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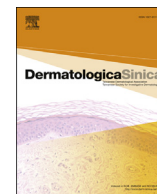
CASE REPORT

Baby with neonatal systemic juvenile xanthogranuloma born within a cross-cousin marriage

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ABSTRACT

Juvenile xanthogranuloma is a non-Langerhans cell histiocytosis seen most commonly in childhood and adolescence. Extracutaneous involvement is rare. We report an interesting and extremely rare case of systemic (skin, lung, spleen, and colon) "juvenile xanthogranuloma" in the neonatal period. Our case was the first ever reported case born to a cross-cousin marriage.

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Introduction

Juvenile xanthogranuloma (JXG) is a rare disease of unknown etiology, which belongs to non-Langerhans cell histiocytosis group.[1] It is a benign, generally asymptomatic condition, most frequently seen in early childhood.[2] In systemic JXG, involvement of the mucosal surfaces, central nervous system, gastrointestinal tract, eye, kidney, liver, spleen, lung, testis, lymph node, muscle, and bone marrow may be seen.[3—5] Here, we report on a 3-month-old baby born to a cross-cousin marriage. When the baby was 10 days old, subcutaneous nodules were noted and eventually diagnosed as JXG. Histopathological examination revealed involvement of the lungs, spleen, and gastrointestinal system.

Case report

The patient was admitted to our hospital at the age of 3 months, because of painless swelling behind the ear and cervical region. It was the third child of the family. No problem was detected in the

perinatal period. Family history revealed that parents were cousins, and the siblings, aged 7 years and 9 years, were both healthy (Figure 1). The patient's growth was normal and appropriate with the age. A nodule (1×1.5 cm^2 in size) was observed at the left retroauricular region that healed with scarring and another (1×1 cm^2 in size) at the right anterior cervical region. Other systems were normal. Laboratory findings were in normal ranges, except for low hemoglobin (7.1 g/dL) and hematocrit (21%), and high erythrocyte sedimentation rate (105 mm/hour) and C-reactive protein (4.83 mg/L). Tests for TORCH infections (*Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, Herpes Simplex*) and tuberculosis were negative, and lymphocyte panel and burst suppression were normal. A chest radiograph revealed bilateral pulmonary nodules and interstitial infiltrates, and this prompted a computerized tomographic examination. Thoracic CT (computed tomography) revealed cavitary lesions, with thick walls and cystic zones, of different dimensions at different locations in both lungs (Figure 2). Bone marrow was normal. Abdominal ultrasonography demonstrated multiple solitary hypoechoic nodules in the spleen. Fundoscopic examination, cranial magnetic resonance, echocardiography, and head and long bone X-rays were normal. During the course of the disease, melena was detected and granular lesions were seen at transverse, sigmoid colons and rectum by colonoscopy. Lung biopsy revealed disseminated histiocytic infiltration at the parenchyma and a number of necrotic granulomas. Immunophenotypically, most of the histiocytic cells were positive for CD68
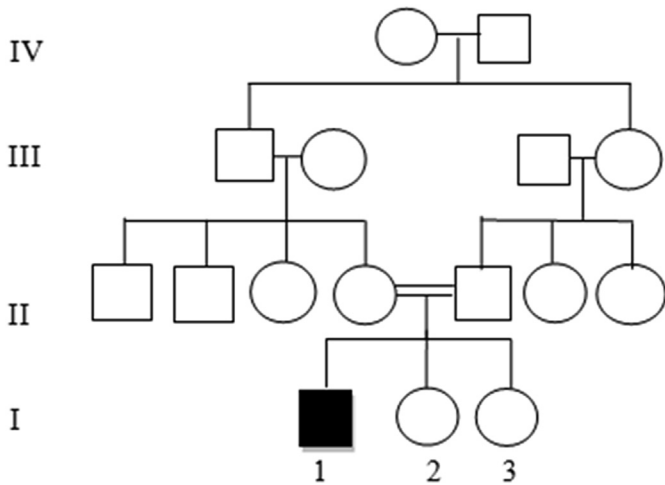
Figure 1 Family pedigree of the patient (1: our case).

Figure 2 Nodular lesions with thick walls and cystic zones in the lung parenchyma.

and negative for S-100 protein and CD1a (Figures 3A and 3B). In the skin biopsies from the cutaneous lesions, the same histiocytic infiltrations were detected with CD68-positive, S-100-negative, and CD1a-negative staining (Figure 4).

Prednisone and vinblastine were started with the diagnosis of systemic JXG. During the 1st month of chemotherapy, abdominal ultrasonography revealed a decrease in the nodular lesions of the spleen and lungs. However, the child died because of respiratory failure following pneumonia during the 2nd month of treatment.

Discussion

Because the most prominent finding of our patient was diffuse cavitary lesions in the lung, differential diagnosis was focused on this finding. Multifocal or diffuse involvement with cavitary lesions may be seen in neoplasms (bronchogenic cancer, lymphoma, and metastasis), many types of infectious processes and abscesses, pulmonary infarct, septic embolism, vasculitis, congenital abnormalities, rheumatoid nodule, and pulmonary Langerhans cell histiocytosis.[6] In our case, as the symptoms initially started in the neonatal period, the most probable reasons ruled out were infectious processes, septic embolism, congenital abnormalities, and pulmonary Langerhans cell histiocytosis. Eventual diagnosis of JXG, which is an extremely rare condition, was made by histopathological examination.

