Case Report

Acute myeloid leukemia along with Gaucher disease in a child

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ABSTRACT

There is sparse literature on the occurrence of acute leukemia in association with Gaucher disease in adults. Earlier, only two cases have been published describing acute leukemia in association with Gaucher disease in the pediatric age group. In this case report, we have described a case of acute myeloid leukemia along with Gaucher disease in an 8-year-old female child who presented with fever with hepatosplenomegaly. Measurement of β-glucosidase activity was the key modality in diagnosis. The possibility that the reduction of the enzyme in Gaucher disease is related to the development of hematological malignancies needs to be explored.

Key words: Gaucher, Leukemia, Pediatric

Gaucher disease is an autosomal recessive lysosomal storage disorder. In this disorder, deficiency of the enzyme glucocerebrosidase leads to the accumulation of glucocerebroside in phagocytes. There is sparse literature on the occurrence of acute leukemia in association with Gaucher disease in adults [1-3]. Only two cases have been published earlier describing acute leukemia in association with Gaucher disease in the pediatric age group [4]. It has been hypothesized that enzyme deficiency in Gaucher disease is the reason behind the development of leukemia [3].

In this case report, we elucidate a case of acute myeloid leukemia (AML) along with Gaucher disease in an 8-year-old female child. We have also summarized the earlier reported cases of acute leukemia with Gaucher disease.

CASE REPORT

An 8-year-old girl child of Indian origin presented with symptoms of fever, weakness, and increasing fatigue for 6 months. There was no history of vomiting. On examination, her weight was 15 kg and height was 110 cm (decreased for age). She had a raised pulse rate of 110/min and normal blood pressure of 108/70 mmHg. Her liver and spleen were enlarged. Lymphadenopathy was absent. There was no neurological or cardiovascular dysfunction.

Investigations showed a hemoglobin concentration of 8.4 g/dl, total leukocyte count of 2100/µl, and platelet count of 1.5×10^5/µl. The differential counts were neutrophils 38%, lymphocyte 48%, monocytes 10%, eosinophils 4%, and basophils 0. Prolonged fever of the patient prompted a bone marrow examination. Bone marrow smears were hypercellular and showed 80% blasts. The blasts were large with granular cytoplasm. The nucleus showed irregular nuclear membrane, open chromatin, and 3–4 prominent nucleoli. Gaucher cells were noted. They were present singly and in clusters. They were large with abundant fibrillary cytoplasm and eccentrically placed nucleus. The cytoplasm had the typical crumpled paper appearance (Fig. 1). Leukopoiesis and erythropoiesis were depressed. Megakaryocytes were adequate and active.

Further investigations were carried out. Gaucher cells were periodic acid–Schiff positive. Flow cytometry showed positivity for CD13, CD33, and CD117 favoring AML. Subsequently, leukocyte β-glucosidase activity was tested and as expected it was reduced. It was 4.2 nmol/h/mg (value in normal subject: 11–67 nmol/h/mg). The diagnosis of AML along with Gaucher disease was made.

Due to financial constraints, the genotype of the patient could not be determined. The chromosomal abnormalities and genetic mutations associated with AML were not evaluated. Family history was negative for acute leukemia or Gaucher disease. At present, the patient is receiving chemotherapy and enzyme replacement therapy.

DISCUSSION

In our patient, there was the concurrent presence of AML and Gaucher disease. An association between acute leukemia and

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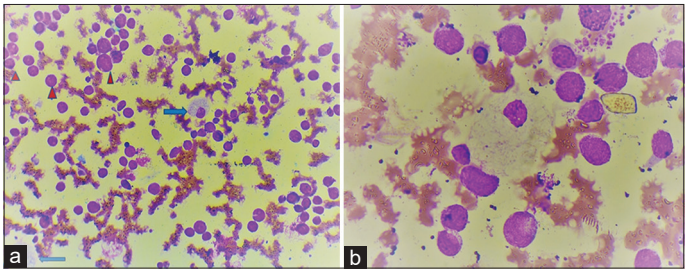

