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Gaucher Disease and Malignancy: A Model for Cancer Pathogenesis in an Inborn Error of Metabolism

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Abstract

Clinical observations spanning almost half a century have demonstrated a consistent association of type 1 Gaucher disease (GD1) and cancers. However, the cellular and molecular bases of the association are not understood. Gaucher disease (GD) is a lysosomal storage disorder due to an inherited deficiency of acid β -glucosidase that underlies the accumulation of glucosylceramide in lysosomes of mononuclear phagocytes and immune dysregulation. The overall cancer risk is markedly increased in GD, and the determinants of malignancy in a subset of patients with GD1 are not known. The association of GD and cancer is most striking for hematological malignancies, with the risk for multiple myeloma estimated at almost 37-fold compared to the general population; some studies have also suggested increased cancer risk for non-hematological malignancies. There is no association of overall severity of GD to risk of cancer, although there is an increased prevalence of splenectomy among patients exhibiting the GD/cancer phenotype. Moreover, there appears to be an increased incidence of multiple consecutive cancers in individual patients. Several factors could contribute to cancer development in GD, including polarization of macrophages to the alternatively activated phenotype, chronic inflammation, chronic B-cell stimulation, splenectomy, hyperferritinemia, lysosomal dysfunction, and endoplasmic reticulum stress. Recent studies have highlighted T-cell dysfunction and modifier genes contributing to an increased cancer risk in GD. Macrophage-targeted enzyme replacement therapy (ERT) reverses systemic features of GD1; while cancer risk appears to be reduced in the era of ERT, it is not known whether this is a direct effect of therapy. Delineation of the mechanisms underlying the increased cancer risk in GD will provide additional novel insights into the role of lipids and

macrophages in cancer pathogenesis and, moreover, have the potential to reveal novel therapeutic targets.

Keywords

glucocerebroside; Gaucher disease; modifier genes; cancer risk; multiple myeloma; multiple cancers; enzyme replacement therapy; substrate-reduction therapy

I. INTRODUCTION

There is an increasing recognition of cancer risk associated with inborn errors of metabolism (IEMs).¹ Although IEMs represent single gene disorders, they lead to the disruption of a wide range of metabolic pathways arising from the accumulation of upstream metabolites, a deficiency of a downstream metabolite, and/or a diversion of the affected metabolic flux to secondary pathways that generate toxic intermediates. New or improved therapies for IEMs have resulted in prolonged life expectancy, and this has unmasked previously unrecognized aspects of the natural history of these diseases, such as the risk of malignancy. Type 1 Gaucher disease (GD1) is an outstanding example that symbolize the paradigm of the association of an IEM with cancer.² In GD1, aberrant macrophage activation and immune dysregulation are associated with increased cancer risk not only in the site of the metabolic disease (i.e., the bone marrow) but also in secondary organs involved in the disease process, such as the viscera.

Gaucher disease is an autosomal recessive disease caused by a deficiency of acid β -glucocerebrosidase (EC 3.2.1.45; lysosomal glucocerebrosidase, GCase) involving the hydrolysis of glucocerebroside in the final step of the sequential enzymatic degradation of complex glycosphingolipids arising from membrane turnover.³ The gene for acid β -glucosidase, *GBA1*, is located on a gene-dense region of chromosome 1q21, closely linked to a highly homologous pseudogene.³ The accumulation of glucocerebroside in mononuclear phagocytes leads to pathognomonic macrophages, the Gaucher cells (GCs), that underlie the heterogeneous multi-organ pathology and a complex multisystem phenotype. There are three broad phenotype classifications of GD, based on the presence and the rate of progression of neurodegenerative disease: type 1 (non-neuronopathic), which accounts for >90% of currently known cases, type 2 GD (acute neuronopathic), which is extremely rare, and type 3 GD (sub-acute neuronopathic), which is also extremely rare.⁴ Common features of all types of GD include hepatosplenomegaly, cytopenia, and diverse patterns of bone and lung involvement. Several unusual clinical manifestations occur that defy the macrophage-centric view of the disease, such as pulmonary hypertension,^{5,6} Parkinson's disease,⁷⁻⁹ and cancers.¹⁰⁻¹³ Because of the primary visceral involvement in GD1, it has become an outstanding target for enzyme replacement therapy (ERT) to reconstitute deficient lysosomal enzyme activity via receptor-mediated delivery of recombinant mannose-terminated GCase administered intravenously.¹⁴ Moreover, other approaches to treatment are being developed, including substrate reduction therapy and small-molecule chemical chaperone therapy for misfolding mutations of *GBA1*.^{15,16} Because of the broad cellular targets beyond the macrophage, these therapies may provide incremental benefit over macrophage-directed therapies.

