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Neurologic Complications in Multiple Myeloma and Plasmacytoma

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Abstract: Neurologic complications in plasma cell malignancies are frequently seen in the practice of neuro-oncology, involving areas such as the peripheral and central nervous system. These can be the first symptoms, leading to the diagnosis of the underlying disease, or they may appear during the course of the illness. Radicular pain secondary to compressive radiculopathy is the most common neurologic complaint. Additionally, neurotoxic side-effects derived from the first-line drugs employed are frequently observed during treatment of the malignancy, particularly sensory distal polyneuropathies. Multiple myeloma (MM) is the most common malignant plasma cell disorder, accounting for approximately 10 % of all haematological malignancies. A wide spectrum of neurological complications has been described associated with MM, ranging from carpal tunnel syndrome to the life-threatening spinal cord compression. Plasmacytoma is defined as a localized proliferation of malignant plasma cells, and it may eventually turn into MM. Plasmacytoma may occur inside or outside the bone marrow, with neurologic involvement depending on the placement of the mass. The POEMS syndrome is a paraneoplastic disorder associated with the presence of a bone plasmacytoma. Peripheral neuropathy is always present in the POEMS syndrome. Moreover, clinical manifestations secondary to central nervous sys-

tem involvement are being increasingly recognized, like papilloedema, stroke, and pachymeningitis. This review will focus on the neurologic complications associated with MM, plasmacytoma, POEMS syndrome, and their management. Furthermore, neurologic complications derived from treatment will also be reviewed, especially the treatment of emergent peripheral neuropathy. **Eur Assoc NeuroOncol Mag 2012; 2 (2): 71– 7.**

Key words: multiple myeloma, plasmacytoma, POEMS, neurological complications, neuropathy, neurotoxicity

Introduction

Malignant plasma cell dyscrasias are characterized by neoplastic proliferation of a single clone of plasma cells, typically producing a monoclonal immunoglobulin called paraprotein. Among them, plasmacytoma and multiple myeloma (MM) represent a spectrum and probably the natural progression of the same illness. Plasmacytoma is defined by the presence of a localized plasma cell tumour without evidence of neoplastic plasma cells in bone marrow (< 5 %) and absence of other features of myeloma. Plasmacytoma most frequently occurs in bone (plasmacytoma of bone), but can also be found outside bone in soft tissues (extramedullary plasmacytoma). Both can present as solitary or multiple lesions, the latter more predictive of progression to myeloma. The POEMS syndrome is a paraneoplastic disorder associated with the presence of a bone plasmacytoma and considered the same entity as osteosclerotic myeloma [1, 2].

Multiple myeloma (MM) is the most frequent malignant plasma cell disorder, accounting for approximately 10 % of all haematological malignancies. MM is defined by the presence of paraprotein in the serum and/or urine (serum > 3 g/dl), at least 10 % neoplastic plasma cells in the bone marrow or their presence in other tissue, and evidence of end-organ damage, related to the underlying plasma cell disorder, including hypercalcaemia (C), renal failure (R), anaemia (A), and bone lesions (B), commonly named CRAB symptoms acronymically. Smoldering or asymptomatic MM is present when monoclonal protein > 3 gr/dl or infiltration at the bone marrow (> 10 %) is not accompanied by CRAB symptoms [1, 3].

Neurologic complications are frequent during plasmacytoma and myeloma, and constitute the most frequent non-CRABpresenting symptom in MM [4, 5]. Patients can present with almost the whole spectrum of neurologic complaints, affecting areas such as peripheral and central nervous system (Table 1). In this article, discussion focuses on neurologic complications associated with plasmacytoma and multiple myeloma, and the therapies employed in their management.

Direct Complications of Myeloma and Plasmacytoma

Spinal Complications

The most common neurologic complaint in these patients is radicular pain, sometimes with associated weakness and numbness, due to nerve-root compression by direct extension of vertebral plasmacytoma or, more frequently, a pathological vertebral fracture with secondary foraminal stenosis [5]. In this setting, the diagnostic approach is magnetic resonance imaging (MRI) or computed tomography (CT) and electromyography when needed. The most frequent local neurologic complication involving the central nervous system (CNS) is spinal cord compression, which can be related with a bone fragment retropulsed from a vertebral fracture or extension of plasmacytoma arising from bone marrow of the vertebral body and extending to the anterior epidural area. Although incidence has decreased in recent years, partially because of extensive use of bisphosphonates, it still occurs in approximately 5 % of patients with MM [5] and in 3 % as the presenting symptom [4]. The thoracic spinal cord is the most frequent level involved [6].

