Case Reports in Neurology

Case Rep Neurol 2022;14:213–222
DOI: 10.1159/000522239
Received: July 1, 2021
Accepted: November 20, 2021
Published online: April 22, 2022

Case Series - General Neurology

Glioblastoma, IDH-wildtype: A New Association with IgM Paraproteinaemic Neuropathy?

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Keywords
IgM paraproteinaemic neuropathy · Waldenstrom's · Glioblastoma IDH-wildtype · Chemoimmunotherapy

Abstract
It is well recognized that B-cell clonal disorders such as Waldenstrom's macroglobulinaemia may affect the central nervous system by direct infiltration of malignant B cells (Bing-Neel syndrome). However, there is no recognition in the current literature of a clear link between paraproteinaemia and primary brain tumours such as glioma. We present 3 cases of classical IgM paraproteinaemic neuropathy who developed glioblastoma in the course of their illness following treatment with chemoimmunotherapy (CIT). Due to the progressive symptomatic nature of their neuropathy, all 3 patients were treated with CIT. The patients presented with glioblastoma, IDH-wildtype at 9 months, 5 years, and 6 years following treatment completion. None of the patients had unequivocal evidence of known predisposing factors for glioblastoma. Both disorders are exceedingly rare and the chance of random association is less than one in a million. Potential common pathogenic mechanisms include the influence of paraproteins and circulating lymphoplasmacytic cells on blood-brain permeability and CNS immune micro-environment as well as raised circulating angiogenic cytokines such as vascular endothelial growth factor. In cases with anti-myelin-associated glycoprotein (MAG) antibodies, surface MAG on glial cells may act as a target releasing cells from growth inhibition.

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We suggest that all glioblastoma cases be screened at diagnosis for serum paraproteins and that such cases be reported to central registries to establish the frequency of the association more accurately.

Introduction

Peripheral neuropathy is described in the literature as a complication of paraproteinaemia (typically IgM) with a prevalence of 0.0008% in the >50 age group [1, 2]. It may also be associated with underlying haematological malignancies such as non-Hodgkins lymphoma, most commonly lymphoplasmacytic lymphoma/Waldenstrom's subtype, or with IgM monoclonal gammopathy of clinical significance (MGCS) [3]. M-protein reactivity towards myelin-associated glycoprotein (MAG) has been demonstrated in approximately 50–60% of cases [2]. Anti-MAG antibodies have the potential to be neuropathic with a typical progressive illness trajectory [4] with overall limited response to treatment [5].

We present 3 cases of classical IgM paraproteinaemic neuropathy with an associated B-cell clone (1 Waldenstrom's macroglobulinaemia [WM], 2 MGCS) who developed glioblastoma (summary shown in Table 1). Of the 3 cases, two were positive for anti-MAG in their serum. Screening for other causes of neuropathy was negative in all 3 cases. Due to the progressive symptomatic nature of their neuropathy, all 3 patients were treated with a chemoimmunotherapy (CIT) protocol of Rituximab, Cyclophosphamide and Prednisolone (R-CP), similar to that shown to be effective in WM [6]. R-CP CIT has been demonstrated to be an effective

Table 1. Summary of demographic, clinical, haematological and neurological data on the cases

	Case 1	Case 2	Case 3
Patient demographic	Caucasian male	Caucasian male	Caucasian male
Age at diagnosis of IgM paraproteinaemic neuropathy, years	56	56	65
Underlying haematological diagnosis	Lymphoplasmacytic lymphoma (WM)	MGCS	MGCS
Baseline Anti-MAG antibody titres before treatment (Bühlmann titre units – BTU)	Absent	64,300	20,500
Paraprotein isotype and level, g/L	IgM kappa 2.6 and 5	IgM lambda 3.6	IgM kappa 4.7
CIT protocol received	Six cycles (every 21 days) of the following regimen: intravenous rituximab 375 mg/m^2, intravenous cyclophosphamide 750 mg/m^2, and oral prednisolone 50 mg/m^2 (days 1–5) [16]		
Timing of glioblastoma diagnosis after IgM paraproteinaemic neuropathy diagnosis, years	14	12	10
Timing of glioblastoma diagnosis after CIT completion	5 years	9 months	6 years
Survival post glioblastoma diagnosis, months	2	2	4

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treatment in patients with IgM paraproteinaemic neuropathy evidenced by sustained clinical and serological improvement over time [7].

