Fabry disease: Four case reports of meningioma and a review of the literature on other malignancies

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by loss of function mutations in the GLA gene at Xq22 with subsequent functional deficiency of alpha-galactosidase A, resulting in the accumulation of globotriaosylceramide (GL-3 or Gb3) in multiple cells types throughout the body. As with other rare metabolic disorders, little is known about the incidence of malignancies in these populations and the relationship to the underlying disease, if any. We report the occurrence of meningioma in four female patients with Fabry disease. The two of the cases are from the same family and shared the same GLA mutation. All four patients underwent surgical excision of their tumor. High resolution light microscopy and electron microscopy examination of one case revealed extensive involvement of tumor cells and associated blood vessels by GL-3 accumulation. Because of the small number of Fabry-associated cancer cases reported in the literature, questions about a possible link between lysosomal storage disorders and the development of malignancy remain open.

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1. Introduction

Meningiomas are the most common primary CNS tumor in the general population with a prevalence of 97.5 in 100,000 in the United States [1], and while most are benign, they often produce debilitating symptoms via their mass effect on the brain. Over the years, the incidence of this tumor and its various risk factors has been examined. Women's risk of meningioma is twice that of men, and may be linked to the expression of hormone receptors observed in some tumors [1]. Some studies suggest a link with hormone replacement therapy [1]. The incidence of meningioma, similar to other cancers of the breast, colon, pancreas, etc., has also been associated with obesity and its associated low-grade chronic inflammatory state [2]. Family history of meningioma in first degree relatives (2-fold increased risk) and exposure to ionizing radiation are also risk factors [1]. Familial cases have been reported both in association with [3] and in the absence of neurofibromatosis [4,5]. However, little has been reported on the occurrence of meningioma in association with metabolic disorders. These are the first reported cases of meningioma occurring in Fabry disease, an X-linked metabolic disorder caused by a deficiency of lysosomal alpha-galactosidase, resulting in cellular accumulation of the lipid globotriaosylceramide (GL-3) and its deacylated product lyso-Gb3 [6,7]. We review the existing reports of cancer occurring in patients with Fabry disease, and discuss the possible association of metabolic lipid disorders with respect to the evolution of malignancy.

2. Materials and methods

We received representative wet tissue samples of surgically excised tumor from case 1. A portion of tumor tissue was fixed in 10% NBF, processed into paraffin blocks, sectioned and stained with routine hematoxylin and eosin as well as immunohistochemistry for vimentin (Abcam, Cambridge, MA). A separate portion tumor tissue was fixed in 3% glutaraldehyde in 0.2 M sodium cacodylate buffer, pH 7.3, and processed into epoxy resin blocks for high resolution light microscopy and electron microscopy as previously described [8]. Previously processed paraffin
blocks from cases 2 and 3 were made available to us and were sectioned and stained with routine hematoxylin and eosin as well as immunohistochemistry for vimentin. All patients and family members provided consent to further examine the pathology and report on these cases.

3. Results

3.1. Case 1

A 41-year old woman was diagnosed with Fabry disease at age 40 as part of a family screening. This patient is the cousin of case 2 and they share the same family mutation in GLA (p. Leu415Pro or p.L415P); their mothers were sisters, both heterozygotes for Fabry disease. Her medical history included mild corneal compromise (cornea verticillata) and mild dysesthesias [9]. She had no signs of renal, cardiac or otologic disease and was not on enzyme replacement therapy. She presented with complaints of a non-specific headache over the prior two months. MRI revealed vertebrobasilar dolichoectasia and convexity meningioma located in the left hemisphere (Fig. 1A). The patient underwent surgical excision of the meningioma and the pathology of the patient’s tumor was reported as a grade 1 meningothelial meningioma. Immunohistochemical staining performed at the treating hospital was reported as 40% of tumor cells strongly positive for progesterone receptor, and 2% of cells weakly positive for Ki-67.

