Received: 26 February 2019 | Revised: 17 June 2019 | Accepted: 21 June 2019

DOI: 10.1002/ccr3.2329

CASE REPORT

Clinical Case Reports Open Access WILEY

A case of bony lytic lesions in a patient with Gaucher disease

Eric McGinnis[1] | **Habib Moshref Razavi**[2]

[1]Division of Hematopathology, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[2]Fraser Health Authority, Royal Columbian Hospital, New Westminster, British Columbia, Canada

Correspondence
Habib Moshref Razavi, Fraser Health Authority, Royal Columbian Hospital, Main Laboratory, 330 East Columbia street New Westminster, BC, Canada V3L 3W7.
Email: habib.moshrefrazavi@fraserhealth.ca

Abstract

Gaucher disease is a clinically heterogeneous disorder of glucocerebroside metabolism and may present incidentally late in life with unexplained thrombocytopenia, splenomegaly, or bony lesions. Clinicians should be aware that patients with Gaucher disease appear to have an increased risk for developing hematolymphoid malignancies, particularly monoclonal gammopathies and plasma cell myeloma.

KEYWORDS

diagnostic immunohistochemistry, Gaucher disease, plasma cell myeloma

1 | CASE HISTORY

A 57-year-old male underwent biopsy of a progressively enlarging scalp lesion, which was found to be a scalp plasmacytoma, and further investigations demonstrated the presence of numerous bony lytic lesions (Figure 1, panel A-B). Serum protein electrophoresis and assessments for free light chains identified hypogammaglobulinemia in the absence of monoclonal protein, and his renal function and calcium were within normal limits. He was subsequently referred for bone marrow biopsy to exclude plasma cell myeloma.

At the time of biopsy, his complete blood count demonstrated mild normocytic anemia (hemoglobin 124 g/L) and thrombocytopenia (platelets 135×10^9/L) and his blood film had no morphologic abnormalities. Histiocytes with abundant lightly basophilic "wrinkled paper" cytoplasm characteristic of Gaucher cells were frequent in bone marrow aspirate specimens (Figure 1, panel C). Trephine biopsy demonstrated extensive infiltration by Gaucher cells with voluminous eosinophilic striated cytoplasm and periodic acid-Schiff (PAS) positivity (Figure 1, panel D-E). Also identified was extensive kappa-restricted plasma cell infiltration (Figure 1, panel F). Ultimately, a diagnosis of nonsecretory plasma cell myeloma was made. Cytogenetic investigations revealed a normal male karyotype. Notable in review of his medical history was persistent unexplained splenomegaly and a remote bone marrow biopsy, performed for investigation of unexplained cytopenias, remarkable for the presence of abnormal cells suggestive of Gaucher cells.

He received combination chemotherapy with cyclophosphamide, bortezomib, and dexamethasone with good response prior to high-dose melphalan chemotherapy and autologous stem cell transplantation. He tolerated his transplant and was discharged to continue long-term follow-up as an outpatient.

2 | DISCUSSION

Gaucher disease (GD) is a metabolic disorder resulting from deficiency of lysosomal glucocerebrosidase and accumulation of unmetabolized substrates in monocytes and macrophages of the reticuloendothelial system.[1] Inheritance is autosomal recessive and the disorder is more commonly identified in patients of Jewish or non-Jewish Caucasian descent.[2] GD is a rare disorder, with worldwide prevalence estimates of <1 in 50 000, but the frequency is significantly higher in populations with founder effects, most notably the

