Case Report

A 30-Year-Old Carrier of Gaucher Disease with Multiple Myeloma

Juskaran Chadha, Tanmay Sahai, Joshua Schwimmer, and Dana Shani

Lenox Hill Hospital, Northwell Health, New York, NY, USA

Correspondence should be addressed to Juskaran Chadha; jchadha88@gmail.com

Received 10 October 2018; Revised 24 December 2018; Accepted 22 January 2019; Published 13 February 2019

Academic Editor: Josep M. Ribera

Copyright © 2019 Juskaran Chadha et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We are reporting a case of a 30-year-old male with no past medical history who presented with new onset of renal failure, anemia, and splenomegaly and was diagnosed with multiple myeloma. Given the splenomegaly and the patient’s Jewish heritage, blood tests were done and the patient was found to be a Gaucher disease carrier. The association of Gaucher disease and multiple myeloma has previously been reported; however, we want to describe the case of a young Gaucher disease carrier who developed multiple myeloma and provide a review of the literature.

1. Introduction

Multiple myeloma (MM) is a clonal disease of the plasma cell, resulting in renal failure, anemia, hypercalcemia, and bone lesions. MM accounts for 1% of all malignancies and up to 10% of hematologic malignancies. In 2015, the annual incidence of MM in the United States was 26,850, with 11,240 deaths [1]. The median age at diagnosis is 65–70 years with increased incidence among African-Americans. The etiology of MM is unknown; however, radiation, exposure to benzene and other organic solvents, chronic antigen stimulation, and certain genetic factors including single nucleotide polymorphism (SNP) variants and HLA types have been linked to increased risk. The international staging system (ISS) is helpful for prognostication and includes measurements of beta-2 microglobulin and albumin levels. In addition, patients with del17p, t(4;14), t(14;16), and t(14;20) have poor prognosis. After risk stratification, patients undergo induction therapy, sometimes followed by autologous bone marrow transplant when indicated, followed by maintenance therapy.

2. Material and Methods

A 30-year-old male with no significant history who was recently treated with levofloxacin for a community-acquired pneumonia presented to the hospital with abnormal renal function and anemia. The patient presented with a normocytic anemia, hemoglobin of 9.3, creatinine of 3.10, and uric acid of 11.1. On CT imaging, the patient had splenomegaly up to 18 cm and innumerable osteolytic lesions, predominantly in the pelvis. The patient was subsequently found to have an IgG lambda M-spike of 6.5 gr/dl. Bone marrow biopsy was obtained and was consistent with plasma cell myeloma. Upon immunophenotypic analysis, monoclonal IgG lambda (CD38 bright) population was present at 15% of the bone marrow. Further evaluation on FISH and cytogenetics revealed a translocation (t(11;14) gene rearrangement and del17p. Patient subsequently underwent treatment at an outside institution. Given his renal dysfunction, he was started on induction therapy with CyBorD (cyclophosphamide, bortezomib, and dexamethasone). Patient achieved partial response with improvement in organ dysfunction and was subsequently transitioned to D-RVD (daratumumab, bortezomib, lenalidomide, and dexamethasone). Patient achieved a very good partial response and had an M-spike of 0.1 gr/dl prior to transplant. He successfully underwent an autologous stem cell transplant with melphalan-200 and was recently discharged with a hemoglobin of 12.2, a creatinine of 0.98, and plans to initiate maintenance therapy. For his bony lesions, he has been tolerating therapy with denosumab.

Given the patient’s Jewish heritage and presence of splenomegaly, testing for Gaucher disease was performed and the patient was found to be a carrier of Gaucher disease.
Peripheral blood specimen was sent off revealing one copy of the c.1226A>G (p.Asn409Ser) mutation in GBA.

3. Discussion

Gaucher disease is an autosomal recessive metabolic disorder secondary to genetic deficiency of the lysosomal enzyme glucocerebrosidase, which allows for the accumulation of its natural substrate glucosylceramide and its decacylated product glucosylphosphoglycosine in the lysosomes of macrophages. These macrophages are known as “Gaucher cells” [2]. In addition, carrier testing via assay of enzyme activity is unreliable due to the overlap of enzyme activity between carriers and noncarriers. Thus, identifying two disease-containing alleles in GBA provides confirmation of the diagnosis [3]. The most common type is Gaucher disease type 1, accounts for almost 95% of Caucasian patients [4]. Hematologic manifestations of the disease include anemia, thrombocytopenia, splenomegaly, and bleeding diathesis. Bone involvement causes stunted growth in childhood. Pulmonary involvement includes interstitial lung disease. There is no primary central nervous system involvement [5]. Acute Gaucher disease designated as type 2 involves the CNS including the brainstem and can lead to premature death. Subacute Gaucher disease, designated as type 3, also involves the CNS; however, systems appear later in life including oculomotor apraxia, spasticity, ataxia, seizures, and dementia.