Clinical features include back pain, which can be associated with radicular pain and motor, sensory, and sphincter impairments to some degree, which can usually be mild and mani-

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fest abruptly when spinal cord compression occurs, making early diagnosis difficult and requiring great awareness by the clinician. Back pain, mainly when recumbent in patients with myeloma, should arouse suspicion of this complication, with mandatory spine MR. When a soft tissue mass is compromising the nerve-root, radiotherapy or even surgical resection may be indicated, with analgesic and decompressive intention. The therapy of choice for spinal cord compression in these patients is radiotherapy, with long-course schedules of at least 30 Gy in 10 sessions [7] in addition to corticosteroids. The role of decompressive laminectomy before radiotherapy is controversial. Current evidence does not support the use of surgical decompression, due to the similar outcome achieved with radiotherapy alone compared to surgery plus radiotherapy [8, 9]. No specific therapy is usually indicated in nerveroot compression without soft tissue mass, and management of pain with medical treatment is the best approach [5].

Percutaneous vertebroplasty is a minimally invasive procedure involving the injection of bone cement within a collapsed vertebral body, which is increasingly indicated in related MM pathological spinal fractures that cause pain unresponsive to conservative treatment. This technique has analgesic and stabilizing effects on the spine, with demonstrated effectiveness [10]. Its major technical drawbacks are the potential for neural comprise and pulmonary embolism of cement into epidural space and perivertebral veins. Percutaneous vertebroplasty is primarily contraindicated if neurological compromise or epidural component is present, owing to the high risk of exacerbating neurological symptoms, although recently published studies show positive evidence of the safety of the procedure in these patients [11].

Cranial Complications

Patterns of intracranial MM include (1) osteo-dural MM or plasmacytoma (cranial MM) and (2) brain parenchyma plasmacytoma [12].

Osteo-dural plasmacytoma is the most frequent form of cranial plasma-cell neoplasm, usually arising from osseous lesions in the cranial vault, skull base, nose, or paranasal sinuses. Clinical presentation includes pain, headache, seizure, or cranial palsies (Figure 1). The isolated primary dural plasmacytoma is very rare because dural deposits usually result from contiguous bone lesions. Radiological findings of cranial plasmacytomas are not specific and usually mimic other neoplastic lesions, with pathology needed to establish the definitive diagnosis. CT scan and MRI show well-defined destructive masses arising from osseus structures, or duralbased mass that may appear iso- to hyperdense on CT scan, T1-weighted images iso- to high signal intensity, and T2weighted images with a hypointense signal on MRI, with variable contrast enhancement [13]. Recently, PET-CT was shown to detect extramedullar plasmacytomas also in the CNS [14]. Among cranial plasmacytomas without MM at diagnosis, cranial base location seems to carry an increased risk of progression to MM compared to dural-based lesions [15].

Treatment of cranial plasmacytoma includes surgical resection with adjuvant focal radiotherapy [16]. When multiple plasmacytoma or MM is present, additional systemic chemotherapy or even a transplant should be considered. Recently, cranial responses to new agents (bortezomib, thalidomide, lenalidomide) have been reported [12]. Much rarer is the presence of an intraparenchymal brain plasmacytoma without evidence of extension from osseus or dura, which can be manifested as brain haemorrhage [17].

Prognosis of MM patients with osteodural plasmacytomas is worse than in MM patients without cranial involvement, with reported median overall survival of 25 and 46 months, respectively [12].

