

LETTER TO THE EDITOR

Glioblastoma with an unusual presentation: a diagnostic challenge[☆]



Dificultad en el diagnóstico de un glioblastoma de presentación inhabitual

Dear Editor:

Glioblastoma (GB) is the most common primary malignant tumour of the central nervous system.¹ GB generally involves the subcortical white matter; infratentorial presentation is rare, with less than 1% of tumours involving the cerebellum.² We present the diagnostic challenge of a case of multifocal GB with striking cerebellar involvement, and the patient's progression after treatment.

The patient was a 49-year-old woman who consulted in late 2014 due to instability and frequent vomiting of 2 years' progression, associated with pronounced weight loss. Physical examination detected ataxic gait and no other alterations. A blood analysis including hormones, vitamins, antibodies, and serology testing yielded normal results. A brain MRI scan (1.5 T; Fig. 1a and b) showed tumefactive appearance of the cerebellum, with diffuse involvement of the vermis, and several T2-hypointense lesions on both cerebellar hemispheres, the periaqueductal region of the midbrain, and the caudate nuclei. Contrast administration revealed linear enhancement in the cerebellar lesions (Fig. 1c). These findings were initially interpreted as being suggestive of an inflammatory or granulomatous process. CSF analysis returned normal results, with the exception of elevated levels of angiotensin-converting enzyme (94 U/L; normal range, 8–53). A body CT scan, ¹⁸F-FDG PET/CT, and ⁶⁷Ga-SPECT/CT all yielded normal findings. Suspecting neurosarcoidosis, we started empirical treatment with prednisone and methotrexate; no clinical changes were observed at 6 months. However, a follow-up MRI study (3 T; Fig. 1d) showed a signal alteration in the left mesial temporal lobe, in addition to the known lesions, which had remained stable. Stereotactic biopsy of a tissue sample from the left anterior temporal lobe identified no alterations. In the early months, no clinical or radiological changes were

observed, although the larger lesion in the left cerebellar hemisphere presented progression at 12 months (Fig. 1e). A spectroscopy study (Fig. 1f) revealed increased creatine and myo-inositol peak, with a normal choline/N-acetyl aspartate (Cho/NAA) ratio, except in the left cerebellar lesion (which presented a Cho/NAA ratio > 2). An anatomical pathology study of a second biopsy sample from the left hippocampus revealed infiltration due to a high-grade neoplastic proliferation, comprising cells with irregular, hyperchromatic nuclei and small foci of necrosis. Findings from a histology study, immunohistochemical analysis, and fluorescence in situ hybridisation (FISH) were compatible with a diagnosis of GB (Fig. 1g and i).

The patient was treated with radiotherapy (60 Gy) and temozolomide (TMZ), and presented radiological improvement 6 weeks after treatment onset (Fig. 1j). We continued treatment with TMZ, administering 6 cycles at 160 mg/m²/4 weeks; due to disease progression, the drug was replaced with irinotecan (CPT-11; 150 mg/m²) and bevacizumab (BVZ, 10 mg/kg) every 4 weeks. The patient died 14 months after onset of antitumour therapy.

Multicentric glioma is rare, and most commonly involves supratentorial regions.³ In our patient, the presence of both supra- and infratentorial tumours, with most pronounced involvement in the cerebellum, and the uncertain clinical course, led to uncertainties about the cause. This case also shows that higher-resolution MRI studies can reveal less visible lesions; spectroscopy studies can also provide key information for guiding aetiological diagnosis towards neoplastic processes.⁴

The standard treatment for GB is based on surgery, where possible, as well as radiotherapy and chemotherapy with TMZ.^{5,6} CPT-11, a topoisomerase I inhibitor, and BVZ, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), are used for second-line treatment, given the high level of vascularisation of these tumours.⁷ Multifocal presentation and cerebellar localisation have been described as independent risk factors for poor prognosis.^{8,9} In this case, the survival time after diagnosis was similar to the overall mean for patients with GB, approximately 12 months.¹⁰

In conclusion, multifocal presentation of GB constitutes a diagnostic challenge, and must be differentiated from such other processes as inflammatory or granulomatous lesions. Spectroscopy can be a valuable tool in guiding diagnosis. Finally, this entity must be considered in patients presenting cerebellar lesions, despite its low prevalence.

