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CASE REPORT

Rapid Vision Loss Due to Multifocal Glioma: A Diagnostic Challenge

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ABSTRACT

Introduction: This is a unique case report in medical literature for its detailing of diagnostics of an uncommon presentation of a rapid unexplained bilateral vision loss of a 73-year-old male diabetic patient. This report highlights the crucial role of advanced molecular diagnostics in difficult neurological cases and also elucidates the difficulties involved in diagnosing optic nerve glioblastoma, an exceptionally rare and aggressive tumour.

Main Concerns and Clinical Findings of the Patient: Slow and progressive loss of vision over 2 months, ultimately developing almost complete visual impairment in both eyes and a defect of right eye field of vision conclusively highlighted that the likely etiology was neuro-ophthalmic. Initially, the conditions were suspected to be an extended spectrum of diabetic eye disease complications but further deterioration was a hint towards something more substantive.

Primary Diagnoses, Interventions and Outcomes: This entailed in-depth diagnosis processes that included an MRI and the analysis of cerebrospinal fluid. The important discovery was through stereotactic biopsies of the optic nerve revealing a high-grade glial neoplasm. Next generation sequencing confirmed the pathology as IDH-wildtype glioblastoma. Despite management, his vision continued to deteriorate. Hence, an aggressive clinical course was followed.

Conclusion: This case highlights the important learning need in considering glioblastoma of the optic chiasm as part of the differential diagnosis of rapid vision loss, which may present as multifocal brain lesions, especially in cases of rapid loss of vision where initial workup is negative. Quite a useful lesson that can be drawn from this case relates to the diagnostic process with advanced molecular profiling, more attention given to clinical suspicion and cutting-edge diagnostic tools applied in atypical presentation of neurological conditions.

Keywords: Optic chiasm; Glioblastoma; Brain tumours; Visual field defects

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Key Summary Points

Here, we describe a unique case of optic nerve glioblastoma presenting as a diagnostic dilemma initially.

This case report highlights the atypical presentation of this tumour, making its diagnosis challenging, and demonstrates the role of next generation sequencing in giving an accurate diagnosis.

This is the first documented complete molecular profiling of optic nerve glioblastoma through next generation sequencing.

Our case report emphasizes considering rare neoplasms in rapid vision loss with inconclusive initial tests.

INTRODUCTION

This case report highlights a rare instance of optic nerve glioblastoma presenting with a rapid vision loss in a 73-year-old diabetic male, a clinical scenario usually overshadowed by more prevalent conditions like diabetic retinopathy. The differential diagnosis and challenge of diagnosing this condition were illustrated by the atypical nature of the presentation, thus reflecting concerns that have been raised because of similar cases [1, 2]. The case only underpins the critical need for consideration of rare neoplasms in differential diagnoses as emphasized by the World Health Organization (2023) and recent literature [3]. This report contributes to medical knowledge because it shows that next generation sequencing can be applied successfully in the diagnosis of a rare, aggressive brain tumour type, thereby helping to address this molecular void for optic pathway glioblastomas.

CASE PRESENTATION

While ethical committee approval was not required for this case report, due to the nature of a case report, informed consent from the patient and next of kin was obtained and documented in writing. A 73-year-old diabetic pseudophakic gentleman presented to his ophthalmologist with generalised hazy vision in both eyes that had been gradually worsening over the course of about 2 months. During this first visit, it was found that his vision had deteriorated from 6/6 to 6/12 bilaterally. However, there were no clinical signs attributable to the symptom. Optical coherence tomography (OCT) scans were unremarkable as well. Comparing with previous OCT scans and a fluorescein angiogram that was conducted 3 months ago, there were no significant changes, with no progression of his diabetic retinopathy or diabetic macular oedema. He underwent thorough bilateral pan-retinal photocoagulation (PRP) in the past, which appeared to be effective. He denied any headaches, scalp tenderness or jaw claudications.

Two weeks later, he returned after experiencing profound vision loss onset over several hours. He described right-sided visual field loss, and his visual acuity had worsened to 6/18 on the right and 6/12 on the left. There were no other neurological symptoms. He had no fever, chills or unexplained weight loss. An urgent magnetic resonance imaging (MRI) brain scan was performed the next day, which demonstrated abnormal enhancement and enlargement of the optic chiasm, plus multifocal enhancing lesions in the anterior corpus callosum, left basal ganglia and midbrain. There were also left mesial temporal lobe pachymeningeal thickening and loss of grey-white differentiation. With the suspicion of an inflammatory or demyelinating disease, he underwent a 5-day course of 1000 mg daily intravenous methylprednisolone. Following the treatment, there was no improvement, but the deterioration of visual fields and vision stagnated. Over the following 6 to 8 weeks, his condition gradually worsened despite oral prednisolone and a trial of plasma exchange.

