Multiple Sclerosis and Related Disorders 13 (2017) 21–24

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Case report

Paraneoplastic acute disseminated encephalomyelitis associated with multiple myeloma

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ARTICLE INFO

Keywords:
Paraneoplastic
Acute disseminated encephalomyelitis
ADEM
Haemorrhage
Myeloma

ABSTRACT

We describe a man recently diagnosed with multiple myeloma who presented with progressive spastic paraparesis, encephalopathy and multifocal MRI lesions with haemorrhage. Brain histopathology was consistent with acute disseminated encephalomyelitis (ADEM) with no new clinicoradiological findings on follow-up. This case emphasises the growing paraneoplastic spectrum, including non-classical but treatable disorders such as ADEM.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a rare inflammatory central nervous system (CNS) demyelinating syndrome. It can be considered a diagnosis of exclusion and should be considered in patients presenting with encephalopathy, multifocal neurological deficit, large white matter centric MRI lesions and clinical stability on follow-up (Pohl et al., 2016). Although it classically follows infection or vaccination, cases associated with malignancy have been described (Appendix A).

Pathology is typified by perivenous demyelination but hyperacute variants with haemorrhage, vasculitis and neutrophilic infiltrate have been reported, usually with high case fatality (Dos Santos et al., 2014).

2. Case

A 67-year-old man presented with two months of weight loss, dyspnoea and lower limb pain. Multiple myeloma was diagnosed with a clonal plasma cell burden of 40%, IgA paraprotein 6.14 g/L and kappa free light chain 75.1 mg/L. There were lytic lesions, anaemia and renal impairment. Two weeks later, he developed a widespread macular rash followed by two days of progressive spastic paraparesis and a T4-5 sensory level. MRI brain and spine demonstrated multiple non-enhancing T2 hyperintense lesions in the posterior cervical cord, pons and periventricular regions. Lumbar puncture demonstrated normal opening pressure, microscopy, biochemistry and cytology. Cerebrospinal fluid (CSF) herpes virus multiplex and JC virus PCR were negative. EBV, CMV, HSV1, HSV2 and VZV serology were consistent with past infection whereas HIV, JC virus and mycoplasma serology were negative. CSF oligoclonal bands were absent and there were insufficient cells for cytological assessment. Serum vasculitic markers, ACE, B12 and anti-neuronal (paraneoplastic) antibodies were negative. NMO and MOG antibodies were not sent as the clinical presentation was not typical for those known to us at the time.

Three days of 1 g intravenous methylprednisolone were administered, followed by 2 g/kg intravenous immunoglobulin over 5 days. Despite treatment he became drowsy and tetraplegic and sustained a generalized tonic-clonic seizure. Electroencephalogram showed diffuse encephalopathy. Repeat MRI brain showed progressive white matter FLAIR/T2 hyperintensities and interval punctate haemorrhages (Fig. 1), without restricted diffusion or enhancement. MRI spine was stable.

(A, B) Axial T2 fluid attenuated inversion recovery (FLAIR) imaging shows progression of white matter centric hyperintense lesions during weeks 1 (1) and 2 (2) after symptom onset. (C) Gradient recalled echo imaging demonstrating intralesional blooming artefact at the caudate nucleus consistent with punctate haemorrhage (3). (D) MRI T2 FLAIR 3 months after symptom onset. (E) Luxol Fast Blue stained section x100 showing multiple perivascular foci of demyelination (4). (F) Luxol Fast Blue stained section x200 showing sharp demarcation between area of demyelination and intact myelin (5) and presence of scattered inflammatory cells around blood vessels (6). (G) Luxol Fast Blue stained section x1000 showing myelin debris within macrophages (7). (H) CD68 immunostained section x400 showing presence of monocyte-macrophages and activation of microglial cells (8).

He underwent 5 cycles of plasma exchange for a fulminant inflammatory encephalomyelopathy. Left frontal lobe brain biopsy showed perivascular demyelination and mononuclear infiltrate without

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http://dx.doi.org/10.1016/j.msard.2017.01.013
Received 14 November 2016; Received in revised form 21 January 2017; Accepted 27 January 2017