Glioblastoma is the commonest primary brain tumour, shows astrocytic differentiation, and is a rapidly progressive tumour of high grade (WHO grade IV). However, overall incidence is still only 3 per 100,000 [8]. Most tumours are seen in Caucasian males with a median age of onset of 64. Recognized risk factors seen in some cases include pre-morbid radiation therapy, an immune tumour local environment, as well as single nucleotide polymorphisms [8] and variations in *IL-2RA* (*CD25*) genes [9]. Glioblastoma is categorized as IDH-wildtype or IDH-mutant. IDH-wildtype glioblastoma typically arises de novo, with no recognizable precursor lesion, and accounts for approximately 90% of glioblastoma [10]. Currently, there are no reports in the literature of glioblastoma related to any form of immunosuppressive therapy.

Current understanding of glioblastoma aetiology is limited and whilst both genetic and environmental factors have been observed to be of epidemiological significance, they do not comprehensively explain the overall burden of disease [8]. We show that the most likely explanation for the occurrence of glioblastoma in our patients is a hitherto unrecognized pathogenic link between IgM paraproteinaemia and glioblastoma, which could provide important insight into glioblastoma pathogenesis and ultimately contribute to the development of new treatments.

Case Presentations

Case 1

A 56-year-old man initially presented with numbness in the feet ascending to mid-calf over the course of 2 years, as well as gait unsteadiness. Neurophysiology was consistent with a predominantly axonal neuropathy with a borderline increase in the terminal latency in a few nerves. The patient was first noted to have an IgM paraprotein a year after presentation, with a normal bone marrow biopsy at this stage. Anti-MAG antibodies were not detected.

The patient developed progressive symptoms over a 9-year period from diagnosis. He underwent re-staging computed tomography (CT), which showed widespread small volume lymphadenopathy and a normal sized spleen. Bone marrow trephine now showed typical features of WM. Serological studies showed two IgM kappa paraproteins totalling approximately 9 g/L with a mild immuneparesis. The diagnosis predated the discovery of the *MYD88* mutation known to be associated with WM and possibly also with paraproteinaemic neuropathy [11]. Repeat anti-MAG titre was again negative. These findings were diagnostic of WM (lymphoplasmacytic lymphoma) with suspected related sensorimotor neuropathy (shown in Fig. 1).

In view of progressive severe symptoms, the patient was treated with CIT in a standard protocol for WM, comprising 6 cycles (every 21 days) of the following regimen: intravenous rituximab 375 mg/m^2, intravenous cyclophosphamide 750 mg/m^2, and oral prednisolone 50 mg/m^2 (days 1–5). Good tolerance was demonstrated. The patient completed the full treatment protocol and received prophylaxis for at least 6 months post-treatment to reduce treatment-related infection risk. He achieved a good partial response in both haematological and serological parameters with stabilization of neurological symptoms. Four years post-treatment, the patient noted significant deterioration in his neurological symptoms although IgM levels remained largely static. He initially had a course of immunoglobulins as a means of halting further disease progression and after satisfying inclusion criteria, was enrolled into the ACE-WM-001 trial, completing 4 cycles of the Bruton Tyrosine Kinase inhibitor, ACP196001, (now known as Acalabrutinib).

A year later, he presented with a generalized tonic-clonic seizure and was found on MRI to have 3 intra-axial enhancing lesions suggestive of malignant tumour with surrounding vasogenic oedema (shown in Fig. 2). He underwent an image-guided left frontal burr hole biopsy.