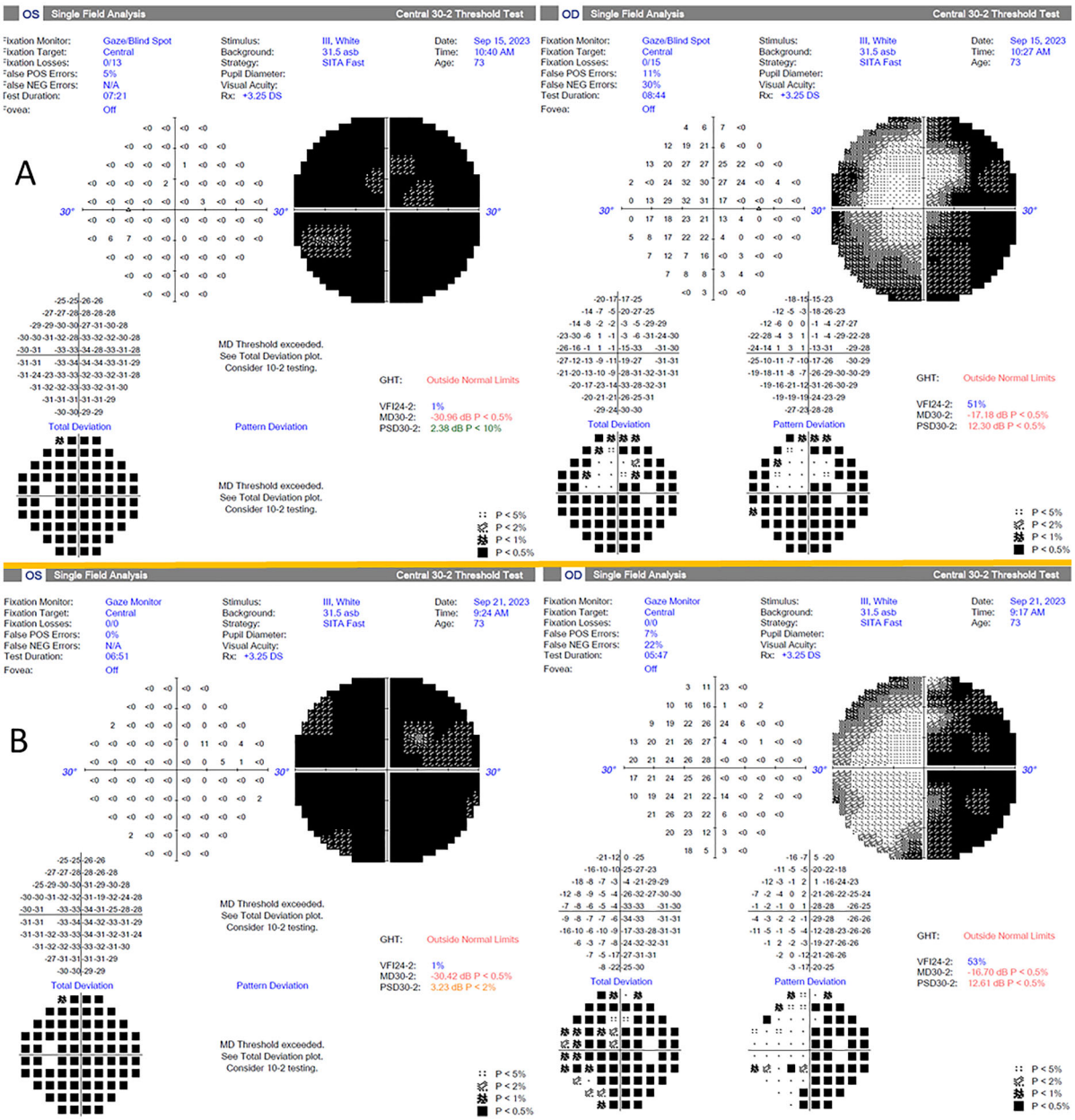

Fig. 1 Serial Humphrey's visual fields (HVF). **A** HVF prior to intravenous methylprednisolone. **B** HVF at Day 5 of methylprednisolone

His visual field deficits progressed, and he developed right arm weakness and unsteadiness (Fig. 1).