Type 1 Gaucher disease is the most prevalent of lysosomal storage diseases. It affects approximately 1 in 40,000 of the general population, but its frequency in Ashkenazi Jews is as high as ~1 in 850.⁴ In addition to its highly heterogeneous phenotype and unpredictable natural history, patients are at risk of cancers. The association between GD and cancer has emerged through many individual case reports and more recently in well-conducted studies of large patient populations followed longitudinally. Interestingly, cancer is often the first consideration by physicians when evaluating a patient with GD, frequently leading to unnecessary investigations and delaying the diagnosis.¹⁷ In fact, the first patient with GD described by Philippe Gaucher in 1882—in whom he observed abnormal, lipid-laden macrophages in the spleen, now referred to as “Gaucher cells” (GCs)—was initially considered to harbor a neoplasm of the spleen.¹⁸ Mechanisms underlying the increased risk of cancer in GD are not understood, and research on this topic may shed important insights into molecular mechanisms of carcinogenesis in general and yield new therapeutic targets. In this review an examination of GD is presented in the context of cancer risk, the spectrum of malignancies that occur in GD1, the magnitude of cancer risk in GD, and potential mechanisms linking the two conditions, as well as therapeutic implications.

II. EARLY CASE REPORTS OF CANCERS IN GD1

More than 50 case reports of hematologic and non-hematologic cancers in GD1 patients over several decades have led to an appreciation of the link between the two conditions.² In these case reports, hematological malignancies were the most commonly described, including B-cell or plasma cell malignancies such as multiple myeloma, acute lymphoblastic leukemia, and chronic lymphocytic leukemia, as well as acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin’s disease, and non-Hodgkin’s lymphoma. Tumors of solid organs have also been reported in GD, including bone,¹⁹ liver,^{11,20–22} kidney,^{11,23} brain,²³ testis,²³ prostate,²³ and colon,²³ as well as melanoma.¹³

The individual case reports of cancers in GD1 prompted Lee et al. in 1982 to compile a registry of 239 GD1 patients. Of 35 patients who died in this cohort, 54% (19/35) of the deaths were attributed to cancer.²³ This study found that multiple myeloma was the most common malignancy in their non-surviving as well as surviving patients. A variety of cancers were described in this report: myeloma (3 cases), acute myeloid leukemia (2 cases), chronic lymphocytic leukemia (1 case), lymphoma (1 case), adenocarcinoma (lung, 2 cases; kidney, 1 case; colon, 1 case), hepatocellular carcinoma (2 cases), carcinoma of the larynx (1 case), carcinoma of mandibular area (1 case), and squamous cell carcinoma (1 case). In 1993, Shiran et al. reported an increased risk of cancer among 48 GD1 patients from their hematology clinic in Israel.²⁴ This study revealed a 14.7-fold increased risk of hematologic malignancy and an overall 3.6-fold increased risk of cancer in GD1 patients compared with healthy controls. In the 10 patients described in the study, 2 had myeloma, 2 had lymphoma, 1 had Hodgkin’s disease, 1 had gastric cancer, 1 had an islet cell tumor, 1 had pelvic sarcoma, and the primary origin of the cancer of 1 patient was unknown. However, this study was subject to a referral bias because all cases were consecutive GD1 patients with cancer that had been referred to the cancer center, leading to an over-estimation of risk. Furthermore, the average age of the GD patients presenting with cancer in this study was 57 ± 18 years. Nevertheless, the case reports and aforementioned studies,