The patient consented to additional histopathologic studies of her tumor, and additional samples of wet tumor tissue were processed for further examination. Hematoxylin and eosin stained paraffin sections revealed a typical meningothelial meningioma with well-defined lobules of meningothelial cells. These cells were positive for vimentin by immunohistochemistry. Vacuolization of tumor cells, mimicking the microcytic and/or clear cell variant of meningioma, as well as vacuolization of associated vascular cells were observed, suggestive of lipid storage (Fig. 1C and F). Epon-embedded sections examined at the light level revealed numerous dense blue granules in the cytoplasm of tumor cells (Fig. 2A), vascular endothelial cells and vascular smooth muscle cells (Fig. 2B), which appeared as zebra bodies, electron dense...

Fig. 1. MRI location and histologic appearance of meningiomas occurring in Fabry patients. Panels A. Case 1, convexity meningioma. Panel B. Case 3, torcular meningioma. Panel C. Case 1 - The tumor cells are meningothelial and arranged in well-defined lobules, with noticeable vacuolization. (paraffin section, H&E, 600× magnification) Tumor cells are also positive for vimentin (insert, 600×). Panel D. Histologic appearance of tumor cells in case 2, note vacuolated appearance (paraffin section, H&E, 600× magnification) and vimentin positivity (insert, 600×). Panel E. Histologic appearance of tumor cells in case 3, note vacuolated appearance (paraffin section, H&E, 400× magnification), presence of typical psammoma bodies (insert, 600×) and vimentin positivity (insert, 600×). Panel F. Histologic appearance of associated tumor vasculature, note vacuolated appearance of VSMCs (paraffin section, H&E, 600× magnification).
granules, and myelin figures on electron microscopy (Fig. 2C through F), characteristic of the GL-3 accumulation observed in Fabry disease.

3.2. Case 2

The patient was a 65-year old female diagnosed at age 63 with Fabry disease (mutation p.Leu415Pro) as part of a family screening. Her son was the index case for the family. The patient is the cousin of aforementioned case 1. Her medical history included corneal involvement (corneal verticillata), mild left ventricular hypertrophy (LVH), and microalbuminuria (150 mg/24 h) with normal eGFR. She had no neuropathic pain in the hands or feet, and had no signs of arrhythmia. The patient was not on enzyme replacement therapy. She presented with a 2 month history of headache and progressive left hemiparesis, and an MRI was performed which revealed periventricular lacunar infarcts and right frontal meningioma adjacent to the motor cortex with mass effect and local compression. She underwent surgical excision of the meningioma, but died 12 days later of sepsis from colonic perforation secondary to diverticular disease. The pathology of this patient’s tumor was reported as a meningioma with clear cell and microcystic features, grade 2. The patient’s family consented to additional histopathologic studies of her tumor. On hematoxylin and eosin sections, the tumor was composed of a mixture of meningothelial areas with moderate vacuolization of tumor cells, as well as areas with marked vacuolization of tumor cells which resemble the microcystic or clear cell variant of meningioma (Fig. 1D). These features may have been the result of GL-3 accumulation (as in case 1), however, there was no wet tissue available from this case to confirm this observation by electron microscopy. Tumor cells were also positive for vimentin.

3.3. Case 3

This 49-year old female patient was diagnosed at age 41 with Fabry disease as part of a family screening. The index case in her family was her father. She is heterozygous for the known familial mutation p.Gly373Ser in exon 7 of the GLA gene. Her father had died at the age of 48 years old, with cardiac and kidney failure. The patient’s two sisters and her daughter are all heterozygotes for Fabry disease. Her alpha-galactosidase A activity was 31 nmol/h/mg of protein (within the normal range) in leukocytes. She exhibited random X chromosome inactivation pattern [10]. Her disease was characterized by mild ENT, cerebral and cutaneous impairments. She reported transient tinnitus and has a few angiokeratoma. She has no signs of renal or cardiac disease and is not on enzyme replacement therapy.

At the age of 44 years old she presented with a few months history of chronic fatigue, nausea, vomiting and impaired equilibrium. An MRI with gadolinium was performed and revealed a voluminous tumor in the posterior cranial fossa measuring 45 mm × 40 mm × 50 mm
(Fig. 1B). This extra-axial lesion was attached to the cerebellar tentorium, adjacent to the confluence of sinuses without obvious signs of venous invasion. The patient underwent emergency neurosurgery for tumor excision. Post-operatively, the patient suffered from impaired equilibrium, which improved after a rehabilitation program. Five years later at age 49, MRI showed tumor recurrence at the torcular measuring 14 × 8 mm, which was treated with radiotherapy.

