



Diffuse large B-cell non-Hodgkin's lymphoma in Gaucher disease

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ABSTRACT

Gaucher disease type 1 (GD1) is the most common lysosomal storage disease and affects nearly 1 in 40,000 live births. In addition, it is the most common genetic disorder in the Ashkenazi Jewish population with phenotypic variation presenting in early childhood to asymptomatic nonagenarians. There have been a number of studies showing an increased risk of certain malignancies in patients, especially non-Hodgkin's lymphoma (NHL) and multiple myeloma.

We describe a 66-year-old Ashkenazi Jewish male with GD1 who was first started on enzyme replacement therapy (ERT) with imiglucerase for GD1 at age 57 years, followed a year later by the diagnosis of diffuse large B-cell non-Hodgkin's lymphoma (DLBCL). He was treated with *R-CHOP* (cyclophosphamide, doxorubicin, vincristine, and prednisone, plus the monoclonal antibody rituximab), however relapsed and developed myelodysplasia necessitating an allo-stem-cell transplantation but succumbed to severe graft vs. host disease. In addition, we also describe a 38-year-old Ashkenazi Jewish male with GD1 who was diagnosed with DLBCL at age 22 years with Gaucher disease diagnosed on pre-treatment bone marrow biopsy which was confirmed by enzyme assay and genotyping. At age 24 years, he was started on ERT with imiglucerase and at age 35 years, he switched to eliglustat. He has remained in remission from the lymphoma.

A meta-analysis of the literature will be elaborated upon and we will discuss the relationship of GD1 to NHL and discuss more recent information regarding lyso-GL1 and the development of NHL and multiple myeloma.

1. Introduction

Gaucher disease (GD1) is an autosomal recessive lysosomal storage disease caused by mutations in the glucocerebrosidase gene (GBA1) on chromosome 1 and the q 21 location, which results in the deficiency of the enzyme beta-glucocerebrosidase [1,2]. Because of this deficiency, glucocerebrosidase accumulates in macrophages in the liver, spleen, bone marrow, and more rarely, the lungs and kidneys. The lipid-laden macrophages can be seen histologically and are the pathognomonic Gaucher cells [3,4]. Progressive deposition results in hepatosplenomegaly, anemia, thrombocytopenia, growth retardation, abnormal bone remodeling, bone infarcts, avascular necrosis, fractures, and in more severe instances, pulmonary hypertension and renal involvement [5]. There is marked phenotypic variation, which is correlated to genotype, leading to presentations in early childhood to rare incidental discovery in nonagenarians [4,6]. Enzyme replacement therapy (ERT) initially and more recently substrate reduction therapy (SRT) have significantly altered the natural history of GD1 [7,8].

GD1 accounts for over 90% of all cases in the United States and is one of the most common lysosomal storage diseases affecting about 1 in 40,000 live births, but in Ashkenazi Jewish people the incidence is approximately 1 in 800 live births [9,10]. Although patients with GD1 have a higher incidence of Parkinsonism, they do not develop the more severe neurological manifestations seen in Types 2 and 3 disease [11,12]. Reports of the association of GD1 and cancer have been much more evident in the literature over the last few decades [13]. There has been a consistent reporting of a significantly higher incidence of multiple myeloma, non-Hodgkins lymphoma (NHL) and hepatocellular carcinoma [14,15]. More recent studies suggest that the lipid-laden macrophages with glucocerebrosidase and lysoGL-1, are alternatively activated leading to release of cytokines that influence the immune system [16,17]. Gammopathies, multiple myeloma, and NHL are felt to be the result of this atypical immune activation [17]. Herein, we report two cases of GD1 associated with NHL. In addition, a meta-analysis of the literature with respect to this association will be made.