Case Rep Neurol 2022;14:213–222
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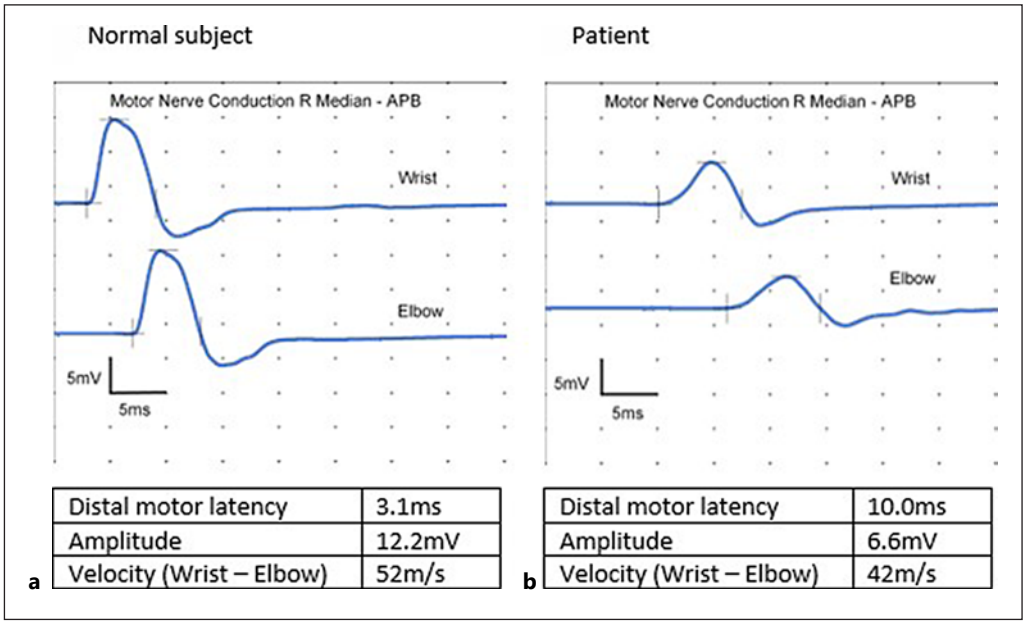

Fig. 1. Motor nerve conduction studies (Median nerve/APB) from a normal subject (**a**) and a patient with IgM paraproteinaemic polyneuropathy and anti-MAG antibodies (**b**). Abnormalities demonstrated in B are reduced motor amplitude; severe prolongation of the distal motor latency (from wrist stimulation to the muscle); and mild slowing of the motor conduction velocity (wrist to elbow), indicating predominantly distal slowing, characteristic of the disorder.

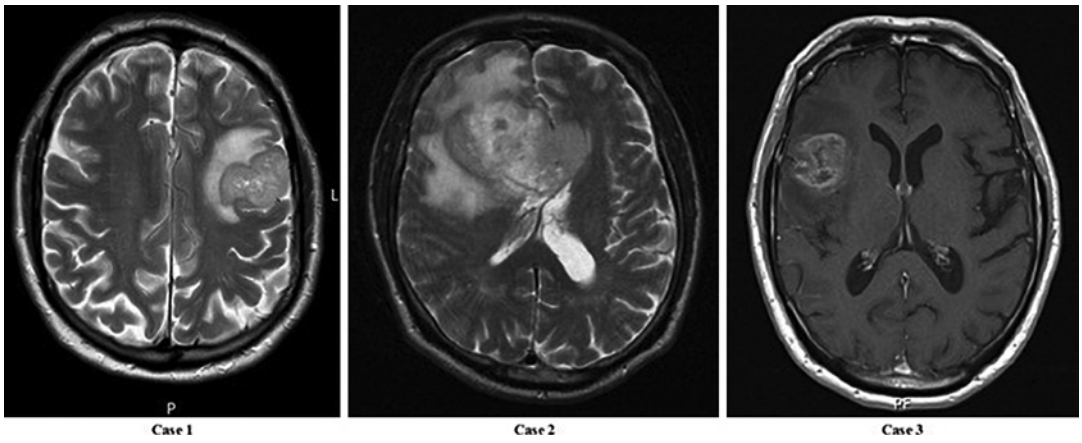

Fig. 2. Axial MRI scans demonstrating lesions suggestive of malignant tumour with surrounding vasogenic oedema (T2 weighted images – Cases 1 and 2; gadolinium-enhanced T1-weighted image – Case 3).

Histological examination demonstrated a tumour with high cell density composed of cells with irregular angulated nuclei and eosinophilic cytoplasm (shown in Fig. 3). Immunohistochemical staining with glial fibrillary acidic protein (GFAP) was positive within the tumour cells and the Ki67 proliferation index was high. Staining for mutant IDH1 (R132H) was negative with ATRX staining retained. The diagnosis was of a glioblastoma IDH-wildtype (WHO grade IV). Treatment plan included 3 cycles of Temozolomide chemotherapy. Radiotherapy was not possible as the tumour could not be encompassed within the radiotherapy field. The patient died within 2 months.

