Molecular Genetics and Metabolism Reports 11 (2017) 75–80

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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

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ARTICLE INFO

Article history:
Received 7 July 2016
Received in revised form 23 September 2016
Accepted 23 September 2016
Available online 1 October 2016

Keywords:
Fabry disease
Meningioma
Globotriaosylceramide
Alpha-galactosidase A
Lysosomal storage disease
Cancer

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 Gb_3) 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. 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.

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-Gb_3 [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

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http://dx.doi.org/10.1016/j.ymgmr.2016.09.005

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 microcystic 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

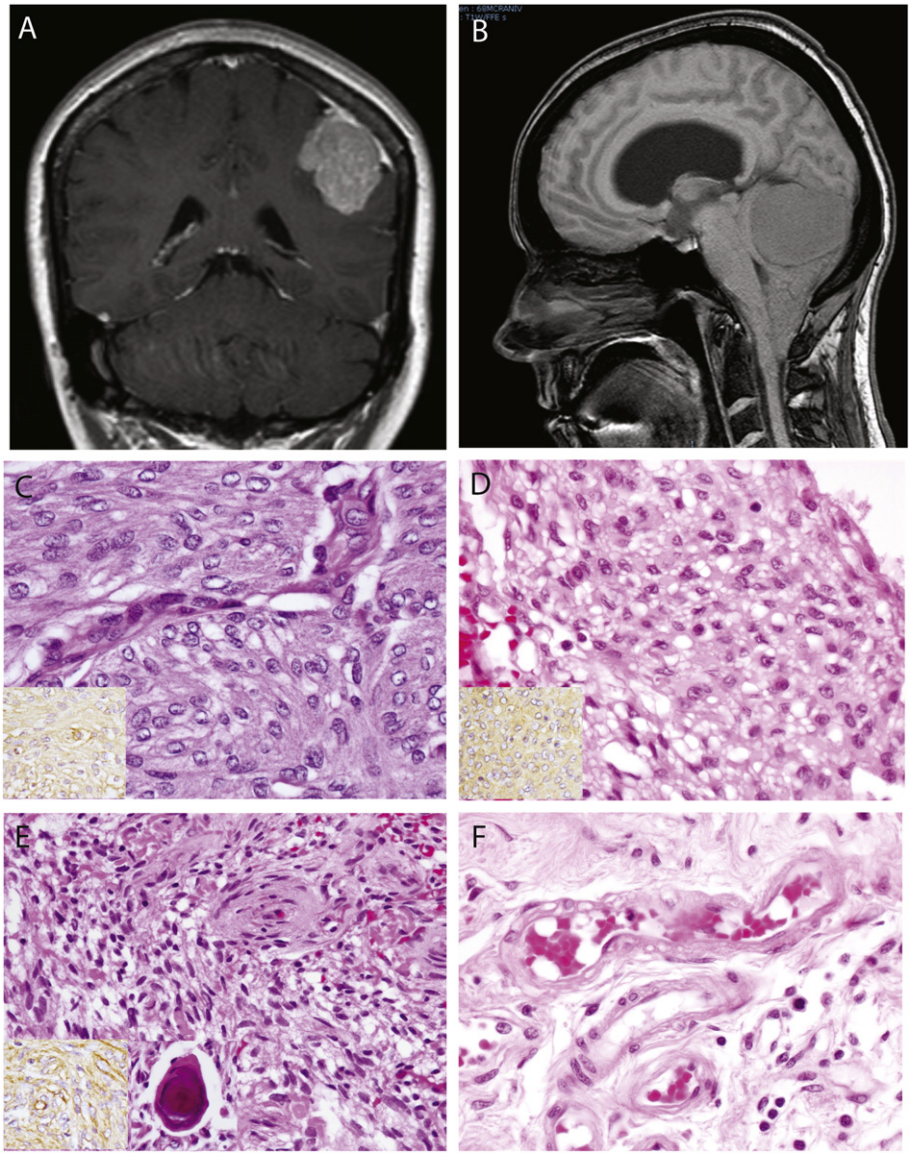

Fig. 1. MRI location and histologic appearance of meningiomas occurring in Fabry patients. Panels A. Case 1, convexity meningioma. Panel B. Case 3, torcular meningioma. Panel C. Case 1 - The tumor cells are meningothelial and arranged in well-defined lobules, with noticeable vacuolization. (paraffin 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).