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2. Case reports

2.1. Case report #1

A 68-year-old Ashkenazi Jewish male was diagnosed with GD1 at age 18 years complaining of left upper quadrant pain. Upon physical examination he was found to have hepatosplenomegaly. Bone marrow biopsy showed 70% of the cellular elements were lipid-laden histiocytes. He was anemic as indicated by an average hemoglobin level of 11.2 g/dL. He also had thrombocytopenia with an average platelet count of 93,000. Leucopenia was diagnosed at age 57 years, with a white blood cell count of 1800 cells per cubic meter of blood, and critically low hemoglobin at 6.8 g/dL and low hematocrit at 19.6. peripheral neuropathy was present throughout the patient's clinical care. He received blood transfusions and other symptomatic measures. At age 57 years he was found to have a low glucocerebrosidase level (4.5 micu/mg which was 15% of normal enzyme activity), as well as the identification of two copies of the c.1226G (p.N370S) mutation, one of the common *GBA1* Ashkenazi mutations. The patient received ERT with imiglucerase every 2 weeks which improved his hematological parameters. The patient had bone pain beginning at age 58 years and experienced an episode of panniculitis. At age 58 years he developed cervical lymphadenopathy which on biopsy showed acute diffuse large b-cell lymphoma. ERT was continued and he received chemotherapy with Rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP). At 18 months he was in remission and platelets were 140,000. At age 62 years he became pancytopenic and a bone marrow biopsy showed myelodysplasia and shortly thereafter the lymphoma relapsed in the soft tissue of his forearm, which was confirmed by biopsy. Fig. 1. Hematopoietic hormones, hemotopoetic stimulating agent, and ERT infusions continued to be administered throughout chemotherapy. Blood counts were significantly impacted by the chemotherapeutic cocktail he received. After undergoing bone marrow ablation, the patient received a Matched Unrelated Donor Peripheral Blood Stem cell transplant at age 64 years. The patient showed no signs of GD1, B-Cell lymphoma, or MDS two years post-transplant. At age 66 years, the patient developed severe graft-versus-host disease (GVHD) with ocular, oral, esophageal, lung, and hepatic involvement and passed away soon after from severe GVHD.

2.2. Case report #2

A 38-year-old Ashkenazi Jewish male presented in his teens with bone infarctions. He had knee pain which was diagnosed as Osgood-Schlatter disease. At age 22 years he developed neck and facial swelling found to be due to a large upper mediastinal mass which was causing a superior vena cava syndrome. Biopsy of the mass showed a diffuse large b-cell lymphoma, stage IA. He was treated successfully with R-CHOP followed by field radiation therapy to the neck and chest with no further relapse of his lymphoma. A bone marrow biopsy for a staging evaluation however showed significant numbers of lipid-laden histiocytes. Radiographic studies showed avascular necrosis of a hip. He was tested for Gaucher disease and found to be homozygous for the c.1226A > G (p.N370S) mutation. He became progressively anemic and thrombocytopenic which led to the initiation of ERT with imiglucerase at age 24 years. Subsequently the hematological and organ volumes improved as had the bone density studies. At age 35 years he was switched to SRT with eliglustat on which he has remained stable.

3. Discussion

Although this paper is primarily concerned with the relationship of GD1 and malignancy, the question of genotype/phenotype correlation is raised in that both cases reported herein had mild to moderate disease, which is consistent with N370S homozygosity [18]. With respect to neurological findings in patients with GD1, there is ample evidence