Multiple investigations were organised (Table 1). Inflammatory or infective aetiologies were considered; however, the patient had no infective symptoms and cerebrospinal fluid (CSF) was bland. CSF was negative for viral PCR, acid fast bacilli on Ziehl-Neelsen stain, cryptococcal antigen, *Tropheryma whipplei* DNA and fungal microscopy and culture. Serial blood cultures were negative too, with negative serum CMV, EBV and Quantiferon Gold. Serum RhF, ACE, ANCA, ANA/ENA, anti-CCP, SPEP, flow cytometry, TSH, anti-neuronal antibodies, anti-NMO and anti-MOG cell-based assay were

negative. Serum paraneoplastic antibodies were negative, and CSF flow cytometry/cytology was unremarkable. Of note, CSF from three lumbar punctures demonstrated very high protein, despite being acellular initially. CSF opening pressure was normal.

Serial MRI scans were organised when the patient developed progressive visual field loss, and they showed progression of lesions (Fig. 2). Whole body PET scan demonstrated only physiological tracer distribution, and computed tomography (CT) scan of the entire body revealed no organomegaly or lung nodules.

Stereotactic biopsies were conducted to address the diagnostic dilemma. A first biopsy of the corpus callosum revealed non-specific inflammatory changes with macrophage accumulation, but no evidence of demyelination, lymphoma, IgG4 or sarcoidosis. A second and diagnostic biopsy of the left optic nerve, frontal lobe and dura was conducted. While no significant histological abnormalities were identified in the dural or frontal lobe biopsies, the second biopsy of the left optic nerve demonstrated histological features of a high-grade glial neoplasm. These included a mitotically active atypical glial cell proliferation with associated necrosis and microvascular proliferation (Fig. 2). A targeted next generation sequencing panel performed on this tissue confirmed the presence of a *TERT* promoter mutation at a variant allele frequency of 19.7%, in addition to homozygous deletion of *CDKN2A* and the absence of *IDH1/2* mutations. Both the morphological findings and molecular phenotype were of an IDH-wildtype glioblastoma. Post-biopsy visual acuity was 6/38 on the right and no light perception on the left. Following diagnosis, the patient was placed on palliative care as per the wishes of himself and his family. He developed a rapid functional decline and had to be cared for in the hospital. The patient died less than 2 months after diagnosis, 5 months after the symptoms first appeared.

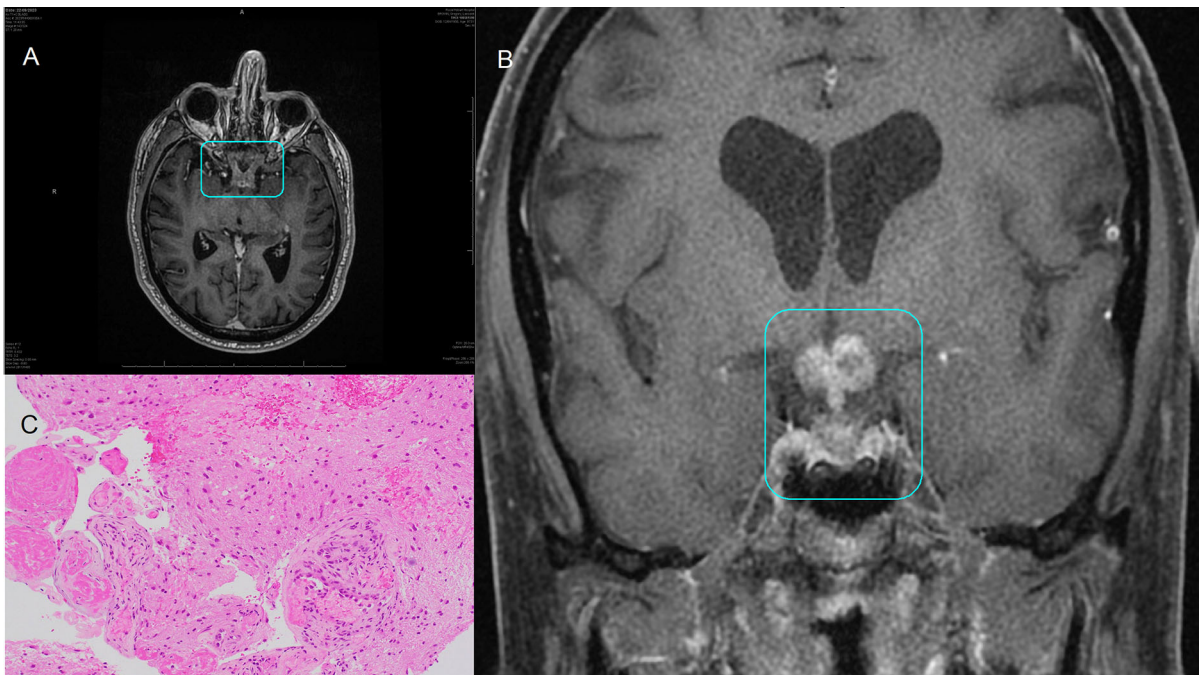

Fig. 2 Investigations. MRI scan and histology of lesions. **A** Axial MRI image of optic chiasm lesion. **B** Coronal (T1 fat saturation and gadolinium contrast) image of chiasmal enlargement and left chiasm haemorrhage. **C** Haemotoxylin and eosin stained section (×200 magnification) demonstrating histological features of a high-grade glioma, including microvascular proliferation (bottom left of image)