Case Rep Neurol 2022;14:213–222
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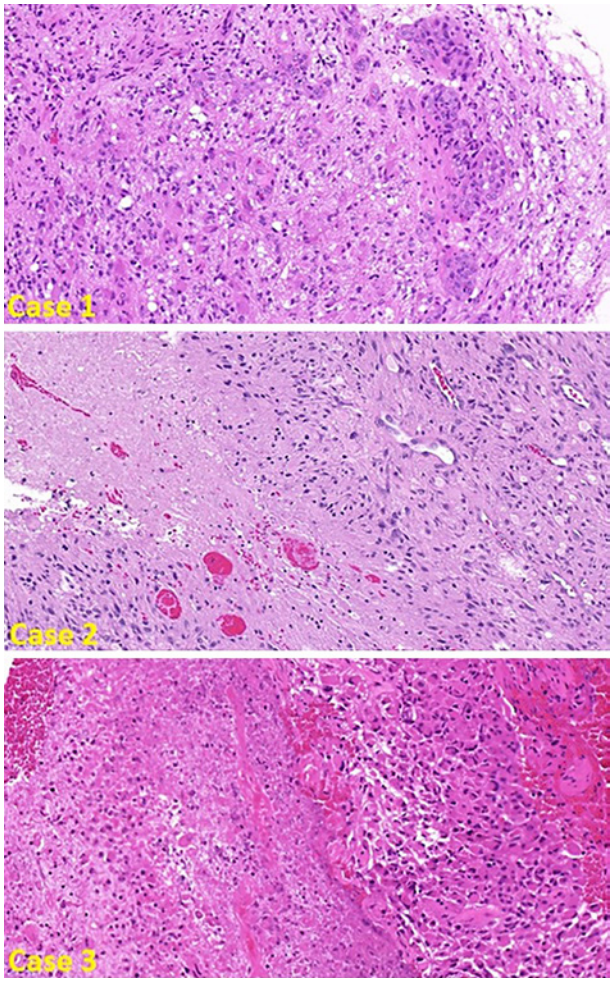

Fig. 3. Biopsies from all 3 patients showed features of Glioblastoma, IDH-wildtype (WHO grade IV) with pleomorphic astrocytic cells, mitotic activity, microvascular proliferation (Case 1) and necrosis (Cases 2 and 3). In each case, the cell proliferation index assessed by ki67 immunohistochemistry was high. IDH1 was assessed as nonmutated by lack of staining for the common IDH-1 (R132H) mutation specific antibody.

Case 2

A 56-year-old man initially presented with numbness in the feet and distal legs with associated sensory ataxia. He later developed sensory symptoms in the hands. Of note, the patient had potential exposure to toxic chemicals in his youth but with no reported radiation exposure. He had a paternal cousin with WM as well as a brother who had non-Hodgkins Lymphoma (NHL) treated to remission. Neither of these cases suffered with neuropathy.

Nerve conduction studies showed findings typical of anti-MAG neuropathy, with conduction velocities within the demyelinating range and disproportionately prolonged distal motor latencies. He was found to have an IgM paraprotein, and anti-MAG titre at diagnosis was 64,300 BTU. Haematological work-up with bone marrow biopsy and CT body scan showed a clonal B-cell population but with <10% infiltration so categorizing as MGCS rather than NHL.

His symptoms worsened over a 10-year period, progressing to disabling unsteadiness. He commenced treatment with standard 5-day courses of intravenous immunoglobulins. Improvement was initially noted but progressively less sustained. Repeated neurophysiological studies remained largely unchanged. The patient was commenced on CIT and achieved a good neurological and serological response.

Nine months post-treatment completion the patient presented with rapid cognitive decline and behaviour change. MRI demonstrated an enhancing lesion centred on the right

Case Rep Neurol 2022;14:213–222
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frontal lobe and extending into the corpus callosum, very suggestive of glioblastoma (shown in Fig. 2). The patient underwent a right frontal craniotomy debulking procedure, which confirmed a histological diagnosis of glioblastoma IDH-wildtype (WHO grade IV) (shown in Fig. 3). Immunohistochemical staining with GFAP was positive, and Ki67 proliferation index was high with no expression of mutant IDH1 detected. In view of the guarded prognosis, treatment was limited to palliative radiotherapy; however, the patient died 2 months following the surgery.

Case 3

A 65-year-old man presented with progressive sensory symptoms in the feet, gradually ascending to the knees over a 3-year period, and at this stage affecting the hands. He had prominent sensory ataxia with gait unsteadiness due to loss of proprioception in the feet. Nerve conduction studies demonstrated a demyelinating neuropathy, with diffuse motor slowing in the lower limbs and disproportionate prolongation of the upper limb distal motor latencies. Sural responses were preserved. Hand digital sensory responses were reduced in amplitude and slow. The patient also reported increased fatigue and poor appetite with occasional spontaneous nosebleeds. Interestingly, he had a number of previous occupational exposures including Formaldehyde, Phenols, and possibly Thallium although not radiation as far as he was aware from his work as a researcher at the Ministry of Defence.