Leptomeningeal Myeloma

Leptomeningeal myeloma (LMM) has an estimated incidence of 1 % of MM patients [18, 19] and is defined as the detection of malignant monoclonal plasma cells in the cerebrospinal fluid in the presence of suggestive symptoms. The most common presenting features include radiculopathy, cauda equina syndrome, encephalopathy, and cranial palsies [18-20]. LMM requires a high index of suspicion, mainly when radicular pain is the clinical presentation. LMM seeding is usually concomitant with aggressive MM rather than a sign of progression to a more advanced disease, and is usually diagnosed at younger ages (54-62 years) and after a median of 13-17 months after MM diagnosis. Inherent biological features of the disease have been suggested by several authors as primarily responsible for predisposition to LMM and conferring a higher risk of CNS relapse: high myeloma burden, increased LDH levels, other extrame-

Table 1. Neurological complications associated with MM and plasmacytoma				
Peripheral nervous system	Central nervous system	Drug-related neurotoxicity		
Radiculopathy Axonal neuropathy Demyelinating neuropathy Small-fibre neuropathy Carpal tunnel syndrome Amyloid myopathy	Spinal-cord compression Cranial plasmacytoma Dural plasmacytoma Leptomeningeal myelomatosis Brain plasmacytoma Stroke Cerebral vein thrombosis Hyperviscosity syndrome Papilloedema Pachymeningitis Toxic encephalopathy, seizures	Toxic encephalopathy, seizures Herpes zoster and post-herpetic neuralgia Steroid myopathy Encephalopathy, seizures Reversible posterior leucoencepha- lopathy syndrome (anecdotal)		

dullary manifestations, IgD paraprotein, lambda subtype, plasma cell leukaemia, plasmablastic morphology, highrisk chromosomal abnormalities, and absence of CD56 in myeloma cells [21]. LMM confers a very poor prognosis and is usually a terminal event. LMM has a median survival of 2 months, increasing up to 4 months in a series treated intensively with radiotherapy as well as systemic and intrathecal chemotherapies [12, 18, 20].



Figure 1. (A, B, C) MRI of the brain shows cranial plasmacytoma in a 61-year-old woman with MM IgA kappa who presented with left exophthalmos. (A) Axial T1-weighted image shows an isointense mass in the left orbit. (B) Axial T2-weighted image shows the mass hypointense. (C) Axial T1-weighted gadolinium-enhanced image shows mild enhancement of the mass. (D) Fused CT and FDG-PET images. (E, F, G, H) MRI of the brain shows a plasmacytoma of the clivus in a 57-year-old woman presenting with diplopia and left-abducens palsy. The sagittal (E) and axial (H) T1-weighted image shows mild enhancement of the plasmacytoma. (G) The axial T2-weighted image shows a hypointense mass. (G) The axial T1-weighted gadolinium-enhanced image shows mild enhancement of the plasmacytoma.

Remote Complications of Myeloma and Plasmacytoma

Peripheral Nervous System

Peripheral neuropathy (PN) is a frequent remote manifestation of malignant plasma cell neoplasms. It can be found in the setting of classical MM or be associated with plasmacytoma of the bone, as part of the POEMS syndrome. This acronym designates osteosclerotic myeloma with polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal protein (M), and skin changes (S). However, not all features in the acronym are present in all POEMS patients, and, conversely, the acronym does not include several of the characteristic features of the syndrome. In 2007, new diagnostic criteria were established, which require the presence of polyneuropathy and monoclonal gammopathy in addition to one of the 3 major criteria (sclerotic bone lesion, Castleman's disease, and vascular endothelial growth factor elevation) and one of the 6 minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilloedema, and thrombocytosis/polycythemia) [22].

Several characteristics allow to distinguish between MM and POEMS neuropathy. In MM, PN is present at diagnosis in approximately 12 % of patients, and up to 50–62 % of MM patients present with subclinical neuropathy when exhaustive neurologic examination and nerve conduction studies are performed [23]. MM-related PN is thought to be related to toxic phenomena, or perineural or perivascular paraprotein deposition. PN in MM usually manifests as length-dependent axonal polyneuropathy, mild in intensity, and affecting more sensory than motor fibres. However, amyloid components can also be present in up to 6 % of patients with MM. In these patients, neuropathy is more frequent, reaching incidences of 30–40 %. Burning pain, autonomic features like orthostatic hypotension, gastric disturbances, and impotence are the main characteristics, secondary to the predominantly small-fibre involvement [24].