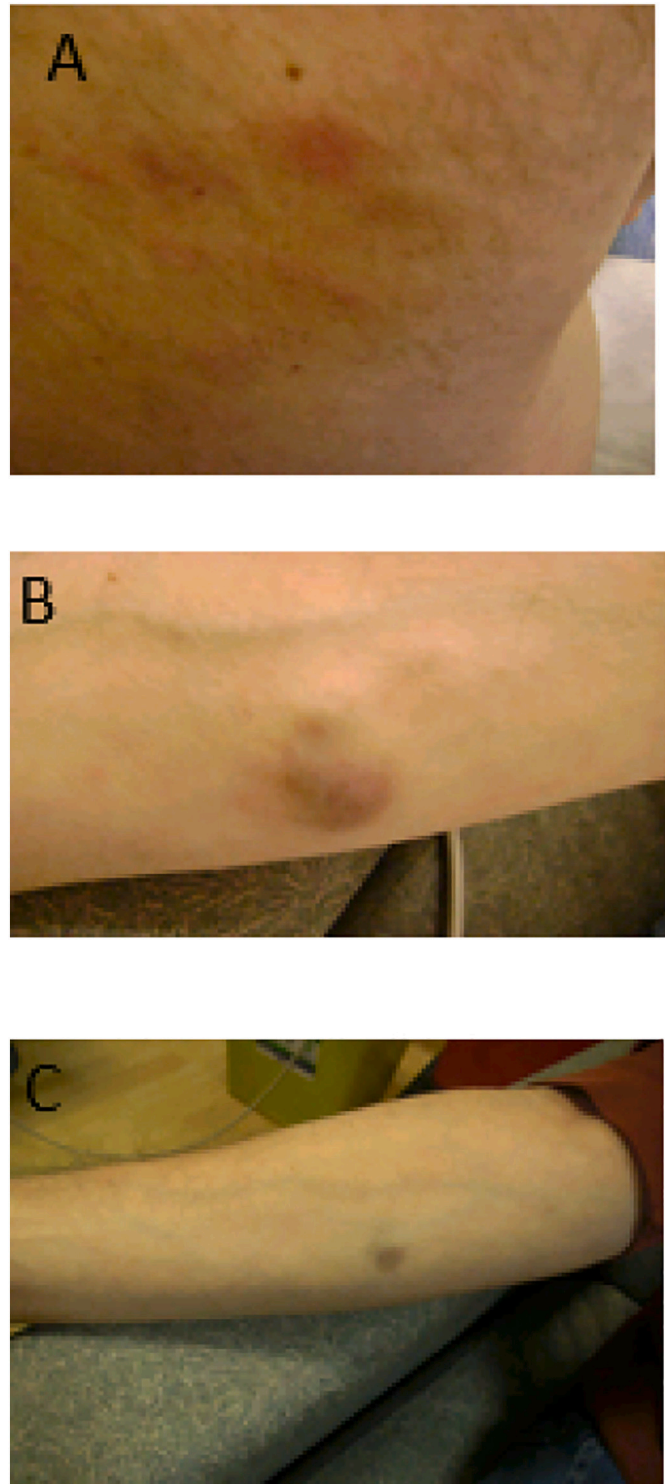


Fig. 1. Case report # 1. High-grade B-cell lymphoma pre-chemotherapy and pre-ERT in the neck (A), right forearm (B) and regression of the lesion post chemotherapy and post-ERT (C).

in the literature that peripheral neuropathy may be increased in GD1 and Parkinsonism definitely has an increased incidence in patients with GD1 [19]. So, the finding of an increased incidence of certain cancers in GD1 patients is of significant interest.

Rosenbloom et al. [14] reviewed the International Collaborative Gaucher Group (ICGG) Gaucher Registry to ascertain the incidence of cancer in 2742 adult patients with GD1 [14]. There were 126 patients

Table 1

Overview of overall incidence of cancer, and B-cell lymphoma/ NHL in large published GD patient cohort studies.

| Study | N | N with cancer (%) | N with NHL |
|-----------------|------|-------------------|-------------|
| Present report | 4 | 2 | 2 |
| Rosenbloom [13] | 2742 | 126 (5%) | 5 |
| Zimran [19] | 500 | 20 (4%) | 3 |
| de Fost [20] | 131 | 14 (10.6%) | 1 |
| Landgren [21] | 1525 | 137 (8.9%) | 9 |
| Taddei [14] | 403 | 46 (11.4%) | 3 |
| Weinreb [22] | NA | 168 | NA |
| Total | 5305 | 345 (6.5%) | 23 (0.004%) |