together with research by Lee,²³ highlighted an association between cancer and GD in the pre-ERT era. In 2005, Zimran et al. revisited the issue in their large clinic for GD1 patients. This study involving 505 GD1 patients of Ashkenazi Jewish ancestry found no overall excess risk of malignancy, with the exception of multiple myeloma.¹⁰ The mean age of this GD1 study population was young at 37 years, which likely contributed to an underestimation of the incidence of cancer.

The association of GD1 and cancer was further examined in a large global registry, the International Collaborative Gaucher Group (ICGG) Registry comprising 2,742 eligible patients.¹² This study found no increase of overall cancer risk (0.79, 95% CI 0.67–0.94). However, there was a 5.9-fold (95% CI 2.8–10.8) increased risk of multiple myeloma. Cancer risk was likely underestimated in this study as well because the age distribution of the study population comprised a younger age group with intrinsically low cancer risk. Moreover, there was incomplete ascertainment because the ICGG is an observational registry to track responses to treatment rather than detailed individual phenotypes (*ClinicalTrials.gov* NCT 00358943). Thus, there is likely to have been incomplete capture of cancer data in this study due to significant under-reporting.

More accurate estimates for cancer rates in GD1 would derive from single-center studies of large patient cohorts longitudinally followed for GD1 as well as comorbidities. Two such studies have been reported from Europe¹¹ and the United States.¹³ Using pooled data of 131 non-Jewish GD1 patients from GD treatment centers in the Netherlands and Germany, de Fost et al.¹¹ demonstrated a 2.5-fold overall increased risk of cancers in their cohort of patients with mean age of 48 years. Fourteen GD1 patients (of 131 patients) developed cancers: 2 patients had multiple myeloma, 2 had hepatocellular carcinoma, 2 had colonic carcinoma, 1 had renal cell carcinoma, 1 had AML, 1 had testicular carcinoma, 1 had hemangioma-endotheliosarcoma, 1 had prostate cancer, 1 had B-cell lymphoma, and 1 had basal cell carcinoma. The risks of hematologic malignancies and multiple myeloma were estimated at 12.7-fold and 51.1-fold, respectively. This was accompanied by an increased prevalence of “monoclonal gammopathy of undetermined significance” (MGUS): 16% in the Netherlands and 7% in Germany (compared to an estimated 1–2% in a population of similar age). Interestingly, doses of imiglucerase enzyme therapy in Germany were higher compared to the Netherlands. Interestingly, the risk of hepatocellular carcinoma was markedly increased to 101-fold in this combined series.¹¹

The second study to assess cancer risk in a large longitudinally followed cohort of GD1 patients was reported from Yale/NYU Gaucher Disease Centers in 2009.¹³ Unlike the European study on non-Jewish patients, the focus of this study was predominantly on Ashkenazi Jewish patients to delineate the natural history of N370S homozygous vs. N370S heteroallelic patients. In general, N370S homozygous patients had slowly progressive GD1 in the skeletal compartment, but visceral and hematologic disease involvement was mild or even undetectable in patients presenting as adults. Because the majority of the patients were of Ashkenazi Jewish ancestry, the relative risk of cancer was calculated in comparison with the Israeli population in the Israeli cancer registry to adjust for ethnic differences in cancer rates. In this study, 55 cancers were reported in 46 patients in a total of 403 patients. There was significantly higher overall risk of cancer in this cohort at 1.80 (95% CI 1.32–2.40). For