Histopathological examination of the primary tumor revealed a transitional meningioma with a mixture of both meningothelial and fibrous patterns with well-developed whorls and psammoma bodies. Tumor cells appeared vacuolated on H&E stained sections, suggestive of abnormal GL-3 storage (Fig. 1E), however, no wet tissue was available for electron microscopy confirmation of this observation. Immunohistochemistry staining performed at the treating hospital reported that approximately 20% of tumor cells were positive for progesterone receptor, and less than 2% of tumor cells were positive for Ki-67.

3.4. Case 4

This 45-year-old female was diagnosed with late-onset Fabry disease at age 40 as part of her family screening. She is a heterozygote for the well characterized p.Asn215Ser family mutation, which is associated with high residual enzyme activity. Although cardiac hypertrophy was present in all males of her family, she had not developed any cardiac enlargement as of her last examination. Similarly, she had neither the renal nor the cerebral involvement typically associated with classic Fabry disease. She has been on enzyme replacement therapy for the last four years, at the patient's request.

At age 41, she began to complain of occasional mild to moderate headache. On routine ophthalmic examination, a progressive axial proptosis was noted in the left eye, with no restriction of the extraocular movements. There was no history of visual loss or diplopia of the left eye. The remainder of the neurological examination was normal, however, the patient reported hearing loss in the left ear, vertigo and dizziness, and intermittent tinnitus.

At age 42, brain MRI performed as part of her annual evaluation revealed a left lateral orbital bone remodeling and thickening (9.6 mm) of the meninges. Based on the imaging and clinical findings, a diagnosis of meningioma was made. Annual MRI surveillance of the lesion over the next three years remained unchanged.

At age 45, she experienced aggravation of the exophthalmos, daily headaches, nausea and vomiting. Brain MRI revealed an increase in tumor size with atrophy of the optic nerve due to local compression and peritumoral edema. The patient underwent left frontal craniotomy with left orbitotomy for surgical removal of the tumor. Her postoperative course was uneventful. She had no neurological sequelae except a temporarily left upper lid ptosis, and mild language disorders, treated with orthoptics and language therapy.

Histopathological examination performed at the treating hospital reported meningothelial meningioma WHO grade 1 [11]. Microscopic analyses reported lobules of meningothelial cells devoid of nuclear atypia, without mitotic activity, organized into small solid layers with a few whorls, and absence of necrosis. Immunohistochemistry staining performed at the treating hospital reported 90% of the tumor cells were positive for progesterone receptor and 6% of the tumor cells were positive for Ki-67.

### Table 1

Case summaries of four study patients with meningiomas and literature review of malignancies in patients with Fabry disease.

