

Acute Lymphoblastic Leukemia During Enzyme Replacement Therapy in Type 1 Gaucher's Disease

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Introduction

An inherited lysosomal storage disorder, Gaucher's disease (GD) occurs due to the deficiency of the glucocerebrosidase enzyme. Type 1 is the most common of the 3 major forms of GD. The clinical manifestations of Type 1 non-neuropathic GD include hepatosplenomegaly, anemia, thrombocytopenia, and bone pain due to skeletal lesions. The gold standard for diagnosis is the detection of low enzymatic activity of β glucocerebrosidase in peripheral blood cells compared with normal controls.¹ Bone marrow examination can be useful to eliminate the suspicion of a hematologic malignancy.

It has been reported that there may be an increased risk of certain cancers in patients with GD.² These include multiple myeloma, chronic lymphocytic leukemia, acute myeloid leukemia, large B-cell lymphoma, and Hodgkin lymphoma, as well as nonhematologic malignancies.^{3,4} Acute lymphoblastic leukemia (ALL) is one of the least reported malignancies linked to GD.

Here, we present a patient with GD who is also diagnosed with ALL during enzyme replacement therapy (ERT). This patient had been described in a previous report before she was diagnosed with ALL.⁵

Case Report

A 38-year-old woman with Type 1 GD was previously diagnosed by another center 18 years ago and had been followed with supportive care for 10 years. She was referred to the Ankara University hematology department with complaints of abdominal fullness and fatigue. Pale

appearance and massive hepatosplenomegaly were present upon physical examination. Pancytopenia was detected in her complete blood count (CBC). Her glucocerebrosidase enzyme level was 1.6 nmol/s/mpgr (5–13.5 nmol/s/mpgr). Bone marrow aspiration and biopsy were consistent with GD. She was a heterogenous carrier for *N370S* and *L444P* mutations according to genetic mutation screening. ERT (with human recombinant glucosylceramide [Cerezyme]) was started. Both hepatosplenomegaly and pancytopenia completely resolved during the ERT for 4 years. In the follow-up, anemia and thrombocytopenia were observed in the CBC (white blood cell: $7.4 \times 10^3/\mu\text{L}$; neutrophil: $1.7 \times 10^3/\mu\text{L}$; lymphocyte: $5.3 \times 10^3/\mu\text{L}$, hemoglobin: 5 g/dL; and platelets: $11 \times 10^3/\mu\text{L}$). Her peripheral blood smear was consistent with 50% blast. Bone marrow aspiration and biopsy revealed ALL infiltration. In the flow cytometry analysis of bone marrow aspiration, blasts were found to be positive for CD19, CD10, Tdt, and HLADR, and negative for CD34. Cytogenetic analysis of the bone marrow revealed a normal female karyotype, 46 XX. After cessation of ERT, the protocol previously defined by Linker and associates⁶ was administered to the patient for treatment of ALL.

Although pancytopenia continued, bone marrow examination showed hematologic remission for ALL after the first cycle. Since the patient did not have a human leukocyte antigen (HLA)-matched sibling, we searched for an unrelated donor for allogeneic hematopoietic stem cell transplantation. The patient refused transplant during follow-up. After the completion of 7 courses of chemotherapy, maintenance treatment was initiated and continued for 6 months. The patient could not tolerate maintenance treatment because of grade 3 thrombocytopenia and increases in liver function tests. Although maintenance treatment was ceased, thrombocytopenia continued. We performed a bone marrow biopsy for the

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evaluation of leukemic remission status. The patient's bone marrow was in remission for ALL, but was consistent with GD. We could not initiate ERT due to insurance constraints; therefore, the patient was referred to the general surgery clinic for splenectomy. Splenectomy was performed, and the patient has been in hematologic remission for 2 years with a normal CBC.

Discussion

There is an ongoing dilemma about the increased risk of hematologic and nonhematologic cancers in GD patients. Shiran and colleagues reported a 14-fold increased risk for hematologic malignancies.⁷ Data from the Gaucher registry of 2,742 patients did not yield statistically significant higher risks of solid tumors and hematologic malignancies, with the exception of multiple myeloma in middle-aged or younger patients. Nineteen patients were diagnosed with a hematologic malignancy in this registry; there was only 1 case of ALL.²