Contemporarily, it has not yet been clarified whether JXG is a reactive or a pathological disorder.[2] Viral infections such as *Cytomegalovirus (CMV)* or *Varicella* has been thought as the trigger factor in some cases.[3,7,8] Neurofibromatosis type 1 (NF1) and juvenile chronic myeloid leukemia may accompany JXG. The incidence of NF1 with JXG is 0.7—18%.[9] Zvulunov et al[10] have reported that the incidence of juvenile chronic myeloid leukemia increases with JXG and NF1 concomitance. In our patient, there were no clinical, radiological, or laboratory findings that support the diagnosis of NF1 or juvenile chronic myeloid leukemia. TORCH serology was found to be negative in our case.

Typically, cutaneous findings of JXG include smooth, nontender, reddish-brown papules and nodules ranging from 1 mm to 10 mm up to 4 cm. Lesions are mostly located in the head, neck, and upper trunk areas. Frequently detected solitarily in children, they can be multiple as well. In two big case series regarding JXG, solitary cutaneous lesions were detected in 67% and 71% of cases, multiple cutaneous lesions in 7% and 10%, soft tissue lesions in 16% and 15%, and systemic lesions in 4% and 5%.[3,4]

Extracutaneous manifestations of JXG are not very frequent; they may occur in 5% of cases. Freyer et al[11] found a total of 36 patients, including two of their own cases. The most common sites of extracutaneous involvement were subcutaneous soft tissue (in 33.3% of the cases), central nervous system (22.2%), liver/spleen (22.25%), lung (16.6%), eye/orbit (11.1%), and oropharynx and muscle (11.1% each). Although these extracutaneous lesions are of a benign nature, significant problems may arise due to pressure effects and possible clinical misdiagnosis as malignant entities.[3,4,12,13] Involvement of the central nervous system and liver was reported
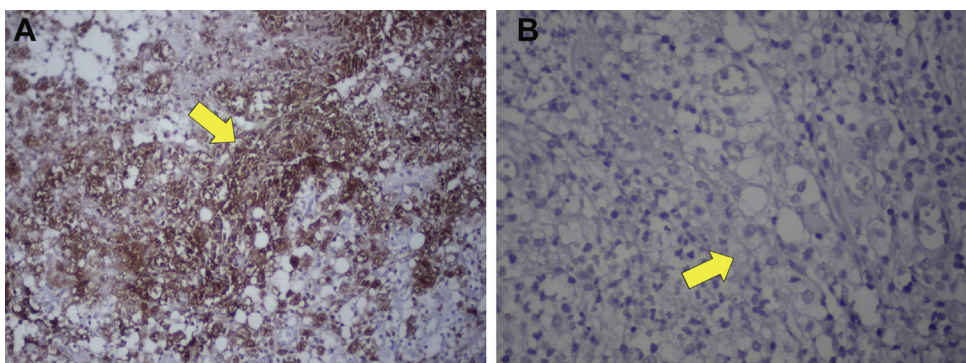
Figure 3 (A) CD68-positive histiocytes and (B) CD1a-negative histiocytes (DAB stain, 400×).
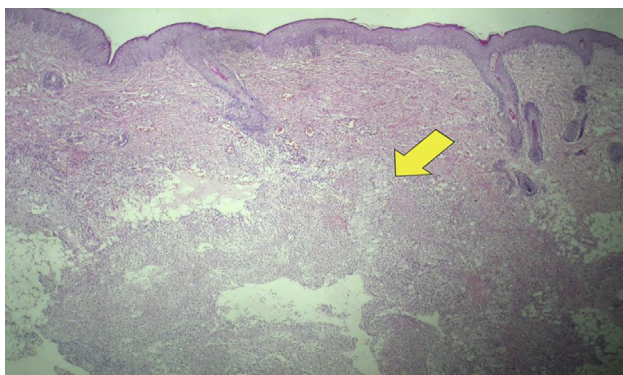
Figure 4 Histiocytic proliferation at dermis (hematoxylin and eosin stain, 40×).

to be related to death.[3,4,14,15] Pulmonary involvement usually manifests as bilateral, diffuse, asymptomatic micro- or macro-nodules.[11,16,17] Interstitial lung pattern and mediastinal adenopathy have been reported.[18] Our case had cavitary lesions, which were an atypical form of pulmonary involvement, distinct from the classical pattern of lung involvement described in the literature. Besides, abdominal ultrasonography revealed spleen involvement. Colon lesions were detected with biopsy.

JXG cells show a consistent immunoreactivity for vimentin, CD68, factor XIIIa, and CD163, and are negative for S-100, CD1a, and langerin.[12,19,20] Histiocytic infiltrations of the dermis have been detected in the skin biopsies; moreover, lung and colon biopsies confirmed the diagnosis of JXG histopathologically and immunohistochemically.

Although JXG is a benign condition, systemic involvement may cause morbidity and mortality.[21,22] Consequently, vinblastin, vincristine, cytarabine, methotrexate, prednisone, and 6-mercap-topurin are used for treatment.[23] Our case had a systemic disease with lung, colon, and spleen involvement; therefore, chemotherapy with prednisone and vinblastin was started. However, the child died in the 2nd month of treatment as a result of respiratory failure due to pneumonia.

Cross-cousin marriage is frequently seen in Turkey; therefore, we often perform genetic investigations when we encounter rare cases with a history of cross-cousin marriage. Since our case was born to a cross-cousin marriage, genetic investigations should have also been performed. However, it is considerably costly and lengthy to explore a genetic anomaly for the first time that was not defined earlier. Hence, we were not able to explore it.

In conclusion, in the differential diagnosis of pulmonary cavitary lesions, non-Langerhans cell histiocytosis should be considered in addition to Langerhans cell histiocytosis. It should also be noted that JXG may present in the neonatal period with systemic involvement. We propose that there can be a genetic predisposition in the etiology of early-onset systemic JXG.

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