Table 1 Investigations leading to diagnosis

Serology			
Blood cultures	Normal	Rheumatoid factor	Normal
CMV	Normal	ACE	Normal
EBV	Normal	ANCA	Normal
Quantiferon Gold	Normal	ANA/ENA	Normal
		Anti-CCP	Normal
Paraneoplastic antibodies	Normal	Anti-neuronal antibodies	Normal
Serum protein electrophoresis	Normal	Anti-NMO antibodies	Normal
Flow cytometry	Normal	Anti-MOG cell based assay	Normal
		TSH	Normal
Cerebrospinal fluid (CSF)			
Viral PCR panel	Normal	Cytology	Normal
Acid-fast Bacilli	Normal	Flow cytometry	Normal
Crytococcal antigen	Normal	Lymphocytes/polymorphs < 1 initially, third lumbar puncture lymphocytes 8	
Tropheryma whipplei DNA	Normal	Protein	**↑1.13/1.08/1.48**
Fungal microscopy and cultures	Normal	CSF opening pressures	Normal
Radiological imaging			
MRI	Abnormal enhancement and enlargement of the optic chiasm, plus multifocal enhancing lesions in the anterior corpus callosum, left basal ganglia and midbrain. Left mesial temporal lobe pachymeningeal thickening and loss of grey-white differentiation. Serial scans demonstrated progression		
Whole body PET	Physiological tracer distribution		
Whole body CT	No organomegaly, no nodules		
Histopathology			
Corpus callosum biopsy	Non-specific inflammatory changes with macrophage accumulation, but no evidence of demyelination, lymphoma, IgG4 or sarcoidosis		
Left optic nerve, frontal lobe, dura biopsy	Optic nerve demonstrated histological features of a high-grade glial neoplasm, including mitotic activity, microvascular proliferation and necrosis		
Next generation sequencing	*TERT* promoter mutation (C228T) and homozygous deletion of *CDKN2A*; no *IDH1/2* or histone H3 mutations		

DISCUSSION

Glioblastoma remains one of the most aggressive types of primary brain tumour, with little change in its management for the past 2 decades. Optic nerve glioblastoma accounts for only about 0.6–1.2% of all gliomas [1]. Patients typically present with progressive vision loss, proptosis and, in some cases, pain [2]. These symptoms can often be mistaken for inflammatory or infectious conditions, leading to potential delays in diagnosis.

In our patient's case, a malignant process was eventually suspected because of poor response to steroids and plasma exchange, extended investigations that were negative and, upon conducting a literature review, noting that the lesions were in typical locations for malignant optic glioma of adulthood (MOGA).

The non-specific clinical presentation of optic nerve glioblastoma necessitates advanced imaging techniques for accurate diagnosis. Magnetic resonance imaging (MRI) is often employed to visualize the optic nerve and its surrounding structures. Specific radiographic features such as enlargement of the optic nerve and contrast enhancement may suggest the presence of a glioma [4], although differentials include inflammatory, infective or infiltrative causes. Importantly, glioblastoma can be partially responsive to steroids, which adds to the diagnostic challenge [5].

The current WHO Classification of Eye and Orbit Tumours states that "very few optic pathway glioblastoma cases have been subjected to molecular genetic profiling" [6]. A case report from 2013 describes a constellation of chromosomal changes [1], while another from 2016 only tested for *IDH1* mutations in their series of three cases, all of which were wildtype [3]. The current case is the first in the literature to document complete molecular phenotyping of an optic nerve glioblastoma via next generation sequencing (Table 1).

The prognosis remains poor because of the tumour's resistance to traditional therapies and its proximity to vital structures [6].

CONCLUSION

This case report demonstrates the importance of the differential diagnosis of glioblastoma in any challenging diagnostic dilemma with rapid vision loss and equivocal results from panels of thorough investigations. Optic nerve glioblastoma is rare, but in similar cases of vision loss and inconclusive investigations, it should be carefully considered and thoroughly looked into. Next generation sequencing has significantly improved diagnostic yield compared to previous similar cases of molecular testing.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. The authors declare that they have no financial or personal relationships with any individuals or organizations that could inappropriately influence their work or interpretation of the research presented in this article.

Ethical Approval. While ethical committee approval was not required for this case report, because of the nature of a case report, informed consent with patient and next of kin was attained and documented in writing. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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