non-myeloma hematologic malignancies, the relative risk was 3.45 (CI 1.49–6.79), and for multiple myeloma, the relative risk was strikingly increased at 25 (95% CI 9.17–54.40). In this study, cancer rates were determined for individual cancer types based on the first malignancy. Therefore, if multiple myeloma was a second or third cancer in an individual patient, it was not counted. When all cases of multiple myeloma were included, irrespective of whether it was the first or second (or third) cancer, the relative risk of multiple myeloma was as high as 37.5-fold. Of the nine patients with multiple myeloma in this study, all except one harbored the N370S homozygous genotype, and all occurred after the age of 50 years. A most striking observation of this study was that of GD1 patients over the age of 70, almost 31% had multiple myeloma (Figures 1 and 2). The study also showed an increased risk of melanoma at 2.26 (95% CI 0.62–5.79). A follow-up study focused on patients with multiple consecutive cancers.⁵ Nine patients (2.2%) developed two or three different types of cancers either consecutively and in one remarkable case, simultaneously. This study revealed that asplenia was a risk factor for single or multiple cancers, but there was no association with the *GBA1* genotype or with the overall GD1 severity. In this series, colectomy in one patient for adenocarcinoma revealed an unexpected lymphoma at a distal site in the surgical specimen, underscoring the extraordinary propensity for malignancy in GD1.²⁵ These findings are strongly suggestive of a role of modifier genes in the development of cancer in GD1. Indeed, biallelic mutation in the *MSH6* gene and *JAK2* mutations have been described underlying T-cell lymphoblastic lymphoma and myeloproliferative malignancy, respectively, in GD1.^{25,26}

The aggregate data of these studies comprising relatively large cohorts of patients are depicted in Figure 1 as a function of the mean age of the study population. All of the studies point to increasing cancer risk with age, which becomes significant after age 40. Examining multiple myeloma specifically and its precursor, MGUS, it is clear that there is an extremely high prevalence of gammopathy in adults, approaching 13–15% (Figure 2). Multiple myeloma occurred in patients only after age 50 in the study by Taddei et al.,¹³ and among N370S homozygous GD1 patients older than 70 years, almost 31% of patients developed multiple myeloma (Figure 2). It seems that if GD1 patients live long enough, the terminal event in the natural history is B-cell clonal proliferation and multiple myeloma.

A study reported by Landgren et al. seemed to cast doubt on the general association of GD1 with cancer and in particular multiple myeloma.²¹ This retrospective study of 1525 adult male military veterans apparently with diagnosis of GD1 (defined as patients with ICD codes 272.2 and 272.7) reported an elevated risk of non-Hodgkin's lymphoma (2.54, 95% CI 1.32–4.88) malignant melanoma (3.07, 95% CI 1.28–7.38), and pancreatic cancer (2.37, 95% CI 1.13–4.98). However, there was no overall increased risk of cancer or of multiple myeloma.²⁷ This study was misleading because the ICD codes 272.2 and 272.7 used to identify patients with 'Gaucher disease' are not specific for GD and include other lipid storage diseases as well as dyslipidemias.²⁸ While this study does not contribute to data on the specific association of GD1 and cancers, it does underscore the intriguing general association of malignancies with lipidoses.

III. PATHOGENESIS OF CANCERS IN GD

Despite the consistent association between malignancies and GD1, the underlying molecular and cellular bases of this association are not understood. Several potential mechanisms that may underlie predisposition to cancer are based on the current understanding of the pathophysiology of GD. These include chronic inflammation, chronic B-cell stimulation, abnormalities of T cell function, aberrant polarization of macrophages to the alternatively activated phenotype, potential role of splenectomy, hyperferritinemia, lysosomal dysfunction, and ER stress. Herein, four potential mechanisms underlying the predisposition to cancer in GD1 are considered: (1) accumulation of bioactive lipids in GD, (2) alternatively activated macrophages, (3) immune dysregulation triggered by glucosylceramide accumulation, and (4) role of genetic modifiers in the development of the GD1/cancer phenotype.