In POEMS, neuropathy is always present, as one of the 2 major criteria necessary for the diagnosis. Frequently, PN is the first complaint and the guide symptom that leads to diagnosis. The characteristics of neuropathy are similar to those of chronic inflammatory demyelinating polyneuropathy (CIDP), and patients may be misdiagnosed with idiopathic CIDP or monoclonal gammopathy of underdetermined significanceassociated neuropathy. Furthermore, acute presentations of POEMS-associated neuropathy have been described as mimicking the Guillain-Barré syndrome [25]. Clinically, they are indistinguishable, although POEMS neuropathy seems more frequently associated with leg pain, muscle atrophy, and distal muscle weakness than classic CIDP [26]. Cerebrospinal examination usually shows albuminocytological dissociation, similar to CIDP and the Guillain-Barré syndrome. Electrodiagnostic tests reveal a demyelinating neuropathy, predominantly in the legs, with distal motor involvement. Compared with idiopathic CIDP, POEMS nerve conduction studies show a more uniform slowing, lack of temporal dispersion or conduction blocks on nerve conduction studies with less prolonged distal motor latency, a higher terminal latency index in the median nerves, and unrecordable tibial and sural responses, suggesting demyelination predominant in the nerve trunk rather than in the distal nerve terminals, and axonal loss in the lower limb nerves [27–29]. Interestingly, detection of this clinical and neurophysiologic pattern can be useful before development of typical systemic manifestations, to be aware of the possibility of POEMS. Regarding the pathologic mechanism, polyneuropathy in the POEMS syndrome is thought to be a direct or indirect effect of angiogenic factors on endoneurial nerve vessels, producing a degree of endoneurial oedema [29, 30]. With regard to treatment, no intervention reverses neuropathy associated with MM, and treating myeloma can cause or exacerbate existing PN. Neuropathy associated with the POEMS syndrome usually improves with plasmacytoma treatment. In contrast to CIDP, plasmapheresis and intravenous immunoglobulin have no clinical benefit. Improvement usually begins within the first 3-6 months after treatment, although delayed recovery is not unknown and can take up to 2 years [22].

Finally, another frequent neurological complaint in multiple myeloma patients is compressive neuropathies secondary to amyloid deposits, such as the carpal tunnel syndrome [5, 31]. Typically, median nerve compression at the wrist is bilateral and not predominant in the dominant hand. Rarely, amyloid can also be detected in muscles, causing weakness, muscle stiffness, pseudohypertrophy, and myalgias [32].

Cerebrovascular Complications

Stroke and venous thrombosis have been classically described with MM, related with the hyperviscosity syndrome and thrombophilia. Hyperviscosity is estimated to occur in 2–6 % of MM, depending on the type of heavy chain involved (IgM > 3 g/dl [very rare in MM], IgG > 4 g/dl, IgA > 6 g/dl). Strokes usually involve small vessels, frequently causing encephalopathy more than focal deficits, in addition to headache, visual disturbances, and mucocutaneos bleeding. Treatment requires urgent plasmapheresis [33]. Further, increased hypercoagulability and thrombophilia are recognized features associated with MM. At least 4 mechanisms of hypercoagulability specifically related to MM have been suggested:

- impairment of the fibrinolytic pathway due to the inhibition of fibrin structure by an abnormal amount of immunoglobulins
- abnormal antibodies acting as an autoantibody against natural anticoagulants
- procoagulant activity caused by the pro-inflammatory status associated with myeloma
- 4. resistance to activated protein C by non-factor V Leiden [34, 35].

Importantly, reports of MM patients treated with thalidomide and lenalidomide suffering from stroke or cerebral vein thrombosis [36] remind us of the increased prothrombotic risk of these drugs in MM.

In addition, cerebrovascular events have also been related with POEMS [37, 38]. In a retrospective study at the Mayo Clinic, nearly 10 % of all POEMS patients developed stroke after POEMS diagnosis. Interestingly, there was no difference between POEMS patients with and without stroke in regard to common cardiovascular risk factors. Only a high platelet count and the presence of plasma cells in the bone marrow at POEMS diagnosis were predictive of a higher stroke risk. In this series, patients with thrombocytosis > 500,000 carried a risk of cerebral infarction of 29 % at 5 years. Noteworthy, none of the events occurred after successful treatment of the underlying syndrome; hence, the importance of treating the underlying disease to minimize the risk of stroke [39].

Other POEMS-Related Central Nervous System Complications

Papilloedema is a characteristic finding in 30–64 % of patients, which can be asymptomatic and usually bilateral. It is associated with intracranial hypertension, inflammation, or an increase of vascular permeability [40, 41]. Related symptoms are headache, transient vision obscuration, enlarged blind spots, and progressive constriction of the visual field. Blurred vision is reported by 45 % of patients when directly questioned [40], and rarely constitutes the first manifestation [42]. In case of symptomatic papilloedema, some authors suggest performing an intracranial pressure study and treatment with acetazolamide if there is evidence of intracranial hypertension [41].