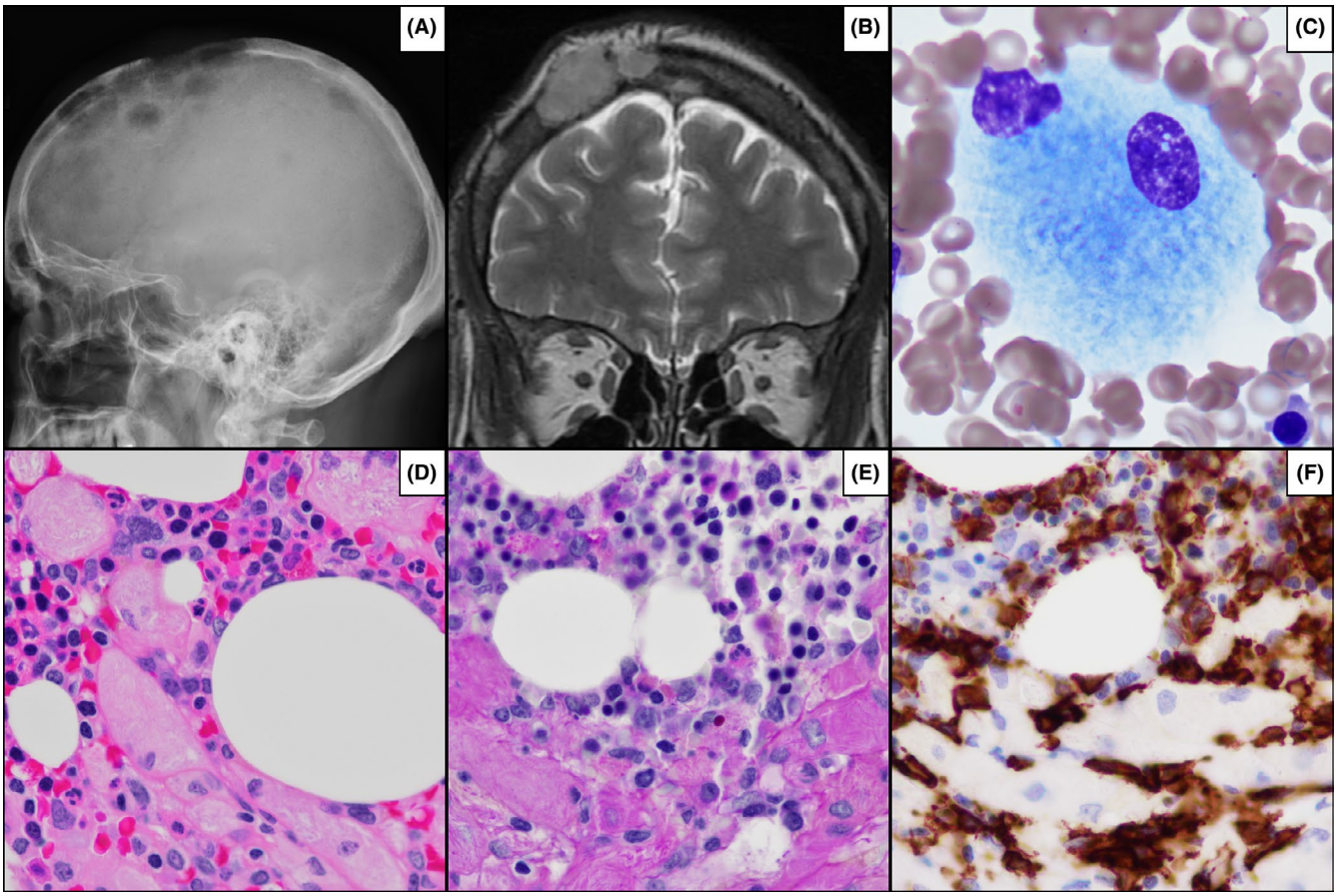

FIGURE 1 Radiographic and pathologic findings in a patient with plasma cell myeloma (with a presenting complaint of enlarging scalp mass), incidentally found to have substantial infiltration of the bone marrow by Gaucher cells. A, plain radiograph of the skull with numerous lytic lesions. B, coronal magnetic resonance image demonstrating the plasmacytoma at the time of diagnosis. C, characteristic Gaucher cells with abundant lightly basophilic cytoplasm were abundant in the bone marrow aspirate specimens; May-Grünwald Giemsa stain, 100 × objective. D, sheets of infiltrating histiocytes with abundant striated eosinophilic cytoplasm and eccentric nuclei, characteristic of Gaucher cells, were identified in the bone marrow biopsy specimen; hematoxylin and eosin stain, 50 × objective. E, infiltrating histiocytes stained positively with periodic acid-Schiff histochemistry, 50 × objective. F, plasma cells were present in significantly increased numbers among the Gaucher cells and were kappa light chain-restricted by immunohistochemistry (not shown); CD138 immunohistochemical stain, 50 × objective