Figure 1: (a) Two large histiocytes (arrow) with characteristic cytoplasm (Gaucher cells) and numerous scattered myeloblasts showing high N:C ratio, open chromatin and prominent nucleoli (May–Grunwald–Giemsa [MGG], 400×); (b) Single large histiocyte showing crumpled paper appearance (Gaucher cell) surrounded by myeloblasts (MGG, 1000×)

Gaucher disease has been suggested earlier [1]. Corbett *et al*. described a 67-year-old man with Gaucher disease who was on transfusional support and later developed AML [1]. There has been a report of a 69-year-old woman who after a few years of being diagnosed with myelodysplastic syndrome (MDS) developed multiple abnormal fractures. Although bone marrow examination did not show any significant finding, β-glucosidase activity was reduced. Enzyme replacement therapy improved symptoms of Gaucher disease and several hematological findings of MDS [5].

Earlier, only two cases have been reported of acute leukemia with Gaucher disease in the pediatric age group. These two cases had acute lymphoblastic leukemia [4]. A 30-year-old male with type 1 Gaucher disease, while on enzyme replacement therapy developed acute lymphoblastic leukemia [3]. In another case, a 31-year-old male with a family history of Gaucher disease developed acute lymphoblastic lymphoma. He was diagnosed to have Gaucher disease at age 14 [2].

It has been hypothesized that the accumulated glucocerebroside provides chronic antigenic stimulus to the immune system and this may be the cause of the increased risk of lymphoproliferative disease [3]. The mean age of hematological malignancy in patients with type I Gaucher disease is reported to be 57 years while some others have reported that cancer risk occurs at all age groups in patients with type 1 Gaucher disease [2,6].

The frequent causes of fever with hepatosplenomegaly in the pediatric age group include hemolytic anemia, leukemia/lymphoma, infections, portal hypertension, and storage disorder. Splenomegaly can be caused by hemoglobinopathies. It is extremely important to differentiate between them as each of them has got different treatment and prognosis. Important investigations include enzyme assay, peripheral blood examination, and bone marrow examination.

The main differential diagnosis of Gaucher disease includes other lipid accumulation abnormalities, such as Niemann–Pick disease and Tay–Sachs disease. In Niemann–Pick disease, the cytoplasm of the macrophages is foamy and vacuolated as opposed to fibrillary in Gaucher cells. Tay–Sachs disease is characterized by the accumulation of GM2 ganglioside in the heart, liver, central nervous system, and spleen. Sea blue histiocytes may be found in chronic myeloid leukemia.

Gaucher-like or pseudo-Gaucher cells in bone marrow can be found in different conditions such as multiple myeloma, acute lymphoblastic leukemia, myelodysplasia, Hodgkin's lymphoma, thalassemias, and disseminated mycobacterium infection [7-12]. They are marrow macrophages related to high cell turnover. Sometimes, pseudo-Gaucher cells in bone marrow can obscure an underlying pathology [7]. Routine hematoxylin and eosin stain cannot distinguish between Gaucher cell and pseudo-Gaucher cell. Electron microscopic features can differentiate between the two with Gaucher cell showing distended lysosome containing lipid in stacks of the bilayer. Low levels of leukocyte β-glucosidase activity confirm the diagnosis of Gaucher disease. Knox-Macaulay *et al*. reported Gaucher-like cells in the bone marrow and liver of a teenager who had acute lymphoblastic leukemia. Leukocytic β-glucosidase enzyme activity was not measured, but bone marrow on electron microscopy was not indicative of Gaucher disease [9].

The gene for β-glucosidase, GBA1, is located on chromosome 1q21 [6]. The accumulation of glucocerebroside in mononuclear phagocytes leads to pathognomonic macrophages, the Gaucher cells. Type I Gaucher disease is associated with hematological malignancies such as multiple myeloma, chronic myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and rarely AML and acute lymphoblastic leukemia. Tumors arising in solid organs have also been reported in Gaucher disease such as bone, liver, kidney, brain, testis, prostate, colon, and skin [6].

CONCLUSION

In this case report, we have described a case of AML along with Gaucher disease in an 8-year-old female child who presented with fever with hepatosplenomegaly. The possibility that the reduction of the enzyme in Gaucher disease is related to the development of hematological malignancies needs to be explored.

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