Studies have noted an increased frequency in Gaucher disease with gammapathy and malignancy. The association with immunologic abnormalities and polyclonal hypergammaglobulinemia may occur at diagnosis in 14-41% of adults [6-9]. In Gaucher disease, the risk of multiple myeloma is 5.9 to 51.1 times higher compared to normal population [10]. Furthermore, lysosomal function, which is affected in Gaucher disease, includes priming of tissues for angiogenesis and metastasis formation [11]. The first reports of this association were made by Goldfarb and colleagues in 1950, where they found polyclonal hypergammaglobulinemia and Gaucher disease in a group of patients under the age of 30 [12]. In 2005, Rosenbaum and coworkers investigated the incidence of cancer in patients with Gaucher disease from patients enrolled in the International Gaucher Registry (ICGG). Data was analyzed on over 2,000 patients, but only 14% of the Gaucher population were older than 60 years. Ten patients were reported to have multiple myeloma, consistent with a relative risk of 5.9%, but there was no increase in risk for other types of cancer [13]. Interestingly, 68% of patients with Gaucher disease are of Jewish descent, most commonly Ashkenazi Jews [14]. They hypothesized that this elevated risk may be due to gene-linkage and coinheritance of proto-oncogenes adjacent to the GBA1 locus at 1q21 [15]. At this point, it is unclear whether GBA1 is itself a cancer gene or if carriers of GBA1 mutation have an elevated risk of cancer [16]. However, it has been theorized that one wild-type copy is sufficient to carry out normal cellular functions [17]. According to a recent review article by Stirnemann et al., carriers of GBA1 mutation have been predisposed to developing Parkinson’s disease; however, risk of neoplasia is still unclear [18].

The pathologic link between Gaucher disease and lymphoproliferative disorders may be related to enhancement in cytokine release [13]. In a further review of the literature, there have been theories that macrophages in Gaucher disease trigger B-lymphocyte immunoglobulin secretion via IL1/IL-6 secretion [19]. In addition, IL-10 level has been found to be higher than normal and can increase the occurrence of auto-antibodies and gammopathies [10, 20, 21]. Additionally, chronic long-term antigenic stimulation also could promote genomic instability [22]. In 2010, a mouse model was created with conditionally deleted GBA1 gene and subsequent analysis revealed significant dysfunction in the macrophages but also thymic T cells, dendritic cells, and osteoblasts in studying cytokine measurements and immunophenotyping [23]. Another hypothesis involves bioactive lipids. Both ceramide and sphingosine-1-phosphate are derived from glucosylceramide and glucosylphosphoglycosine. Ceramide works to induce apoptosis while sphingosine-1-phosphate promotes development, cell growth, angiogenesis, and oncogenesis. Ultimately, the different ratio of these bioactive lipids may correlate with increased incidence of dysregulation of humoral immunity and B-cell malignancy in Gaucher disease [24, 25]. Further studies have shown that b-glucosylceramide 22 and glucosylphosphoglycosine, which are two sphingolipids that accumulate in Gaucher disease, can be detected by a unique subset of type 2 natural killer T cells [26]. Moreover, these studies show that injection of these sphingolipids in vivo led to a rise in lipid specific type 2 natural killer T cells and subsequently the increase in downstream activation of B-cells and production of antibodies [27].

4. Conclusion

In summary, the association between Gaucher disease and malignancy is well-documented in the literature. Multiple studies have shown pathologic links between Gaucher disease and increased risk of malignancy, specifically multiple myeloma. Interestingly, the association of malignancy with Gaucher disease carriers still has not clearly been defined. Fortunately, the patient presented was successfully treated for his myeloma and is in clinical remission.

Given the paucity of literature on Gaucher disease carriers, this case report and the review of literature should serve to increase awareness of the potential for malignancy, especially hematologic malignancy, in patients who are Gaucher disease carriers.

Conflicts of Interest

The authors and declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

J. Chadha conducted research and wrote the paper. T. Sahai conducted research and edited the paper. J. Schwimmer edited the paper. D. Shani edited the paper.
References

[1] R. Siegel, D. Naishadham, and A. Jemal, "Cancer statistics, 2013,” CA: A Cancer Journal for Clinicians, vol. 63, no. 1, pp. 11–30, 2013.

[2] J. Parkin and R. Brunning, "The pathology of the Gaucher cell," in Gaucher Disease: A Century of Delineation and Research, R. Desnick, S. Gatt, and G. A. Grabowski, Eds., p. 151, Alan R Liss, New York, NY, USA, 1982.

[3] G. M. Pastores and D. A. Hughes, "Gaucher disease," in GeneReviews®, M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, and A. Amemiya, Eds., University of Washington, Seattle, Seattle, WA, USA, 2000.

[4] J. Charrow, H. C. Andersson, P. Kaplan et al., "The Gaucher Registry: demographics and disease characteristics of 1698 patients with Gaucher disease," Archives of Internal Medicine, vol. 160, no. 18, pp. 2835–2843, 2000.

[5] A. H. Futerman and A. Zimran, Gaucher Disease, Taylor & Francis Group, Boca Raton, FL, USA, 2007.

[6] G. E. Marti, E. T. Ryan, N. M. Papadopoulos et al., "Polyclonal B-cell lymphocytosis and hypergamaglobulinemia in patients with Gaucher disease," American Journal of Hematology, vol. 29, no. 4, pp. 189–194, 1988.