A. Accumulation of Bioactive Lipids

Deficiency of acid β -glucosidase leads to florid accumulation of glucocerebroside in lysosomes of mononuclear phagocytes due to high turnover of complex glycosphingolipids derived from endogenous as well as exogenous membranes. Studies of *in vitro* cell models of Gaucher cells have revealed that progressive accumulation of lysosomal glucocerebroside is followed by extra-lysosomal accumulation of this lipid as well.²⁹ Concomitantly, lysosomal glucocerebroside is deacylated by a previously unknown mechanism and transported out of the lysosomes.³⁰ In the extra-lysosomal compartment, glucocerebroside, and glucosylsphingosine become substrates for neutral glucocerebrosidase, encoded by the *GBA2* gene, generating highly bioactive lipids, ceramide, and sphingosine, respectively.³¹ In fact, recent studies point to potent effects of glucosylsphingosine in mediating cellular dysfunction in GD.³² Moreover, glucosylsphingosine was recently validated as a new biomarker of GD.³⁰ Eventually, increased flux through this pathway should lead to increased levels of sphingosine-1-phosphate that is recognized to have proliferative pro-mitogenic, anti-apoptotic and pro-angiogenic effects.³⁴ Together, these effects create an environment that is highly conducive to tumorigenesis.³³

Among the non-hematological malignancies described in GD, one of the most intriguing is hepatocellular carcinoma (HCC) with >100-fold higher risk compared to the general population.^{11,23,34} HCC has been described in GD1 in the setting of non-cirrhotic liver.²⁰ Moreover, cholangiocarcinoma has also been described in GD1.³⁵ Interestingly, evidence has been presented to demonstrate impressive capacity for biliary secretion of glucosylsphingosine in association with marked propensity for cholesterol gallstone formation in GD1.³⁶ Taken together, investigations into the potential role of glucosylsphingosine in promoting tumorigenesis appear to be justified.

B. Alternatively Activated Macrophages

The hallmark of GD is the Gaucher cell (GC), the glucosylceramide-laden macrophage with the characteristic morphology of a 'wrinkled-paper' of lysosomal glucosylceramide storage structures within the cytoplasm. Acid β -glucosidase is present in all cell types involved in lysosomal hydrolysis of endogenous and exogenous glucosylceramide; overt storage of

glucosylceramide occurs in mononuclear phagocytes due to turnover of effete cell membranes. GCs are not inert storage cells for excess glucosylceramide; rather, they are chronically activated macrophages that underlie the diverse clinical manifestations of GD. These mature, activated macrophages of predominantly the alternatively activated phenotype are surrounded by newly formed, highly inflammatory macrophages in tissues.³⁷ This cellular pathology is reflected in elevated plasma levels of several proinflammatory and anti-inflammatory cytokines, chemokines, and hydrolases. Serum biomarkers used as clinical indicators of total body burden of GCs (e.g., chitotriosidase and CCL18) reflect a predominance of the alternatively activated phenotype of tissue macrophages in GD.^{37,38} Moreover, elevated levels of IL-13 and IL-4 in the sera of the mouse model of GD1 suggest strong stimuli to polarization of macrophages toward the alternatively activated phenotype and Th2 response.³² Factors released by GCs and surrounding macrophages, such as IL-6 and CCL18, have been proposed to underlie the common occurrence of gammopathies in GD.³⁹ Tumor-associated macrophages have been implicated in carcinogenesis, the angiogenic switch, local invasion, and metastasis. Tumor-associated macrophages have many properties of alternatively activated macrophages. Therefore, the microenvironment created by GCs appears to be highly conducive to tumorigenesis.