(5%) who had cancer, and when compared to the publicly available SEER (Surveillance, Epidemiology, and End Results) (National Cancer Institute, Bethesda, MD) data, the overall incidence of cancer was decreased, but the incidence of myeloma was significantly increased (risk ratio 1.6). There were five cases of NHL, which suggested a slightly increased risk but did not reach a level of significance with the risk ratio for hematological malignancies, 1.23. The cancer incidence in this study was based on co-morbidities and serious adverse events reported to the Registry. So, it was felt that many cases of cancer were underreported [14]Table 1

Zimran et al. reported their experience in a Gaucher Clinic where most of the patient were N370S homozygotes with mild disease and most were untreated for the GD1 [20]. Of their 500 patients there were 20 cancer cases and 5 had NHL. The cancer risk was not felt to be increased, but the mean age of these patients was 38 years, which may have missed cancer diagnosed in later life. de Fost et al. assessed the cancer risk in 131 patients with GD1 from both Germany and the Netherlands [21]. Fourteen patients had cancer (mostly myeloma and hepatocellular carcinoma), and only one case had NHL. For mostly non-Ashkenazi population the risk ratio for developing cancer was 2.5. Landgren et al. reported an NHL risk ratio of 2.54 (9 patients) in a group of 1525 US veterans with GD1 [22]. However, a letter to the editor regarding this paper pointed out that the incidence of GD1 in this population was extremely high because it was based on ICD-9 codes for lipidoses, which also includes lipid disorders and potentially other diseases [23]. The authors of the letter felt that the reported results were therefore unvalidated [23]. Taddei et al. studied the GD1 patients from two centers and reported on 403 patients of whom 46 developed 55 cancers [15]. Since these patients were predominantly Ashkenazi, the incidence was compared to an age- and sex-matched Israeli population [15]. There was an increased risk of hematological malignancies (risk ratio 3.45) with the majority myeloma and there were 3 cases of NHL [15]. In 36 patients, the cancer diagnosis preceded the GD1 diagnosis [15].

Also of interest is a study by Weinreb and Lee [24], which looked at the cancer deaths prior to and after the initiation of ERT ; there was seemingly a decrease in cancer deaths in the ERT era, but this could be as much attributable to improvements in cancer care as opposed to ERT. The authors revisited this question in a group of 175 GD1 patients who were never treated with ERT [25]. Of these patients, 57 died of cancer, of which myeloma, NHL, and leukemias predominated as the cause of death. A report by Cappellini, Rosenbloom et al. [14] in 1998 patients from the ICGG Gaucher Registry found 61 cases of hematological malignancies, 25 of which were NHL and 22 myeloma [26]. This study was very meticulous with retrospective review of all patient charts [26]. There is increasing evidence in the literature that Gaucher cells act as alternatively activated macrophages due to the storage of glucocerebroside and Lyso-GL-1 in the lysosomes [17,27,28]. There is increased release of cytokines and lysosomal GL-1 may act as an antigen for the development of monoclonal antibodies and ultimately myeloma [17,28,29]. In addition, the development of malignancy, especially NHL, also appears to be the result of immune system dysregulation

[25]. Further studies to fully elucidate these mechanisms is needed and may serve to further our understanding of cancer causation in general, and, more specifically in Gaucher disease. With ERT, many patients with more severe GD1 now live with a chronic disease, and issues of malignancies may become increasingly important.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval for this study was provided by the Office of Research University of California, Irvine, CA. Informed consent was obtained from both patients to use data from their clinical evaluations and their medical records.

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CRedit authorship contribution statement

Grant Bonesteel: Writing - original draft; **J. Jay Gargus:** Writing - review & editing; **Emily Curtin:** Writing - review & editing; **Mabel Tang:** Writing - review & editing; **Barry Rosenbloom:** Data curation, Writing - review & editing; **Virginia Kimonis:** Conceptualization, Methodology, Data curation, Writing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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