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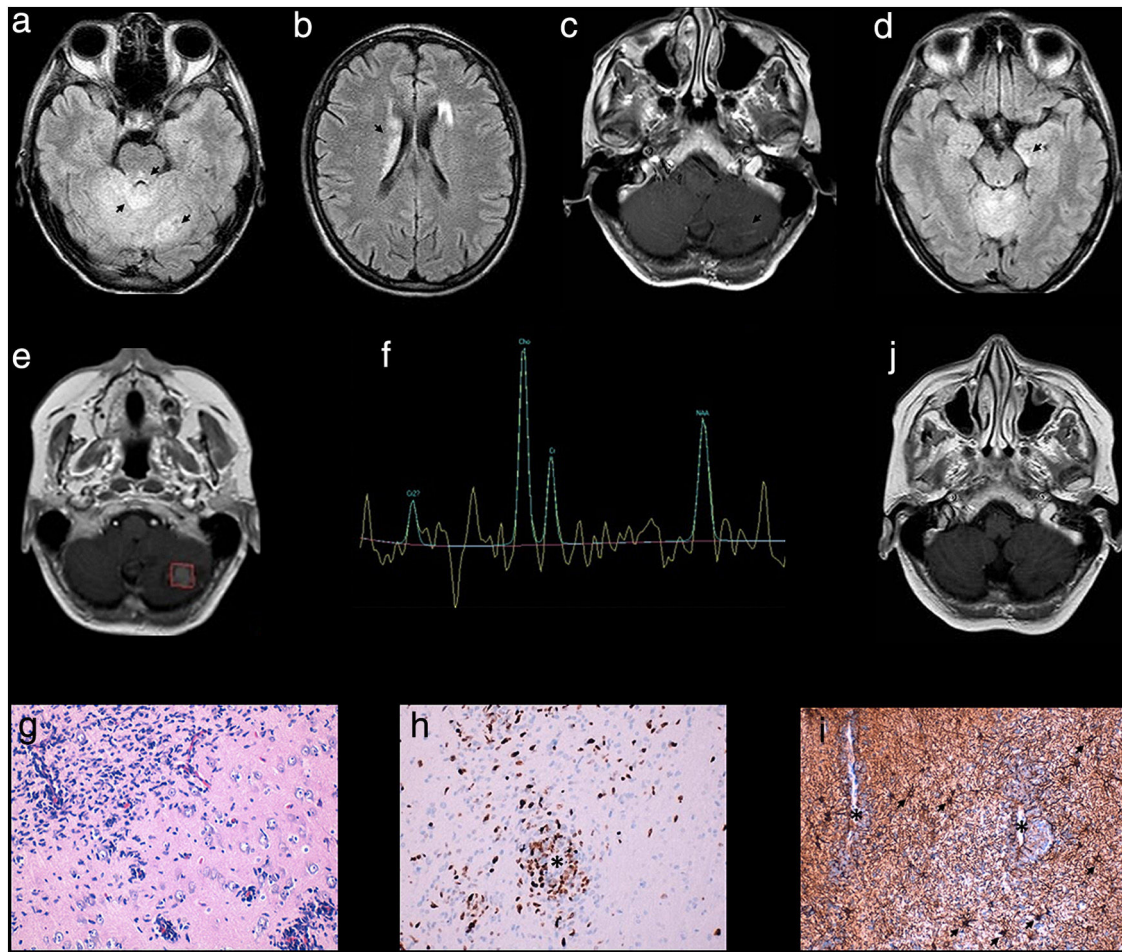


Figure 1 MRI findings: signal alterations in the cerebellum, midbrain, and caudate nuclei (a and b: 1.5 T, FLAIR sequence). Linear contrast enhancement of the cerebellar lesions (c: gadolinium-enhanced T1-weighted sequence). At 6 months, signal alteration was observed in the left mesial temporal lobe (d: 3 T, FLAIR sequence). At 12 months, the larger lesion, in the left cerebellum, presented pseudonodular contrast uptake (e: gadolinium-enhanced T1-weighted sequence), with a Cho/NAA ratio > 2 on the spectroscopy study (f). Six weeks after onset of radiotherapy and TMZ treatment, the cerebellar signal alteration had reduced (j: FLAIR). A histology study showed infiltration of astrocytes, forming sleeves around blood vessels (g: hippocampus section; haematoxylin and eosin stain; magnification $\times 400$). Immunohistochemistry showed a high proliferative index and perivascular localisation of tumour cells (asterisk) (h: MIB-1 [Ki-67] staining; magnification $\times 200$), and reactive astrocytes (arrows) distributed uniformly in contraposition to the dense perivascular aggregation of tumour cells, with variable expression of glial fibrillary acidic protein (asterisks) (i: GFAP staining; magnification $\times 200$).