C. Immune dysregulation in GD

The accumulation of glucocerebroside in the lysosomes of tissue macrophages result in macrophage activation and secretion of cytokines. This cytokine response is highly conducive to chronic B-cell stimulation, evidenced by extremely high prevalence of gammopathies in GD patients.⁴⁰ In this setting, in a background of a genetic predisposition, it seems likely that monoclonal B cells will thrive. Indeed, Kaplan-Meier plots of incidence of polyclonal and monoclonal gammopathies in GD show a temporal sequence that is consistent with this notion: 32% of GD1 patients in a large cohort had polyclonal gammopathy at a mean age of 62 years, 3.2% had MGUS at a mean age of 78 years, and 2.2% had multiple myeloma at a mean age of 84 years.^{13,41} Moreover, cytokines such as IL6 that stimulate B cells are consistently elevated in GD plasma of GD1 patients as well as of mouse model of GD.^{32,42} Indeed, levels of pro- as well as anti-inflammatory cytokines, chemokines, and growth factors are altered in GD. Elevations of IL-1, IL-6, IL-10, CCL18, and TNF- α have been reported in sera of GD1 patients.^{42–45} The aberrant activation of macrophages and induction of inflammatory responses in GD could occur in the absence of overt lysosomal storage, as systemic inflammation is evident in L444P homozygous mice, which demonstrate minimal storage of glucocerebroside.⁴⁶

Immune dysregulation arising from accumulation of lipids in GD may result in impaired immune surveillance. For example, there is evidence of reduced T-cell numbers in peripheral blood of GD1 patients (CD8>CD4) that correlate with severity of skeletal involvement and reverses upon ERT.⁴⁷ In conditional KO mouse model of GD1, there is severe impairment of T-cell differentiation and maturation in the thymus; moreover, the thymus might be an important site for B-cell production, reflecting strong B cell-tropic environment created by Gaucher cells.³³ In this model the immune cell composition of the thymus exhibited the earliest alterations suggestive of impaired T-cell maturation, aberrant B-cell recruitment, enhanced antigen presentation, and impaired egress of mature

thymocytes.³³ These changes correlated strongly with disease severity. In contrast to the profound defects in the thymus, only limited cellular defects were detected in peripheral lymphoid organs, mainly restricted to GD mice with severe disease.³³ In addition, impaired T-cell proliferation and function, reduced NK T-cells, and/or decreased dendritic cells were also detected.^{47,48} In a study of 5 GD1 patients defective T-cell function was evident through a reduction of E-rosetting capacity that was proposed to result from hyperferritinemia commonly found in GD.⁴⁹ Hyperferritinemia is common in GD, and ferritin release from GCs has been implicated in reducing T-cell function and IgM release from B cells.^{50,51} Moreover, the lipid-laden CD1d complex, through which NK T cells recognize glycolipids and MHC class II molecule expression, has been found to be elevated in patients with GD as well as in control monocytes treated with an inhibitor of GCase.⁴⁷ Interestingly, ERT induced a decrease in MHC-class II expression and partial correction of the CD4+ T-cell imbalances.⁴⁷ Taken together, converging evidence points to global immune dysregulation that appears to be strongly conducive to promote malignancy.

D. Genetic Modifiers Underlying the GD–Cancer Phenotype

The *GBA1* gene is a housekeeping gene, and its product, acid β -glucosidase, is involved in hydrolysis of glucocerebrosides in the lysosomes. It is in the mononuclear phagocytes that turnover of effete cell membranes generates large amounts of glycosphingolipids, leading to massive lysosomal accumulation of the substrate forming classic Gaucher cells. Quantitatively, a minor substrate of acid β -glucosidase is glucosylsphingosine, a bioactive lysolipid that appears to be the more potent lipid in mediating cellular dysfunction in GD.³² More than 300 unique mutations have been reported in *GBA1*; they include missense mutations, splicing defects, frame-shift mutations, and complex alleles representing a hybrid gene formed from a combination of the active gene and closely linked pseudogene.⁵² These mutations lead to a complete loss of the enzyme protein in the most severe neuronopathic forms, misfolded GCase protein, reduction of catalytic activity or intracellular stability, and/or subcellular trafficking. Despite the multiplicity of mutations, only five common mutations account for almost 90% of the disease alleles in the Ashkenazi Jewish patients and approximately 50% of the disease alleles in the non-Jewish patients.⁴