Ashkenazi Jewish population.[3,4] Population estimates appear likely to underestimate the true prevalence of GD due to the clinical heterogeneity and frequency of relatively nonspecific symptoms, with the potential for mildly affected patients to remain undiagnosed for long periods of time.[4]

Gaucher disease is subdivided based on clinical features: type 1 is not associated with central nervous system involvement, type 2 is characterized by severe central nervous system involvement and death in early childhood, and type 3 is characterized by central nervous system involvement of later onset and more indolent course.[5] Of patients documented in the GD Registry, the vast majority (94%) presented with type 1 disease, with a broad age range at time of diagnosis (1 to 81 years).[2] Type 1 GD is highly clinically heterogeneous: clinical features commonly identified include variable combinations of mild anemia, thrombocytopenia, hepatomegaly, splenomegaly, bone pain, and radiographic bone abnormalities.[2]

Gaucher disease is pathologically characterized by tissue infiltration by cells of the monocyte-macrophage system engorged with accumulated glycolipid substrate.[6] Gaucher cells have characteristic "tissue-like" cytoplasmic texture and eccentric nuclei, and stain positively with periodic acid-Schiff and tartrate-resistant acid phosphatase histochemistry.[7] It is important to be aware that cells with this morphology are not pathognomonic of GD and may be identified in other disorders (so-called pseudo-Gaucher cells), classically chronic myeloid leukemia.[8] Methods used to diagnose GD in patients reported to the GD Registry have included (alone or in variable combination) enzyme activity assay, molecular genetic assessment, bone marrow biopsy, and organ biopsy.[2] Identification of pathogenic mutations or deficient enzyme

activity have the advantage of specificity for GD relative to histopathology, but unfortunately do not appear to reliably predict clinical phenotype.[9] Treatment of GD relies mainly on enzyme-replacement therapy, although novel therapies are entering clinical use (or the realm of clinical investigation).[9]

Several studies have identified an increased relative risk of malignancies in the population with GD. While several reports have identified increased risks of a diverse range of malignancies (including hematolymphoid malignancy and various carcinomas or adenocarcinomas), assessment of larger groups of patients with GD has suggested that the greatest relative risk increase appears to be for the development of plasma cell myeloma or monoclonal gammopathy of undetermined significance (MGUS).[10-14] The estimated relative risk of plasma cell myeloma in these patients ranges broadly, from approximately 6 to 50 times that of a population of similar age.[11-14] The frequency of MGUS, a plasma cell neoplasm with the potential for progression to overt myeloma, has been identified at frequencies as high as 19% in a Netherlands cohort of patients with GD, compared with a frequency of approximately 1% in a non-GD population of similar age.[14] Interestingly, MGUS patients with GD in this cohort also had an increased frequency of biclonal and triclonal gammopathy relative to that seen in the non-GD population.[14]

The mechanism by which GD results in increased frequency of plasma cell neoplasms is not well understood. Proposed mechanisms include accumulation of bioactive lipids and cellular immune dysregulation resulting from accumulation of glucosylceramides with aberrant macrophage activity.[15] Interestingly, investigation of a series of GD patients with polyclonal or monoclonal gammopathy demonstrated immunoglobulin reactivity against lysolipids in a large proportion of cases (91% of polyclonal and 78% of monoclonal gammopathies) compared with non-GD patients with MGUS or plasma cell myeloma (approximately 30%), suggesting a possible role for chronic antigenic stimulation by unmetabolized substrates in the development of GD-related plasma cell neoplasms.[16]