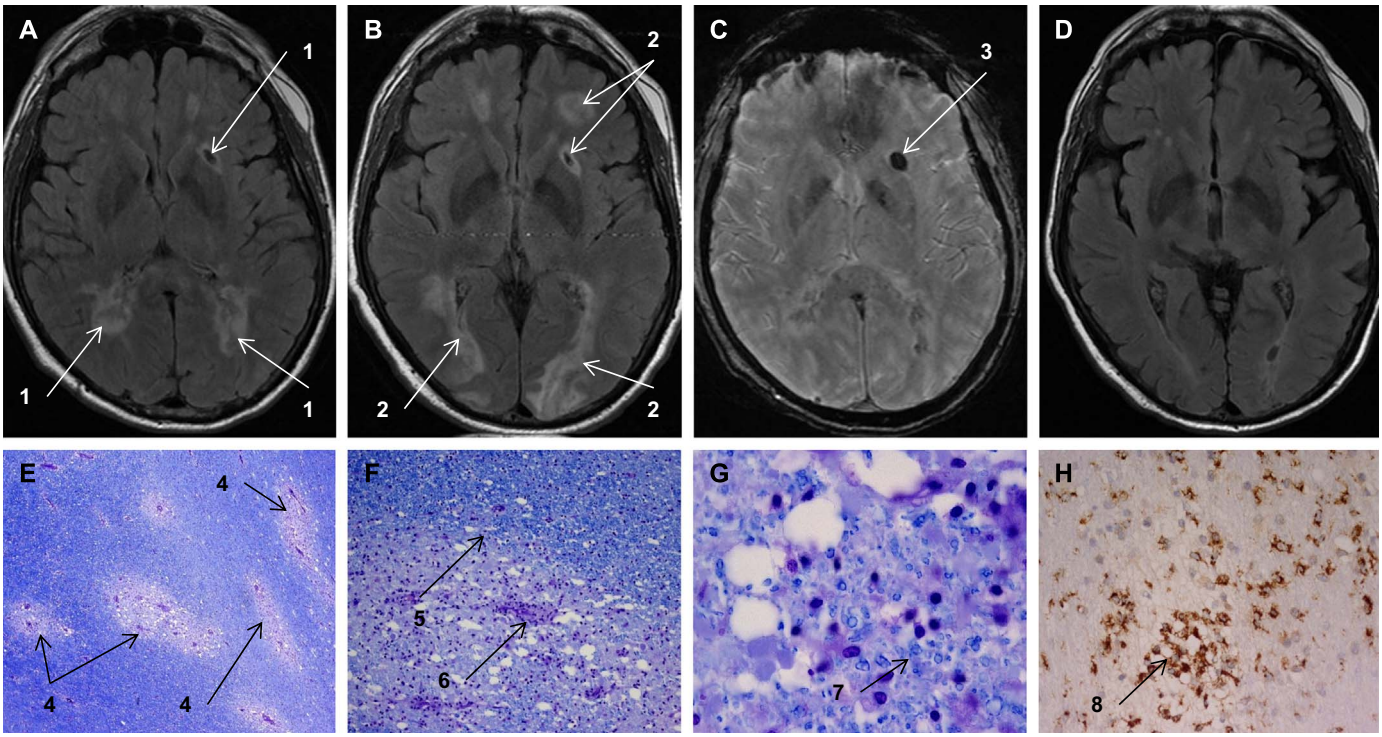

Fig. 1. MRI imaging of the brain and histopathology from left frontal lobe biopsy.

haemorrhage or vasculitis. There was no polyoma virus or evidence of lymphoma or myeloma.

Weekly oral cyclophosphamide and dexamethasone were commenced for myeloma treatment. At three months, his upper limb strength had improved but he remained paraplegic with cognitive deficits.

3. Discussion

This patient's presentation, histopathology and stability on clinical and radiological follow-up were consistent with ADEM. Absent oligoclonal bands is typical of ADEM and the lack of enhancement and normal CSF contents has been reported (Pohl et al., 2016). The aetiology in our patient has not been established. Our patient did have a preceding rash and hence a concomitant malignancy and post infectious ADEM cannot be excluded. The lack of additional infectious symptoms, negative infective serology and the temporal relationship to the myeloma diagnosis raises the possibility of paraneoplastic ADEM. Prompt treatment of the underlying malignancy, which may have prevented the uncommon occurrence of relapse (multiphasic ADEM), and the lack of a known specific paraneoplastic antibody make it challenging to further clarify the exact aetiology. The presence of malignancy may trigger an autoimmune response through T cell activation or molecular mimicry. It is possible that clonal plasma cells produce a disease modifying antibody which cross reacts with myelin to induce central demyelination similar to the established association between demyelinating neuropathy, myelin-associated glycoprotein antibodies and IgM paraproteinaema.

ADEM has been described in association with haematological and solid malignancies (Appendix A). Most patients appeared to have a favourable outcome however the vast majority of these patients were diagnosed clinically as ADEM without supportive histopathology so it is difficult to make a direct comparison to the current case. To our knowledge, there is only one report of histologically proven ADEM associated with myeloma. Sheng et al describe a patient with visual and language deficits who had an exquisite clinical and radiological response to dexamethasone, that was maintained with myeloma directed chemotherapy (Sheng et al., 2006). In comparison, our patient had a fulminant clinical course and punctate haemorrhages on MRI despite aggressive immunotherapy, more suggestive of a hyperacute variant, acute haemorrhagic leucoencephalitis (AHL) (Dos Santos, Martin, 2014). However, discordant with the radiology, there was no perivascular haemorrhage on biopsy. The converse situation has also been described. Young et al described six of 13 suspected ADEM cases with perivenous demyelination, and additional histopathological necrosis and haemorrhage without corresponding radiological haemorrhage (Young et al., 2010). The reason for this discrepancy is unclear but is likely due to sampling error.

Paraneoplastic syndromes are considered relentless, progressive and immunotherapy resistant. Treatment is directed at the underlying cancer. There is, however, an ever expanding list of autoimmune encephalopathies with highly specific autoantibodies which can be immunoresponsive. Many of these have an associated cancer. MOG antibodies have been described in paediatric ADEM. It has been detected in other adult inflammatory demyelinating diseases such as recurrent optic neuritis and neuromyelitis optica phenotype but rarely in adult ADEM. MOG antibodies were not sent in our patient as it was not felt to be typical of its known presentations at the time. Its place in diagnosis and management is still being defined (Pohl et al., 2016). In the largest case series of MOG positive adult patients, a clinical diagnosis of ADEM and MOG antibodies was only reported in one of 56 patients (Sepúlveda et al., 2016). Sera were sent for patients with NMO or suspected related syndromes and therefore may not be representative of adult ADEM. Unlike our patient, most patients in this series had CSF pleocytosis, had no reported neoplastic association, frequently relapsed and achieved a good clinical outcome. It is suggested MOG antibodies may have utility as a prognostic marker.

4. Conclusion

Not traditionally included in the clinical approach to ADEM this case highlights a potential treatable paraneoplastic syndrome that should be considered in patients with a malignancy presenting with neurological deficit and encephalopathy.