GD1 manifests as variable combinations of visceral, hematological, and skeletal involvement, and its heterogeneous phenotype does not show an exact correlation with the *GBA1* genotype. However, the presence of at least one N370S mutation absolutely precludes neuronopathic GD, and L444P homozygosity tends to result in neuronopathic disease (type 2 or type 3 GD).⁴ In GD1, there is a broad correlation of overall disease severity with *GBA1* gene mutation such that N370S homozygous patients in general tend to have milder type 1 GD, while compound heterozygous patients (N370S/84GinsertionG or N370S/L444P) on average exhibit more severe disease. However, among patients harboring the same *GBA1* genotype, there is extreme variability of disease severity noted among affected sib-pairs and even in identical twins.^{3,52–55} The extraordinary phenotypic variation in GD1 is most strikingly exemplified among patients who are homozygous for the N370S mutation.¹³ By one estimate, as many as half of N370S homozygous individuals never come to medical attention, yet among the symptomatic individuals, some patients present with severe disease during childhood, while the others present later in life with slowly progressive skeletal

disease.⁵⁶ Interestingly, occurrence of multiple myeloma is mostly noted among N370S homozygous individuals over the age of 50 years who exhibit minimal evidence of visceral or hematologic GD.¹³ The association of N370S homozygous *GBA1* genotype and multiple myeloma likely reflects the fact that this group of patients has the longest survival compared to more severe genotypes. However, there remains the intriguing possibility that N370S homozygous mutation, a protein-folding mutation that can be ameliorated by proteasome inhibitors, might uniquely confer increased myeloma risk, and this merits further investigation.⁵⁷ Other than this association, there is no genotype/phenotype correlation of *GBA1* gene mutations with respect to occurrence of cancer in GD1.

The extreme phenotypic variability of GD1 has focused attention on the potential role of modifier genes. Several candidate genes in inflammatory pathways have been studied on the basis of current understanding of the pathophysiology, but no consistent associations have emerged. In one study, there was an association of SNPs in the vitamin D receptor gene and cancer in GD patients compared with control non-GD population.⁵⁸ A recent GWAS study of N370S homozygous patients, stratified according to overall disease severity, identified SNPs in linkage disequilibrium with *CLN8* gene that appears to protect against development of severe disease.⁵⁹ This study reported data consistent with the notion that the SNPs in the *CLN8* gene region were associated with their increased expression and that *CLN8* functioned as a sphingolipid sensor and/or in sphingolipid trafficking to protect the cells from toxic effects of the accumulating glycosphingolipids. An important caveat in the study of phenotype variation in GD is variability of overall disease severity (i.e., exemplified by severity score index⁶⁰ or DS3⁶¹ and is distinct from occurrence of unusual phenotypes of GD. For example, occurrence of cancers,^{13,23} pulmonary hypertension,^{5,6} and Parkinson's disease⁶² are stochastic features that do not demonstrate strict correlation with overall disease severity. This latter type of phenotypic variation is likely to be determined by the impact of modifier gene(s) with a large effect. For example, biallelic mutation in the *MSH6* gene⁶⁹ and *JAK2* mutations²⁶ have been described as underlying T-cell lymphoblastic lymphoma and myeloproliferative malignancy, respectively, in GD1.