3 | CONCLUSION

Gaucher disease is a clinically heterogenous disorder that may remain clinically silent or minimally symptomatic until late in adult life and should be considered in the differential diagnosis of unexplained hepatomegaly, splenomegaly, or cytopenias. When patients with GD are identified, it is important to be vigilant for the development of malignancies, in particular, those of plasma cell lineage, as the relative risk of their development is increased in this population. The mechanism by which GD predisposes to the development of plasma cell neoplasms is not fully understood and requires further investigation. Importantly, Gaucher cells infiltrating the bone marrow may mask the extent of abnormal plasma cell infiltrates, and immunohistochemical staining can be invaluable in identifying the true burden of plasma cells for appropriate classification of suspected plasma cell neoplasia.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

EM: performed chart review, literature review, and manuscript preparation. HM: case pathologist, reviewed, and revised manuscript.

ORCID

Eric McGinnis https://orcid.org/0000-0003-3360-5471
Habib Moshref Razavi https://orcid.org/0000-0002-1374-5963

REFERENCES

1. Brady RO, Kanfer JN, Bradley RM, Shapiro D. Demonstration of a deficiency of glucocerebroside-cleaving enzyme in Gaucher's disease. *J Clin Invest*. 1966;45:1112-1115.
2. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher Registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med*. 2000;160:2835-2843.
3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA*. 1999;28:249-254.
4. Beutler E, Nguyen NJ, Henneberger MW, et al. Gaucher disease: gene frequencies in the Ashkenazi Jewish population. *Am J Hum Genet*. 1993;52:85-88.
5. Brady RO. Gaucher's disease: past, present and future. *Baillieres Clin Haematol*. 1997;10(621):34.
6. Cox TM, Cachón-González MB. The cellular pathology of lysosomal storage diseases. *J Pathol*. 2012;226:241-254.
7. Parkin JL, Brunning RD. Pathology of the Gaucher cell. *Prog Clin Biol Res*. 1982;95:151-175.
8. Kattlove HE, Williams JC, Gaynor E, Spivack M, Bradley RM, Brady RO. Gaucher cells in chronic myelocytic leukemia: an acquired abnormality. *Blood*. 1969;33:379-390.
9. Gary SE, Ryan E, Steward AM, Sidransky E. Recent advances in the diagnosis and management of Gaucher disease. *Expert Rev Endocrinol Metab*. 2018;13:107-118.
10. Shiran A, Brenner B, Laor A, Tatarsky I. Increased risk of cancer in patients with Gaucher disease. *Cancer*. 1993;72:219-224.
11. Zimran A, Liphshitz I, Barchana M, Abarahamov A, Elstein D. Incidence of malignancies among patients with type I Gaucher disease from a single referral clinic. *Blood Cells Mol Dis*. 2005;32:197-200.
12. Rosenbloom BE, Weinreb NJ, Zimran A, Kacena KA, Charrow J, Ward E. Gaucher disease and cancer incidence: a study from the Gaucher registry. *Blood*. 2005;105:4569-4572.

13. de Fost M, vom Dahl S, Weverling GJ, et al. Increased incidence of cancer in adult Gaucher disease in Western Europe. *Blood Cells Mol Dis*. 2006;36:53-58.
14. de Fost M, Out TA, de Wilde FA, et al. Immunoglobulin and free light chain abnormalities in Gaucher disease type I: data from an adult cohort of 63 patients and review of the literature. *Ann Hematol*. 2008;87:439-449.
15. Wątek M, Piktel E, Wollny T, et al. Defective sphingolipids metabolism and tumor associated macrophages as the possible links between gaucher disease and blood cancer development. *Int J Mol Sci*. 2019;20:E843.
16. Nair S, Branagan AR, Liu J, Boddupalli CS, Mistry PK, Dhodapkar MV. Clonal immunoglobulin against lysolipids in the origin of myeloma. *N Engl J Med*. 2016;374:555-561.

How to cite this article: McGinnis E, Moshref Razavi H. A case of bony lytic lesions in a patient with Gaucher disease. *Clin Case Rep*. 2019;7:1685–1688. https://doi.org/10.1002/ccr3.2329