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ADULT ONSET GAUCHER'S DISEASE: A RARE ENTITY WITH UNUSUAL PRESENTATION

Pathology

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ABSTRACT

Gaucher's disease arises due to mutation in GBA1 gene leading to a lack of β-glucocerebrosidase, an enzyme involved in lysosomal biochemistry, which leads to accumulation of the substrate, glucosylceramide. There is a paucity of literature pertaining to this disease, especially with respect to adult population, in the Indian subcontinent. We present a case of a 38 year old male, born of non-consanguineous marriage, presenting with pain and swelling of left lower limb since 2 months and a history of trauma 2 months back. What was first thought of simply as an injury to the left ankle later got diagnosed as Gaucher's disease thanks to a detailed clinical history taking and relevant investigations. Skeletal manifestations of Gaucher's disease is rare and should be considered in the differential diagnoses, if the patient presents with other accompanying symptoms.

KEYWORDS

INTRODUCTION:

Gaucher disease is an inherited error of metabolism due to deficiency of glucocerebrosidase, which is caused due to mutation in GBA1 gene, leading to excessive accumulation of the substrate, glucosylceramide, in liver, spleen, bone, bone marrow etc. (1). There are three subtypes of Gaucher's disease, based on the presence or absence of neurological involvement. Type 1 is the chronic non-neuronopathic form. Type 2 is the acute neuronopathic form, which is characterized by progressive neurological involvement in addition to hepatosplenomegaly. Type 3, the subacute neuronopathic form, is seen in children aged between 2 and 6, and involves mild neurological findings and hepato splenomegaly. Beta-glucocerebrosidase enzyme deficiency is the common feature of all three subtypes. The clinical manifestations of the accumulation of glucosylceramide are pancytopenia, hepatosplenomegaly, pulmonary involvement, bone lesions and renal injury (2).

Case History:

A 38-year-old male, born of a non-consanguineous marriage, with a history of fall 2 months back, presented in the department of orthopedics with complaints of pain in the left lower limb below left ankle after the fall. The patient had some difficulty in walking but improved gradually. On examination, the patient had pallor, and local examination revealed a soft to cystic swelling measuring 6 cm × 5 cm on the medial side of the left lower limb below the ankle joint. The patient was given a course of analgesics and anti-inflammatory medications however, did not show improvement on follow up 1 week later. On a more detailed enquiry, the patient complained of moderate pain at the same site even before the trauma. The patient also gave a history of low platelet count since childhood. X ray of the left ankle showed a lytic lesion measuring 2 cm ×2.5 cm below the left ankle joint, which on MRI was suggestive of a bone infarct. Hepatorenal doppler scan showed gross splenomegaly with prominent splenic veins. The patient was then referred to the hematologist in view of pancytopenia (Hb – 9.4 g/dL, platelets – 26,000/µL, WBC count – 2100/µL). Blood glucose, renal function tests, ESR, CRP and Hb electrophoresis were within normal limits. The clinical impression given was pancytopenia secondary to hypersplenism with bone infarct. Bone marrow examination was done to work-up the pancytopenia.

On microscopic examination, the bone marrow aspirate showed hypercellular fragments and smear along with erythroid hyperplasia (40%). The erythroid cells showed micro- and macro-normoblastic maturation. The megakaryocytic and myeloid series were normal in number and maturation. Also seen on smear were singly scattered and small clusters of large cells with a single eccentric nucleus and abundant crumpled paper like cytoplasm suggestive of Gaucher cells. Bone marrow biopsy showed hypercellular marrow spaces with erythroid hyperplasia and normal megakaryocytic and myeloid series. It also showed sheets of storage cells with crumpled tissue paper like cytoplasm. Reticulin stain showed grade 2-3 fibrosis, which could explain the pancytopenia. The impression on bone marrow examination was storage disorder – Gaucher disease with dimorphic anemia. Enzyme studies revealed low activity of β-glucosidase, confirming the diagnosis of Gaucher disease.

DISCUSSION:

Most lysosomal storage disorders (LSDs) present in pediatric patients. Adult disorders are, with some exceptions, less common than the childhood cases. The clinical picture of LSDs in adults is not only less severe, but often shows quite different signs and symptoms than the early onset form, making their early diagnosis difficult. Metachromatic leucodystrophy, GM1 and GM2 gangliosidoses, type 1 Gaucher disease and aspartyl glucosaminuria are some of the lysosomal storage disorders manifesting as adult diseases (3).