An IgM kappa paraprotein was found at 4.7 g/L with no immuneparesis. Anti-MAG antibody was positive (17,800 BTU). A bone marrow aspirate and trephine showed a clonal B-cell population but with <10% infiltration so categorizing as MGCS rather than NHL. CT scan was normal with no pathological lymph node enlargement or splenomegaly. The patient was treated with 6 cycles of CIT. He demonstrated good tolerance and sustained neurological and haematological benefit following treatment.

Six years later, the patient presented with rapid onset left sided facial weakness and slurred speech. MRI demonstrated an enhancing lesion in the right frontal lobe, suggestive of a malignant neoplasm (shown in Fig. 2). The patient underwent a craniotomy for partial debulking, with histological analysis confirming glioblastoma IDH-wildtype (WHO grade IV) with GFAP immunoreactivity, lack of staining for IDH1 (R132H), retained ATRX and a high Ki67 proliferation index (shown in Fig. 3). The patient completed radical chemoradiotherapy (40 Gy in 15 fractions) with concomitant Temozolomide. He was concurrently also diagnosed with prostate cancer and completed a 3-week course of localised radiotherapy and Bicalutamide hormonal treatment. He died 4 months later.

Discussion

Both IgM paraproteinaemic neuropathy and glioblastoma are very rare disorders. Peripheral neuropathy is described in the literature as a complication of paraproteinaemia (typically IgM) with a prevalence of 0.0008% in the >50 age group [1]. WM is also a rare tumour and accounts for up to 2% of non-Hodgkin lymphomas with an age-adjusted incidence rate of 7.3/1,000,000 in the European standard male population [12]. As IgM MGCS and WM are considered to be different stages of the same disease process, they will be grouped as such for the purpose of this discussion [13].

The 3 cases presented here occurred in a group of 25 patients followed up for 12 years (total 300 "patient years"). With a glioblastoma annual incidence of 3.19/100,000 or 0.0000319, the likelihood of observing a single case during this time period in 25 patients is $0.0000319 \times 300 = 0.0096$. Therefore, the chance of seeing 3 cases is $0.0096 \times 0.0096 \times 0.0096 = 8.8 \times 10^{-7}$. The chance of these 3 cases occurring randomly is less than one in a million.

Case Rep Neurol 2022;14:213–222
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Table 2. Immune status of patients at time of glioblastoma diagnosis

Case number	IgG, g/L	IgA, g/L	IgMm g/L	Peripheral blood lymphocytes, 10^9/L
Case 1	5.7	0.9	3.8	0.7
Case 2	6.1	0.4	2.2	1.1
Case 3	8.7	2.0	2.6	1.2

There are currently no reports in the literature of paraproteinaemia co-existing with glioblastoma, but this may be due to lack of recognition within existing reporting systems. Traditional registries such as the Cancer Registry and death certificates may not capture relatively benign comorbidities such as paraproteinaemia. In order to define the frequency of this association, we propose that all glioblastoma patients undergo screening for serum paraproteins at glioblastoma diagnosis to quantify combined incidence.

We think it unlikely that the association is due to the CIT treatment regimen itself. The R-CP regimen with which these patients were treated, as well as closely related CIT regimens, have been used extensively in haematological and rheumatological practice over a number of decades, and whilst a link between glioblastoma pathogenesis and its immune micro-environment is well recognized, there are no existing reports in the literature of glioblastoma related to prior administration of chemotherapeutic or immunosuppressive therapy. Moreover, none of our patients suffered from infections, and their immune status at time of glioblastoma diagnosis did not show any substantial compromise (shown in Table 2). There was no clear suppression of normal immunoglobulins and only mild lymphopenia in 1 patient, suggesting adequate systemic immune competency at time of glioblastoma diagnosis.

Instead, we present here two main lines of evidence pointing to the most plausible explanation being a hereto unrecognized predisposition to glioblastoma in patients with IgM paraproteinaemia: (a) there are other individual case reports in the literature of glioblastoma in patients with concurrent WM [14–16] none of whom had received prior chemotherapy or any immunosuppressant treatment for their haematological diagnosis; (b) there are several plausible mechanisms by which IgM paraproteinaemia or WM could influence glioblastoma pathogenesis. Recognition of a possible link between IgM paraproteinaemia/WM and glioblastoma is of undoubted clinical importance because of its potential relevance to glioblastoma pathogenesis of which little is known.