It has been postulated that the pathogenesis of cancer development in patients with GD should be related to glucocerebrosidase deposits. However, data are insufficient to determine whether ERT leads to cancer development. Marti and coworkers reported that chronic stimulation of the immune system by stored glycolipids in Gaucher cells results in lymphoproliferation.^{8,9} Recently, Ranade and associates reported on a patient with GD Type 1 who developed ALL 1 year after discontinuation of ERT.¹⁰ They claimed that increased glucocerebrosidase deposits as a result of discontinuing ERT could lead to lymphoproliferation. Additionally, a defect in the cellular immunity may conclude with malignancy. In contrast, our patient developed ALL during ERT. Lo and coworkers stated that ERT targets only macrophages, but pathophysiologic processes continued on non-macrophage cells.¹¹ Hence, those cells might have an increased role in cancer development. There are no written guidelines regarding treatments for malignancies associated with GD. We treated our patient using the classic ALL strategy previously described by Linker and associates.⁶ We could not continue maintenance therapy of ALL due to grade IV hematologic toxicities and grade II liver toxicities. Furthermore, we could not administer ERT to the patient due to insurance problems. Therefore, we preferred splenectomy for improvement of hematologic parameters at the end of chemotherapy. It has been reported that the risk of cancer in patients with GD may be increased after

splenectomy.¹² It has been postulated that splenectomy can increase the accumulation of Gaucher cells in bone marrow and other organs. In mouse models, enhanced natural killer-cell-mediated pathways (as a result of a lack in cytokine elaboration after splenectomy) can promote tumorigenesis and metastasis.¹³ Currently, our patient has been in hematologic remission with normal CBC 2 years after splenectomy.

Conclusion

In summary, controversy remains whether hematologic malignancies (except monoclonal gammopathies) are increased in GD patients. ALL is one of the least common hematologic malignancies in GD. Standard treatments should be safely used in patients with ALL that is associated with GD. Consequently, ERT for GD can contribute to the development of malignancy. Splenectomy in the late period can still be used as another therapeutic option in patients with incomplete blood count recovery due to continuing GD after ALL.

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Review

Hematologic Manifestations and Leukemia in Gaucher's Disease

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Overview

Bozdag and associates¹ described a case of acute lymphoblastic leukemia (ALL) in Type 1 Gaucher's disease (GD). A 38-year-old woman with a known history of GD presented with severe fatigue, pancytopenia, and massive hepatosplenomegaly with a low glucocerebrosidase enzyme level consistent with the diagnosis of GD. A bone marrow examination also supported the diagnosis of GD. She was started on enzyme replacement therapy (ERT) with complete resolution of her symptoms, and improved cytopenias and hepatosplenomegaly. While on ERT, she was diagnosed with Philadelphia (Ph) chromosome–negative standard-risk ALL, with normal cytogenetics. She was treated with induction chemotherapy and achieved complete hematologic response after the first cycle. Her maintenance therapy was limited by thrombocytopenia. She was referred for splenectomy as she could not afford ERT. She remained in remission 2 years after the diagnosis of ALL without any evidence of relapse, and is currently undergoing surveillance.

GD is the most commonly inherited lysosomal storage disorder occurring due to the deficiency of glucocerebrosidase enzyme, and is highly prevalent among Ashkenazi Jews. It is a multi-system disorder resulting from accumulation of the lipid-laden macrophages in the spleen, liver, bone marrow, bone, and other tissues/organs. Other mechanisms proposed in the pathogenesis of GD include macrophage activation and increased expression of genes leading to changes in the immune system.² Enzyme

assay is the recommended diagnostic test. Patients may also have elevated serum angiotensin-converting enzyme (ACE) levels, hyperferritinemia, thrombocytopenia, and low high-density lipoprotein (HDL) cholesterol; all reported as helpful surrogates in the diagnosis of GD. Care needs to be taken when interpreting bone marrow biopsies, as pseudo-Gaucher cells (seen in conditions like chronic myeloid leukemia, lymphoma, sickle cell disease, and infections) can lead to false-positive results.³ ERT remains the standard of care, and splenectomy should be reserved for complicated cases, such as refractory hypersplenism and/or symptomatic splenomegaly.⁴

Hematologic Manifestations

Although anemia and thrombocytopenia in GD patients are usually a manifestation of hypersplenism, caution is needed in their interpretation, as they could also herald the presentation of an underlying hematologic malignancy. Various hematologic conditions should be considered in the differential diagnosis of such a presentation. Multiple coagulation factor deficiencies are noted in patients with GD, with less than 50% of coagulation factors XI, XII, VII, X, V, and II occurring in approximately 30–60% of patients with GD.⁵ Deficiency of the coagulation factors may be related to chronic, ongoing, low-grade activation and/or subsequent lysis by fibrinolytic system related to mononuclear cell activation.⁵ Some of the coagulation factor defects are partly corrected by ERT, and the coagulation factor deficiencies are more pronounced in patients with an intact spleen compared to splenectomized patients.⁵ Clinical bleeding, however, primarily correlates to the severity of thrombocytopenia and to defective platelet adhesion function.⁵ Some physicians routinely employ platelet aggregation and adhesion studies prior to surgical procedures in such cases.⁶