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Muscle weakness, joint laxity and keloids. A more than suggestive association[☆]



Debilidad muscular, laxitud articular y queloides. Una asociación más que sugerente

Dear Editor:

Collagen VI (ColVI)—related myopathies encompass a group of diseases ranging from milder muscle disorders, such as Bethlem myopathy, to more severe forms, such as Ullrich congenital muscular dystrophy.^{1–4} From a phenotypic viewpoint, these disorders are characterised by muscle weakness, joint contractures in flexion, joint hypermobility predominantly affecting distal joints, and skin alterations (follicular hyperkeratosis, “velvety” skin, and keloid scars). Collagen VI is a structural protein of the extracellular matrix, comprising 3 subunits, encoded by the genes *COL6A1*, *COL6A2*, and *COL6A3*. Although new mutations in these genes are constantly being reported,⁵ establishing a genotype-phenotype correlation is challenging due to the clinical heterogeneity and genetic overlaps.^{6,7}

We present the case of a 58-year-old man with history of early-onset, slowly progressing limb-girdle muscular dystrophy associated with respiratory involvement and no known genetic defects. Diagnosis had been established when the patient was 2 years old due to delayed acquisition of developmental milestones; weakness predominantly affected distal muscles, and a muscle biopsy revealed signs compatible with muscular dystrophy. At the time of assessment at our department, the patient presented proximal muscle weakness but did not require support to walk. The examination revealed 4/5 muscle strength at the level of the shoulder and pelvic girdles, joint hypermobility predominantly in the hands (Fig. 1B), con-

tractures in the metacarpophalangeal and interphalangeal joints (Fig. 1A), and keloid scars in the area where the muscle biopsy specimen was taken (Fig. 1C). From a respiratory viewpoint, the patient presented a pattern of moderate restrictive pulmonary function,⁸ with complementary tests revealing no cardiac alterations. He also presented increased creatine kinase levels ($\times 2$). A muscle MRI scan was performed to confirm suspicion of ColVI-related myopathy and to guide the genetic study. The MRI scan (Fig. 1D) showed a pattern compatible with ColVI-related myopathy, and a genetic study revealed that the patient was a heterozygous carrier of variant p.Gly289Val in the gene *COL6A2* (reference sequence: NM_001849.3:c.866G>T NC_000021.8:g.47535933G>T); this finding is compatible with diagnosis of Bethlem myopathy. This mutation causes an amino acid change involving glycine at position 289 of the α_2 chain of collagen VI, which forms part of the Gly-X-Y motif in the N-terminal region of the triple helical domain of the protein, with this amino acid being substituted by valine. This missense mutation was classified as probably pathogenic in the EmVClass catalogue, but had not been listed in any other genetic database, nor had it been reported in previous publications. However, our patient's clinical characteristics and muscle MRI findings support the pathogenic nature of the mutation. A family segregation study did not identify the mutation in our patient's parents, meaning that the mutation was de novo.

We present a case of Bethlem myopathy secondary to a novel *COL6A2* mutation (c.866G>T, p.Gly289Val); this mutation had not previously been described as pathogenic in the literature. ColVI-related myopathy should be suspected in patients with predominantly proximal muscle weakness and distal joint hypermobility, distal muscle contractures, and skin alterations (typically keloids). Muscle MRI reveals a characteristic pattern,⁹ and diagnosis can be confirmed with genetic studies, although a clear genotype-phenotype correlation cannot be established.

From a genetic viewpoint, Ullrich congenital muscular dystrophy has typically been reported to follow an autosomal recessive inheritance pattern, whereas Bethlem myopathy is thought to follow an autosomal dominant pattern. However, both inheritance patterns have been described in the spectrum of ColVI-related myopathies.^{5,10–13} Genetic sequencing enables analysis of

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