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LETTER TO THE EDITORS

Progressive neurological deficits in multiple myeloma: meningeal myelomatosis without MRI abnormalities

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Dear Sirs,

Multiple myeloma (MM) is characterized by the accumulation of monoclonal plasma cells [12], with common nervous system involvement including peripheral neuropathy and epidural compression [2]. In contrast, intraparenchymal lesions and infiltration of cerebrospinal fluid (CSF) and leptomeninges (meningeal myelomatosis) are rare; CSF infiltration occurs in 1% of MM patients [4], which is less common than in solid tumours (1–5%) and much less than in lymphoma and leukaemia (5–15%) [1, 7]. We present a MM patient with progressive and stepwise, multifocal neurological symptoms. Craniospinal MRI was normal, but CSF examination confirmed the diagnosis of meningeal myelomatosis.

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A 63-year-old male visited the emergency department with double vision and repetitive short-lasting episodes of light-headedness and headache when standing up without loss of consciousness. Nine months earlier he had been diagnosed with Durie-Salmon stage IIIA (International Scoring System stage 3) IgA-kappa MM, with bone lesions (skull, spine, long bones) and an extramedullary left psoas muscle mass. Three cycles of induction chemotherapy with thalidomide, doxorubicine, and dexamethasone were followed by melphalan with stem cell rescue. Four months later, he experienced a relapse with reoccurrence of the psoas lesion and new extramedullary (paranasal sinuses and paravertebral) lesions, for which lenalidomide, dexamethasone and radiotherapy of the psoas lesion was initiated.

At the time of presentation in the emergency department, just after initiation of lenalidomide and dexamethasone, no abnormalities of ocular motility could be found although the patient still experienced double vision. A mild paresis of the right peroneus muscle, hypoesthesia of the first to third right toes, and absent achilles tendon reflexes were noted. Differential diagnosis was broad (Table 1). Electrocardiography, laboratory investigations and gadolinium-enhanced brain MRI (Fig. 1a1) were normal.

One week later, the double vision and light-headedness had disappeared, but the patient had developed a mild paresis of the right biceps and triceps muscles with normal tendon reflexes. Because of the multifocal neurological deficits, the revised differential diagnosis (Table 1) included cervical epidural MM localization and meningeal myelomatosis. However, CT of the neck and cervical spine MRI were normal. Right arm electromyography revealed signs consistent with a C5 or C6 radiculopathy.

Table 1 Differential diagnosis of neurological complications of multiple myeloma and suggested ancillary investigations for each of these diagnoses [2, 8, 9, 13]

Causes	Diagnosis	Ancillary investigation(s)
Directly related to MM	1. Cranial nerve palsy due to skull base lesion(s)[a]	CT of skull base, cranial ceMRI
	2. Spinal epidural localization, resulting in	Spinal MRI
	(a) myelopathy[b]	
	(b) radiculopathy[b]	
	(c) cauda equina syndrome	
	3. Localised plexus or peripheral nerve compression[b]	Plexus MRI, EMG
	4. Amyloid related neuropathy[a]	EMG, biopsy
	5. Central nervous system involvement	
	(a) intraparenchymal plasmocytoma	Brain ceMRI
	(b) CSF infiltration/meningeal myelomatosis[a, b]	Craniospinal ceMRI, CSF investigation
	6. Obstructive hydrocephalus (due to 5b) [3]	Brain CT or MRI
Indirectly related to MM	1. Metabolic encephalopathy (due to hypercalcaemia[a], uremia, hyperviscosity syndrome)	Serum laboratory investigations
Related to treatment	1. Infection[a]	Serum laboratory investigations, dedicated studies for suspected infection
	2. Metabolic encephalopathy	Serum laboratory investigations
	3. Radiation toxicity:	
	(a) Neuropathy[5]/plexopathy	EMG (ceMRI)
	(b) myelopathy	Spinal ceMRI
	(c) encephalopathy	Brain ceMRI
	4. Chemotherapy-induced peripheral neuropathy[a]	EMG

ceMRI contrast-enhanced magnetic resonance imaging; *CSF* cerebrospinal fluid; *CT* computed tomography; *EMG* electromyography

[a] Differential diagnoses at first presentation

[b] Differential diagnoses at second presentation

Another week later, the patient developed a slight dysarthria and severe weakness of the left anterior tibial muscle. Lumbar epidural compression, meningeal myelomatosis or infection were considered, but gadolinium-enhanced lumbar spine MRI was normal (Fig. 1a2). However, CSF examination showed 133×10^6 leucocytes/L and an elevated total protein level of 0.63 g/L; flow cytometry demonstrated 92% monoclonal plasma cells (Fig. 1b, c).

We concluded that the patient's multifocal neurological abnormalities were due to meningeal myelomatosis. He was treated with biweekly intrathecal methotrexate and prednisone. After two courses, no more plasma cells could be detected in the CSF, CSF leukocyte count (1×10^6/L) and total protein level (0.34 g/L) normalised and his neurological symptoms had improved. Three months later the patient died from progressive systemic disease. Autopsy confirmed the diagnosis of meningeal myelomatosis.

In this MM patient, the uncommon occurrence of meningeal myelomatosis was associated with negative craniospinal MRI. This patient's history stresses that, in cases with a high clinical suspicion of meningeal myelomatosis, a normal MRI should be followed by CSF examination.