[7] A. Brauthar, D. Elstein, G. Pines, A. Abrahamov, and A. Zimran, "Effect of enzyme replacement therapy on gangliosides in Gaucher disease," Blood Cells, Molecules, and Diseases, vol. 32, no. 1, pp. 214–217, 2004.

[8] Y. Shoenfeld, A. Beresovski, D. Zharhary et al., "Natural autoantibodies in sera of patients with Gaucher’s disease," Journal of Clinical Immunology, vol. 15, no. 6, pp. 363–372, 1995.

[9] M. De Fost, T. A. Out, F. A. De Wilde et al., "Immunoglobulin and free light chain abnormalities in Gaucher disease type 1: data from an adult cohort of 63 patients and review of the literature," Annals of Hematology, vol. 87, no. 6, pp. 439–449, 2008.

[10] B. E. Rosenbloom, N. J. Weinreb, A. Zimran, K. A. Kacena, J. Charrow, and E. Ward, "Gaucher disease and cancer incidence: a study from the Gaucher Registry," Blood, vol. 105, no. 12, pp. 4569–4572, 2005.

[11] S. M. Davidson and M. G. Vander Heiden, "Critical functions of the lysosome in cancer biology," Annual Review of Pharmacology and Toxicology, vol. 57, no. 1, pp. 481–507, 2017.

[12] A. R. Goldfarb, D. H. Atlas, and P. Gaberman, "Electrophoretic studies in Gaucher’s disease," American Journal of Clinical Pathology, vol. 20, no. 10, pp. 963–965, 1950.

[13] G. M. Pastores and D. A. Hughes, "Lysosomal storage disorders and malignancy," Diseases, vol. 5, no. 1, 2017.

[14] G. J. Morgan, F. E. Davies, W. M. Gregory et al., "First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomized controlled trial," The Lancet, vol. 376, no. 9757, pp. 1989–1999, 2010.

[15] D. L. Stone, N. Tayebi, E. Orvinsky, B. Stubblefield, V. Madike, and E. Sidransky, "Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease," Human Mutation, vol. 15, no. 2, pp. 181–188, 2000.

[16] R. Ayto and D. A. Hughes, "Gaucher disease and myeloma," Critical Reviews in Oncogenesis, vol. 18, no. 3, pp. 247–268, 2013.

[17] E. Levy-Lahad and A. Zimran, "10 Gaucher’s disease: genetic counselling and population screening," Baillière’s Clinical Haematology, vol. 10, pp. 779–792, 1997.

[18] J. Stirmemann, N. Belmatoug, F. Camou et al., "A review of Gaucher disease pathophysiology, clinical presentation and treatments," International Journal of Molecular Sciences, vol. 18, no. 2, p. 441, 2017.

[19] R. Costello and T. O’Callaghan, "Pro-inflammatory cytokines and the pathogenesis of Gaucher’s disease: increased release of interleukin-6 and interleukin-10," QJM: An International Journal of Medicine, vol. 90, no. 1, pp. 19–25, 1997.

[20] M. De Fost, S. vom Dahl, G. J. Weverling et al., "Increased incidence of cancer in adult Gaucher disease in Western Europe," Blood Cells, Molecules, and Diseases, vol. 36, no. 1, pp. 53–58, 2006.

[21] M. Arends, L. Van Dussen, M. Biegstraaten, and C. E. M. Hollak, "Malignancies and monoclonal gammapathy in Gaucher disease: a systematic review of the literature," British Journal of Haematology, vol. 161, no. 6, pp. 832–842, 2013.

[22] S. Koduru and E. Wong, "Dendritic cell–mediated activation-induced cytidine deaminase (AID)–dependent induction of genomic instability in human myeloma," Blood, vol. 119, no. 10, pp. 2302–2309, 2012.

[23] P. K. Mistry, J. Liu, T. N. Yang et al., "Glucocerebrosidase gene–deficient mouse recapitulates Gaucher disease displaying cellular and molecular dysregulation beyond the macrophage," Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 45, pp. 19473–19478, 2010.

[24] Y. Hannum and L. Obied, "Principles of bioactive lipid signalling: lessons from sphingolipids," Nature Reviews Molecular Cell Biology, vol. 9, no. 2, pp. 139–150, 2008.

[25] B. M. Barth, S. S. Shanmugavelandy, D. M. Tacelosky, M. Kester, S. A. F. Morad, and M. C. Cabot, "Gaucher’s disease and cancer: a sphingolipid perspective," Critical Reviews in Oncogenesis, vol. 18, no. 3, pp. 221–234, 2013.

[26] S. Nair, C. S. Boddupalli, R. Verma et al., "Type II NKT-TFH cells against Gaucher lipids regulate B-cell immunity and inflammation," Blood, vol. 125, no. 8, pp. 1256–1271, 2015.

[27] S. Nair and A. R. Branagan, "Clonal immunoglobulin against lysolipids in the origin of myeloma," The New England Journal of Medicine, vol. 374, no. 6, pp. 555–561, 2016.