Potential pathogenic mechanisms for a link between glioblastoma and IgM paraproteinaemia are as follows:

1. IgM paraproteinaemia and/or circulating lymphoplasmacytic cells may influence the CNS immune micro-environment. In the approximately 3 decades since the early WM/glioblastoma case reports, molecular and genetic studies of glioblastoma pathogenesis have demonstrated that glioblastoma is characterized by its ability to build an immunosuppressive environment, which blocks antitumour immunity and promotes tumorigenesis. There are many drivers of glioblastoma-induced immunosuppression, including the production of immunoregulatory cytokines (TGFb1 and IL10), enzymes (IDO), or prostaglandins (1–3 glioblastoma) [17]. Involvement of B cells in glioblastoma biology has only relatively recently been studied, and it is known that there is B-cell infiltration in glioblastoma [18], and that B cells harvested from glioblastoma tumours have a suppressive effect on activated CD8 T cells [17]. It is therefore plausible that in IgM paraproteinaemia, brain infiltration by partially differentiated B cells could contribute to glioblastoma tumorigenesis via effects on the immune micro-environment.

2. Circulating high titres of anti-MAG antibody could have a tumorigenic effect on CNS glial cells. Myelin-associated glycoprotein is expressed by myelinated cells not only in the peripheral nerves (Schwann cells) but also in the central nervous system (oligodendrocytes) [19]. Numerous publications demonstrate the physiological role of anti-MAG as an inhibitor of axon regeneration and its critical role in axon-glial communication [20]. One of the major routes of glioma dissemination is along white matter fibre tracts. In human glioma cell culture, MAG binds to a receptor termed "Nogo-66" and inhibits migration of glial cells [21, 22]. High serum anti-MAG antibody titres (found in two out of 3 patients here) could therefore act as a tumour cell growth factor.
3. Elevated circulating angiogenic cytokines could predispose to the development both of paraproteinaemic neuropathy and of glioblastoma. Angiogenesis is essential in the early pathogenesis of glioblastoma, and one of the cytokines which plays a role is vascular endothelial growth factor (VEGF) [23]. VEGF plays a causative role in the demyelinating neuropathy seen in POEMS syndrome, and it has been demonstrated that serum VEGF is significantly increased in patients with IgM paraproteinaemic neuropathy when compared to patients with MGUS or myeloma without neuropathy [24]. This could therefore be a risk factor common to the development both of glioblastoma and of IgM PPN.
4. The presence of circulating WM cells and IgM paraprotein could affect the blood-brain barrier, i.e., the unique properties of the CNS microvasculature which tightly regulate molecular and cellular movement. Perivascular lymphoplasmacytic infiltration influences vascular permeability and blood-brain barrier function, leading to a reactive gliosis, which promotes gliomatous growth [15].

Conclusion

This report highlights a likely association between IgM paraproteinaemic neuropathy and IDH-wildtype glioblastoma. This appears to be relevant to patients both with and without high levels of circulating anti-MAG antibody, and both with and without bone marrow meeting a threshold for WM diagnosis (i.e., patients both with WM and with MCGS). Whilst the evidence at present points away from a direct causal link between use of immunosuppression and glioblastoma, we suggest clinicians be cautious about CIT in this specific patient group. We suggest that neurologists and haematologists should be vigilant for patients who develop both IgM paraproteinaemia and glioblastoma and that such cases are reported to a central National Registry. Further research in this area could provide key insights into the pathogenesis of glioblastoma, a rapidly progressive fatal tumour still described as having sporadic epidemiology without clear risk factors except male sex, age, and prior radiation treatment and could potentially lead to new treatments for glioblastoma.

Acknowledgments

The authors would like to thank Drs., Ashwin Pinto, Chinar Osman, Robert Lown, and Mr. Jonathan Duffill for their help with patient care and thank Professor Issy Reading who was consulted by the research team for statistical advice.

Statement of Ethics

Written informed consent was obtained from the next of kin of the patients for publication of this case series and accompanying images. Ethics approval was not required.

Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to authorship and publication of this manuscript.

Funding Sources

There are no funding disclosures to declare.

Author Contributions

A.S.D. and N.T.H.C. identified the possible link; D.M.L. wrote the draft manuscript; D.A. provided the neurophysiology figure and corresponding legend; J.A.R.N. provided the histopathology slides and corresponding legend; A.S.D. and H.A.K. were the physicians in charge of patient care; all authors reviewed the submitted manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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