^2

DISCUSSION

Juvenile xanthogranuloma and acute lymphoblastic leukemia (ALL) are two distinct medical entities. JXG represents the most common form of non-Langerhans cell histiocytosis, predominantly occurring during infancy, with up to 17% being congenital, and 70% presenting before the first year of life. Incidence is unknown, with a

higher predisposition in males in cases of multiple JXG.[1,2,5] Conversely, ALL is a malignant hematologic disease targeting lymphocytes, affecting individuals of all ages, although more common in children aged 3 to 7 years.[3] The concurrent existence of non-Langerhans cell histiocytosis and leukemia is rarely reported, and its etiology remains unclear. Cases of JXG associated with juvenile myelomonocytic leukemia, T-cell and B-cell acute lymphoblastic leukemia, acute monocytic leukemia, and neurofibromatosis type 1 have been described.[4,5] Patients with acute myeloid leukemia (AML) seldom develop histiocytic disorders. Aditionally, it is more commonly observed a diagnosis of non-Langerhans cell histiocytosis preceding leukemia.[5] Regarding the association between ALL and non-LCH, few reports exist in literature of patients without previous suggestive XGJ dermatosis being diagnosed with ALL. Pawińska et al published a case of a 15-year-old patient, similarly initially diagnosed with ALL, later developing non-LCH.[6]

Initially, the appearance of AML after JXG was thought to possibly indicate secondary neoplasia triggered by chemotherapeutic agents used in non-Langerhans cell histiocytosis treatment.[5] However, evidence suggests a plausible linkage between these two diseases due to shared T-cell receptor and immunoglobulin rearrangement, along with shared mutations in RAS and CDKN2A, confirming a clonal relationship between them.[7] The role of RAS family genes in non-LCH etiology hasn't been fully defined, but RAS-RAF-MEK pathway activation is a distinctive feature of this disease.[8] Conversely, CDKN2A deletion is a common genomic alteration in ALL.[9] These shared alterations in both CDKN2A and RAS likely confer an underlying genomic basis to ALL and non-LCH, establishing leukemia predominance as an inevitable malignant disease concurrent with both non-LCH and LCH, rather than a chance occurrence.[7] GATA3 has been identified as a frequently mutated gene in ALL, while BRAF mutations are found in both LCH and non-LCH.[8,10] Specifically, CREBBP mutation in ALL predisposes to LCH development. These findings reinforce the claim that non-LCH isn't a secondary malignant neoplasm resulting from DNA damage due to cytotoxic agent exposure in ALL treatment, but rather stems from shared genomic alterations common to both diseases.[7]

CONCLUSION

The clinical case presents the unusual coexistence of two seemingly distinct medical entities: juvenile xanthogranuloma and acute lymphoblastic leukemia. JXG is a benign disorder of non-Langerhans histiocytes, predominantly observed in children, while ALL is a malignant hematologic disease affecting lymphocytes and can occur at any age, being more common in children. The association between JXG and ALL is uncommon, and its etiology is not fully understood. Although there are case reports describing the coexistence of non-Langerhans cell histiocytosis and leukemia, the underlying reason remains under investigation. In this specific case, the patient was initially diagnosed with ALL and later developed juvenile xanthogranuloma. Our work highlights the importance of considering the possibility of the coexistence of apparently disparate disorders in a patient, especially when there are unusual clinical findings. Furthermore, understanding shared genetic bases may have important implications for the diagnosis and management of these patients. However, further research into the exact mechanisms linking these two diseases is needed to improve understanding of their clinical and genetic relationship.

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