IV. SPLENECTOMY

In the pre-ERT era, splenectomy was performed frequently for relief of cytopenia and pressure symptoms. In a longitudinal follow-up of 48 splenectomized GD1 patients, Fleshner et al. reported that splenectomy was associated with more aggressive skeletal disease as well as a predisposition to malignancy.⁶³ In a study of N370S GD1, patients with single or multiple cancers were more likely to be asplenic.²⁵ However, another similar study of cancer risk in GD1 failed to find an association between asplenia and cancer.¹⁰ Relevant to this topic is the finding that compared to GD1 patients with intact spleen, the life expectancy of asplenic GD1 patients was reduced from ~6 years to 13 years.^{63,64} Interestingly, splenectomy has been shown to promote tumorigenesis in mouse models through NK-cell-mediated pathways.⁶⁵

There has been a dramatic decline of splenectomy in GD1 patients since the advent of imiglucerase enzyme therapy,¹⁵ which may contribute to declining rates of cancer in the new generation of GD1 patients.

V. CANCER RISK IN GD1 IN THE ERA OF ALGLUCERASE/IMIGLUCERASE ENZYME REPLACEMENT THERAPY

More than 10 years ago, Dr. Norman Radin proposed a role for glycosphingolipids in tumorigenesis and metastatic spread based on the ability of sphingolipids to promote DNA/chromosomal damage and to generate reactive oxygen species and angiogenesis. Indeed, preliminary data suggested that modulation of glucocerebroside levels using an inhibitor of glucocerebrosides synthase blocked growth of cancer lines.⁶⁶ Therefore, it is of considerable interest to learn whether cancer risk has been ameliorated in the era of macrophage-directed enzyme therapy, which reverses visceral manifestations, abrogates the chronic inflammatory state, and has obviated the need for splenectomy.⁶⁷ In 1982, the RE Lee Gaucher Registry at the University of Pittsburgh (a Registry from the pre-enzyme therapy era) reported on 35 patients who had died: cancer was the cause of death in 54% (19/35).²³ In contrast, among the 137 patients who died during the period when imiglucerase became the standard of care for GD1 (1991–2004), 28 deaths (20%) were attributed to cancer (20%).⁶⁴ Compared with the pre-enzyme therapy era, the prevalence rates of cancers since imiglucerase became the standard of care, appear to show a downward trend. Interestingly, a study reporting cancer prevalence rates in Amsterdam (where low-dose ERT is used) and Düsseldorf (where high-dose ERT is the standard of care) found cancer prevalence rates of 14% (9/63) versus 7% (5/68), respectively, corresponding to cancer-related death rates of 5% (3/63) versus 3% (2/68), respectively.¹¹ Additionally, it is of interest that deaths associated with multiple myeloma in GD1 fell from 9.7% in the pre-ERT era to 0.7% during the period after imiglucerase became the standard of care. It should be kept in mind that the treatment of multiple myeloma and other cancers has markedly improved since the pre-ERT era, and this situation has most likely contributed to seemingly reduced number of cancer-related deaths among GD1 patients in the era of enzyme therapy. What contribution imiglucerase made, if any, will have to await carefully conducted clinical studies and delineation of basic mechanisms that link the two conditions together and an elucidation of how exogenous enzyme therapy might impact on these processes. It will be of particular interest to determine whether new, specific, and potent inhibitors of glucosylceramide synthase, such as eliglustat tartrate, will ameliorate cancer risk in light of their broader cellular targets beyond the macrophage.⁶⁸

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ABBREVIATIONS

DS3	disease severity scoring system
ER	endoplasmic reticulum
ERT	enzyme replacement therapy
GCase	glucocerebrosidase

GCs	Gaucher cells
GD	Gaucher disease
GD1	type 1 Gaucher disease
GWAS	Genome wide association studies
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
SRT	substrate-reduction therapy
SSI	severity score Index

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FIGURE 1.

Summary of life time probability of total, hematologic and non-hematologic cancers in GD1 from five major studies as a function of mean age of the study populations. Compiled from Rosenbloom et al (2005),¹² Zimran et al (2005),¹⁰ Taddei et al (2009),¹³ de Fost et al (2006)¹¹ and Shiran et al (1993).²⁴

FIGURE 2.

Prevalence of MGUS and multiple myeloma in longitudinally followed cohort of 403 GD1 patients (based on Taddei TH et al, 2009¹³).