| Reference | Tumor type | Gender | Age at cancer diagnosis | Cancer treatment | Age at Fabry disease diagnosis | ERT treatment | Follow-up | GLA mutation |
|-----------|------------|--------|-------------------------|------------------|-------------------------------|---------------|-----------|--------------|
| Thurberg et al., case 1 | Meningioma | F | 42 | Surgical removal | 40, family screening | None | Alive at age 43 | p.Leu415Pro (cousin of case 2) |
| Thurberg et al., case 2 | Meningioma | F | 66 | Surgical removal | 61, family screening | None | Patient died 12 days post-op, unrelated to neurosurgery | Alive at age 50 |
| Thurberg et al., case 2 | Meningioma | F | 44 | Surgical removal of primary tumor at age 44; tumor recurrence at age 49 treated with radiotherapy | 41, family screening | None | Alive at age 50 | p.Gly373Ser exon 7 |
| Cybulla et al. [12] | Retro-orbital meningioma | F | 42 | Surgical removal | 40 | Yes | Alive at age 45 | p.Asn215Ser exon 5 |
| Cybulla et al. [12] | AML | M | 30, presented with chronic renal failure | NA | Post-mortem | None | Died at age 32 | NA |
| Cybulla et al. [12] | ALL | M | 3 | NA | 40, presenting with chronic renal failure | Yes | Alive at age 43 | NA |
| Tisi et al. [13] | Small lymphocytic lymphoma | F | 62 | Chemotherapy | 52, presenting with proteinuria | Yes | In remission | c.644A>G, p.Asn215Ser, exon 5 |
| Blanco et al. [14] | Renal cell carcinoma, bilateral | M | 69 | Bilateral nephrectomy (sequential nephrectomies, 3 years apart) | 69, diagnosed in first resected kidney | none | Died at age 72 | p.Phe113Leu, exon 2 |
| Cassiman et al. [15] | Renal cell carcinoma, bilateral | M | 60 | Bilateral nephrectomy | 67, diagnosed based on history and low enzyme activity | none | Alive at age 67 | c.A27G>A, exon 3 |
| Pagni et al. [16] | Renal cell carcinoma, unilateral | F | 51 | Nephrectomy | 45, presenting with proteinuria | yes | Alive at age 51 | g.1170C>T, exon 1 |
cessful treatment of a mouse model of renal cell carcinoma with a
duce any potential increased cancer risk in these rare disease
malignant melanoma and pancreatic cancer[19]. Other researchers
higher risk of certain malignancies, including non-Hodgkin lymphoma,
somal beta-glucosidase[18], patients were shown to have a 2
In Gaucher disease, a sphingolipidosis due to the de
lignancies have also been reported in other lysosomal storage diseases.
association of elevated glucosylceramide with Gaucher-associated ma-
pro-apoptotic and anti-proliferative properties, and recent reviews ex-
free ceramide, as occurs in normal cells. Ceramide is a molecule with
sequence of altered or lowered ceramide levels. Ceramide is bound
sphingolipidoses, or disorders of sphingolipid metabolism. These disor-
mal anti-proliferative and pro-apoptotic function[24], and possibly re-
availability of free ceramide and allow it to exert its anti-tumor effect
The small numbers of cancer cases reported in these populations make it difficult to reach a definitive conclusion about a causal link between sphingolipid accumulation and cancer risk; it may well be that authors do not systematically report all cases of malignancies in associ-
are rare lysosomal disorders. The further study of cancer biology in
tumors arising in these rare disease patient populations may also help to
shed additional light on our current understanding of lipid dysregula-
the cancer biology of the general population.