Symptoms and signs of meningeal myelomatosis are usually multifocal, including non-specific prodromes, cranial nerve neuropathy and radiculopathy (all present in our case) and may vary greatly according to involved structures. Contrast-enhanced MRI is often used to diagnose neoplastic meningitis, but sensitivity is much lower for hematologic malignancies (20–37% for leukaemia and lymphoma) than for solid tumours (85%) [10]. In contrast, MRI was false-negative in only 8% of a group of myelomatous meningitis patients [8, 9].

There is no standardized treatment for meningeal myelomatosis. Treatment options include craniospinal radiation or intrathecal chemotherapy, often accompanied by systemic chemotherapy [2, 8, 11, 13], but survival is generally short [6, 8, 13].

In conclusion, meningeal myelomatosis, although rare, should be considered in MM patients with progressive multifocal neurological deficits, even when MRI is normal. CSF investigation is mandatory in an early stage to prevent delay in diagnosis and treatment.

Conflict of interest N. W. C. J. van de Donk received research funding from Celgene.

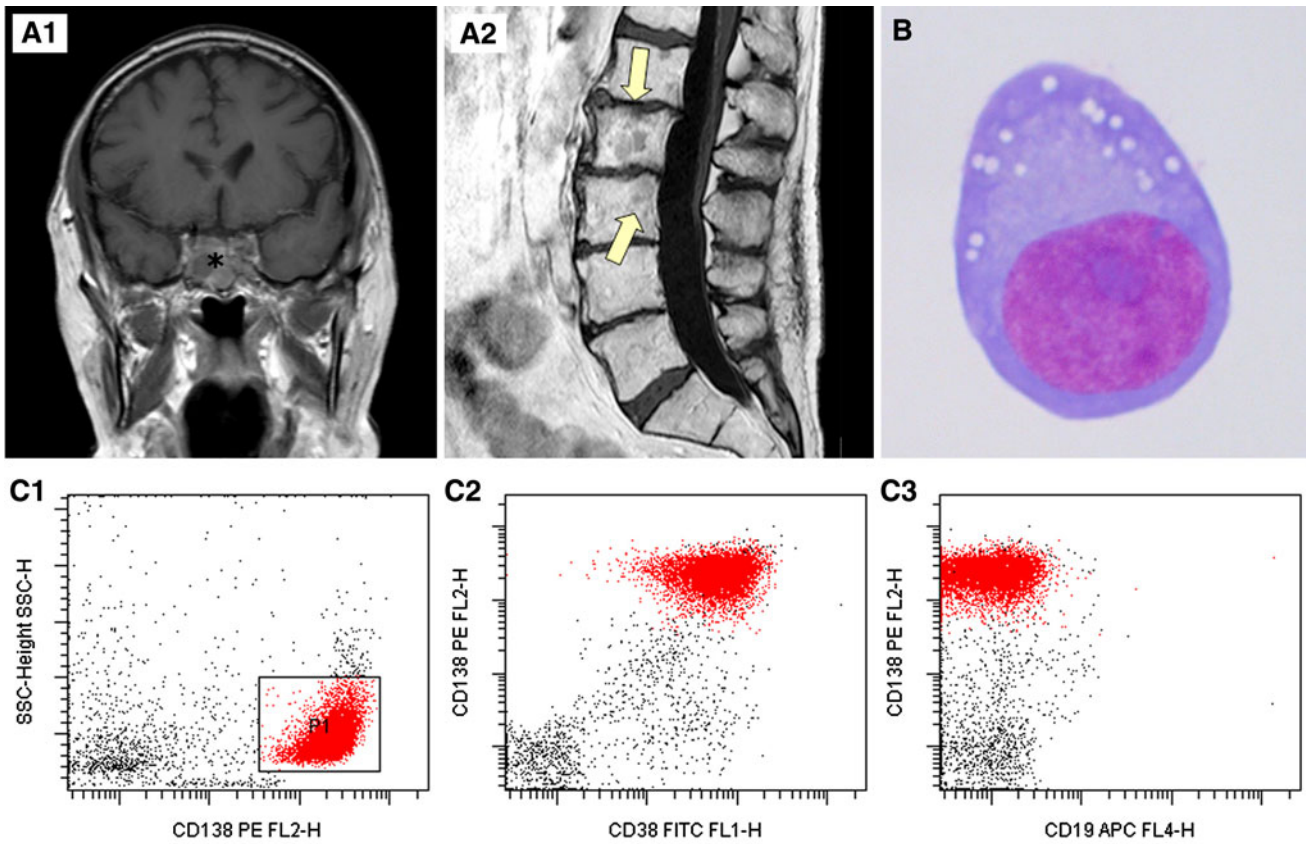

Fig. 1 Studies from presented patient. **a** T1-weighted gadolinium-enhanced MRI of **a1** brain and **a2** lumbosacral spine. Pathologically enhancing multiple myeloma lesions are visible in the sphenoid sinus (*asterisk*, **a1**) and lumbar vertebrae (*arrows*, **a2**). No pathological gadolinium-enhancement of the nerve roots or meninges is visible. **b** Microscopic image of cerebrospinal fluid showing the presence of a myeloma plasma cell with perinuclear halo and eccentrically located nucleus with prominent nucleoli. **c** Flow cytometric analysis of cerebrospinal fluid demonstrating **c1** CD138+, **c2** CD38+, and **c3** CD19- cells, which is typical for malignant plasma cells

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