Malignancy in GD

As the authors have described, controversy exists about the increased risk of malignancy in GD. Shiran and colleagues reported a 14-fold increased risk of hematologic malignancy in patients with GD based on the hospital registry retrospective data.⁷ Population-based retrospective data from a larger Gaucher registry involving 2,742 patients showed a significant increase of myeloma-related disorders in patients with GD, but only a relative risk of 1.23 for hematologic malignancies, which is not statistically significant when compared to the normal population.⁸ Rosenbloom and coworkers recommend screening for monoclonal gammopathy of unknown significance (MGUS) with a baseline serum immunoelectrophoresis upon initial diagnosis, and then every 1–2 years in patients older than 50 years, and annually in patients with GD because of the increased risk.⁸

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The authors suggest that the use of ERT was somehow related to the development of ALL in their patient. However, this is countered by a previously reported case by Ranade and associates, whereby the patient with Type 1 GD was reported to have developed ALL 1 year after the discontinuation of ERT.⁹ It was postulated that increased glucocerebrosidase deposits as a result of discontinuation of ERT could lead to lymphoproliferation and hence increased risk of malignancy. However, since ERT targets only macrophages, it may not reverse all of the pathophysiologic processes that continue in the non-macrophage cells, thus theoretically not mitigating complete cancer risk.¹⁰ In the absence of any larger trials, there is currently no concrete evidence implicating ERT in cancer genesis.

Splenectomy in GD

In a cohort study involving 403 patients, Lo and colleagues noted an increased risk of cancer after splenectomy in patients with GD. They proposed that splenectomy may lead to increased substrate deposition in the bone marrow, resulting in increased inflammatory pathways predisposing to cancer.¹⁰ Splenectomy also encourages accelerated crystal deposition in bone and other organ tissues, leading to increased bone and soft tissue disease in patients with GD.¹⁰ However, there is also some evidence for the possible protective role of splenectomy in childhood ALL. It was observed that childhood ALL patients in complete remission after induction chemotherapy benefitted from the addition of splenectomy compared to standard postremission chemotherapy. In this setting, children who underwent splenectomy had longer relapse-free survival without a significant increase in complication rates compared to children who received chemotherapy alone. This was explained by the presence of leukemic cells in the spleen, even after the bone marrow showed complete hematologic response.¹¹ However, subsequent trials in acute nonlymphocytic leukemia (ANLL) by Dutcher and coworkers failed to show such an advantage with the addition of splenectomy to standard postremission chemotherapy.¹²

Treatment of Ph-Negative ALL

Bozdag and associates used the regimen published by Linker and colleagues,¹³ which consists of daunorubicin, vincristine, prednisone, and asparaginase for induction chemotherapy of ALL. The patient achieved complete response after the first cycle of induction therapy. There is no single regimen of choice in Ph-negative ALL, and all regimens contain an anthracycline, vincristine, and a corticosteroid.¹⁴ However, some non-anthracycline-containing regimens¹⁵ have also been employed with similar

overall survival rates and could be considered in patients with cardiac problems. The type of consolidation therapy to use in Ph-negative ALL patients who achieve complete remission is a topic of much controversy. In Ph-positive ALL, the National Comprehensive Cancer Network (NCCN) guidelines strongly recommend hematopoietic stem cell transplantation (HSCT) in first remission.¹⁶ Post-remission therapy, including consolidation and maintenance therapy, is most commonly administered to patients with standard-risk Ph-negative ALL; stem cell transplant is usually reserved for patients with high-risk disease.^{14,16} This approach is supported by data from the French comparative study group, which showed no improved survival with allogeneic transplant over chemotherapy in patients with standard-risk Ph-negative ALL.¹⁷ However, a prospective study by the Medical Research Council and Eastern Cooperative Oncology Group (ECOG) that involved 1,521 patients with ALL showed results that favored transplant in younger Ph-negative patients with standard-risk disease, with overall 5-year survival rates of 53% versus 45% for the chemotherapy group after achieving complete remission.¹⁸

In summary, substrate deposition can lead to chronic stimulation of the immune mechanisms in patients with GD, thus theoretically creating a favorable microenvironment for cancer pathogenesis. However, larger population studies are required to confirm such an association. ERT remains the preferred treatment; whether it reduces the risk of cancer development is unknown.

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