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References
[1] J. Wiemels, M. Wrensch, E.B. Claas, Epidemiology and etiology of meningioma, J.
-Neuro-Oncol. 99 (2010) 307–314.
[2] P. Rajaraman, Hunting for the cause of meningioma-obses is a suspect, Cancer
Res. 4 (9) (2011) 1353–1355.
[3] M. Maxwell, D.S. Shih, T. Galanopoulos, et al., Familial meningioma: analysis of ex-
pression of neurofibrinomatosis 2 protein Merlin: report of two cases, J. Neurosurg.
88 (1998) 562–569.
[4] R.J. Joynt, G.E. Perrett, Familial meningiomas, J. Neurosurg. Psychiatry 28
(1965) 163–164.
[5] J.R. McDowell, Familial meningioma, Neurology 40 (1990) 312–314.
[6] D.P. Germain, L. Poenaru, Fabry disease: identification of novel alpha-galactosidase
A mutations and molecular carrier detection by use of fluorescent chemical cleavage of
mismatches, Biochem. Biophys. Res. Commun. 257 (3) (1999) 708–713.
[7] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 10.
[8] B.L. Thurberg, H. Rennke, R.B. Colvin, et al., Globotriaosylceramide accumulation in
the Fabry kidney is cleared from multiple cell types after enzyme replacement ther-
apy, Kidney Int. 62 (6) (2002) 1933–1946.
[9] J.M. Politié, D. Bouhassira, D.P. Germain, C. Goizet, A. Guerrero-Sola, M.J. Hilz, E.J.
Hutton, A. Karaa, R. Louisot, N. Ucelyer, L.K. Zeltzer, A. Burlina, Pain in Fabry disease:
practical recommendations for diagnosis and treatment, CNS Neurosci. Ther. (2016).
in press.
[10] L. Echevarria, K. Benistan, A. Toussaint, O. Dubourg, A.A. Hagege, D. Eladari, F.
Jabbour, C. Beldjord, P. De Mazancourt, D.P. Germain, X-chromosome inactivation
in female patients with Fabry disease, Clin. Genet. 89 (1) (2016 Jan) 44–54.
[11] A. Perry, D.N. Louis, B.W. Scheithauer, H. Budka, A. von Deimling, D.N. Louis, O.
Hiroko, O.D. Wiestler, W.K. Cavenee, Meningiomas in WHO classification of tumours
of the central nervous system, Lyon, France: International Agency for Research on
Cancer 2007, pp. 164–172.
[12] M. Cybull, M. Kleber, K.N. Walter, et al., Is Fabry disease associated with leukemia?
Brit. J. Haematol. 135 (2006) 264–275.
[13] M. Cesati, A. Zampetti, M. Fellerer et al., Small lymphocytic lymphoma in a patient
with Fabry disease, Leuk. Lymphoma 54 (1) (2013) 184–185.
[14] J. Blanco, J. Herrero, L.F. Arias, et al., Renal variant of Anderson-Fabry disease and bi-
ilateral renal cell carcinoma, Pathol. Res. Pract. 200 (2005) 857–860.
[15] D. Cassiman, K. Coe, E. Lerut, et al., Bilateral renal cell carcinoma development in
long-term Fabry disease, J. Inherit. Metab. Dis. 30 (2007) 830–831.
[16] F. Pagni, F. Pieruzzi, S. Zannella, et al., Possible pathogenic relationship between
Fabry disease and renal cell carcinoma, Am. J. Nephrol. 36 (2012) 537–541.
[17] M.B.S. Lopes, S.R. VandenBerg, Tumors of the central nervous system, in: C.D.M.
Fletcher (Ed.), Diagnostic Histopathology of Tumors, 2nd ed.Churchill Livingstone,
London 2000, pp. 1566–1561.
[18] D.P. Germain, Gaucher’s disease: a paradigm for interventional genetics, Clin.
Genet. 65 (2) (2004 Feb) 77–86.
[19] O. Landgren, I. Turesson, G. Gridley, et al., Risk of malignant disease among 1525
adult male US veterans with Gaucher disease, Arch. Intern. Med. 167 (2007)
1189–1194.
[20] B.E. Rosenblom, N.J. Weinreb, A. Zimran, et al., Gaucher disease and cancer inci-
dence: a study from the Gaucher registry, Blood 105 (2005) 4569–4572.
[21] M. Arends, L. van Dussen, M. Biegstraaten, et al., Malignancies and monoclonal
gammopathy in Gaucher disease; a systematic review of the literature, Br. J.
Haematol. 161 (2013) 832–842.
[22] N. Tamasawa, S. Takayasu, H. Mrakami, et al., Reduced cellular cholesterol efflux and
low plasma high-density lipoprotein cholesterol in a patient with type B Niemann-
pick disease because of a novel SMPD-1 mutation, J. Clin. Lipidol. 6 (2012) 74–80.
[23] M.M. McGovern, N. Lippa, E. Bagiella, et al., Morbidity and mortality in type B
Niemann–pick disease, Genet. Med. 15 (8) (2013) 618–623.
[24] B. Ogtretten, Y.A. Hannun, Biologically active sphingolipids in cancer pathogenesis
and treatment, Nat. Rev. Cancer 4 (2004) 604–616.
[25] S. Chatterjee, A. Pandey, The yin and yang of lactosylceramide metabolism: implications in cell function, Biochim. Biophys. Acta 2008 (1780) 370–382.

[26] B.M. Barth, S.S. Shanmugavelandy, D.M. Tacelosky, et al., Gaucher’s disease and cancer: a sphingolipid perspective, Crit. Rev. Oncog. 18 (3) (2013) 221–234.

[27] L.K. Ryland, T.E. Fox, T.P. Loughran, et al., Dysregulation of sphingolipid metabolism in cancer, Cancer Biol. Ther. 11 (2011) 2,138–2,140.

[28] S. Chatterjee, N. Alsaeedi, J. Hou, et al., Use of a glycolipid inhibitor to ameliorate renal cancer in a mouse model, PLoS One 8 (5) (2013), e63726.