The incidence of Gaucher disease's (GD) is around 1/40,000 to 1/60,000 births in the general population, but it can reach 1/800 births in the Ashkenazi Jewish population (4). The exact incidence and prevalence in Indian population is not known owing to a paucity of reported cases of Gaucher disease in the literature with reference to the Indian subcontinent (5). In the largest study of Gaucher's disease in Indian population conducted by Barney et al, the median age of diagnosis was 2 years and the neuronopathic type was more prevalent (6). The overall mean age of onset of patients in the Gaucher Registry (run by the International Collaborative Gaucher Group) is at 20.4 years old, the majority (56%) of patients experienced onset before 20. However, this Registry primarily includes symptomatic and treated patients, and thus the mean age is probably skewed (4). The age of diagnosis in our patient (38 years) was much higher than both the Indian and international demographic data.

The common clinical presentations in type 1 GD include splenomegaly, hepatomegaly, fatigue, focal lesions in visceral organs, pancytopenia and bone involvement. Our patient gave a history of low platelet since childhood which was not investigated further. The patient also complained of chronic moderate pain at ankle joint followed by traumatic fracture which led to his presentation to the hospital. Given that the presence of skeletal symptoms as initial manifestation of GD is less known compared to the other symptoms, a delay in diagnosis in patients with no hematologic alterations or visceromegaly is frequent (7). In an analysis of 887 patients with non neuronopathic GD, the most common patient-reported bone symptom was pain; skeletal abnormalities, such as fractures, and avascular

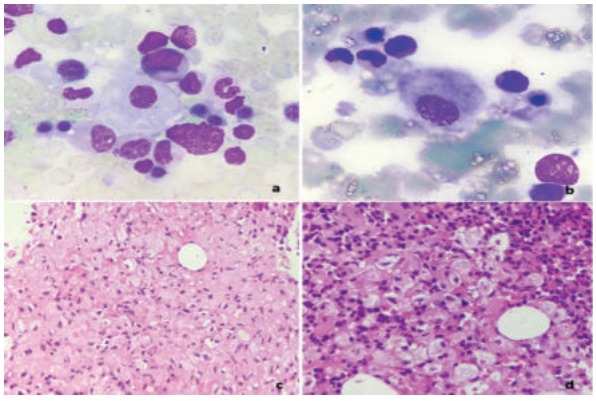
necrosis were rare (12). In the present case, a history of trauma led the clinicians farther from a suspicion of LSD. According to a study by Mistry et al, GD patients may visit up to eight (mean: 3.0) different specialists before a diagnosis is established (13). The Gaucher Earlier Diagnosis Consensus initiative, which consisted of 22 specialists in GD, identified that lack of disease awareness, overlooking mild early signs, and failure to consider GD as a diagnostic differential were major barriers to early diagnosis (11). Delay in diagnosis and initiation of treatment also lead to premature mortality in Indian settings as per Barney et al (6).

Much evidence demonstrates substantial improvement of hema tological and visceral parameters upon introduction of specific enzyme replacement therapy (ERT) for Gaucher patients (10). However, bone pathology remains the main problem for GD I patients even after the introduction of enzyme replacement therapy. Despite bone disease being a painful and disabling manifestation of GD 1, early intervention with ERT may delay the irreversible complications like osteonecrosis.

CONCLUSION

Adult onset and skeletal symptoms, being unusual manifestations of a rare and mostly under-reported disease cause delay in the diagnosis of Gaucher's disease. There is a need for an increased awareness, especially among the non-specialist clinicians to include storage disorders in the list of differential diagnoses in cases of cytopenias and organomegaly. The importance of timely diagnosis of GD in patients presenting with bone symptoms lies in the possibility of initiating early treatment that would avoid the irreversible and incapacitating skeletal complications that frequently develop in these patients throughout the natural course of the disease.

Figure



a, b: Bone marrow aspirate smears showing Gaucher cells with eccentric nuclei and abundant "crumpled paper" appearance of the cytoplasm; c, d: Bone marrow biopsy

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