Recently, Briani et al described pachymeningeal involvement in 9 out of 11 patients with POEMS. Pachymeningitis was asymptomatic, and findings on MRI showed meningeal thickening and enhancement, more evident in the falx cerebri and the medial portion of the cerebellar tentorium. Pathological studies in 2 patients showed absence of inflammatory changes, increased vessel density and thickness, over-expression of VEGF and VEGFR2 on arterial smooth muscle and meningothelial cells, and proliferation of meningothelial cells. Histology findings were distinct from pachymeningeal specimens of other aetiologies. The authors point out that pachymeningeal involvement may be part of the POEMS spectrum and could have been overlooked [43].

Metabolic Complications of Myeloma and Plasmacytomas

It should be kept in mind that metabolic disturbances are frequently associated with MM, such as renal insufficiency with uraemia, hypercalcaemia, and hyperammoniaemia [44], can precipitate or aggravate an encephalopathy or cause seizures. Regardless of its origin, MM-associated encephalopathy is more frequently seen in terminal stages of the disease. The best management approach includes symptomatic and targeting therapies against myeloma. Finally, the possibility of CNS infection in the appropriate setting should also be considered in the differential diagnosis, owing to the immunosuppressive nature of these diseases.

Treatment-Related Neurologic Complications

Neurological impairment in these patients can be due to the therapy with cytostatic drugs (vincristine, high-dose melphalan), immunomodulatory drugs such as thalidomide or corticosteroids, and bortezomib. Neurological complications associated with stem cell transplantation are beyond the scope of this review.

PN is the main non-haematological dose-limiting side effect of bortezomib, thalidomide, and vincristine, which may impair the quality of life of MM patients [45–49]. Table 2 summarizes the main features of these induced peripheral neuropathies. Identification of risk factors associated with the development of drug-induced neuropathy is a matter of research to optimize the safety management of these patients, with conflicting results with regard to age, pre-existing neuropathies, or diabetes mellitus. Only dosage is an involved factor in all cases. Meanwhile, close neurological monitoring of patient candidates for these therapies seems the best way to minimize the risk of severe and disabling neuropathies, advising the treating physician in the application of dose modification guidelines, without negative impact in MM response [51, 52]. NCS should be performed at baseline to detect subclinical PN and during follow-up it can help to discriminate peripheral neuropathy from other complications like radiculopathy.

Varicella-zoster virus reactivation is a common and serious adverse event related to bortezomib treatment, with an incidence rate of 10–60 % and a higher risk of post-herpetic neuralgia [53]. Therefore, prophylactic use of acyclovir is advocated in these patients, although the potential renal and neurological toxicity related with long-term acyclovir treatment should be borne in mind [54].

Steroid myopathy is frequently seen in high-dose dexamethasone schedules, as with the classical VAD protocol (vincristine, adriamycin, and dexamethasone), with an 8-% incidence described [55]. Diagnosis is mostly clinical, with predominant psoas and quadriceps involvement; muscle enzymes are rarely increased, and electrophysiological analyses demonstrate unspecific and variable abnormalities. Muscle biopsy should remain exceptional, since there are no specific anatomopathological findings. Treatment is based on reduction or, if possible, discontinuation of the steroid or replacement by

	Bortezomib	Thalidomide	Vincristine
Incidence ¹	35–47 % 9–19 % ≥ grade 3	23–75 % 25–30 % ≥ grade 3	28 % 13 % ≥ grade 3
Time of onset	Early 8 % PN > 2 after one cycle 25 % PN > 2 after 2 nd or 3 rd cycle	Gradual 38 % at 6 months 75 % at one year	Gradual 4 % PN > 2 after one cycle
Related with cumulated dose	Yes Plateau in risk at > 30 mg/m²	Yes Treatment duration (> 6 months) or > 20 gr	Yes > 2 mg/m ² sensory signs > 8 mg/m ² motor signs
Neuropathy features	Sensory, painful, distal	Sensory-motor, distal, and proximal	Sensory-motor, painful, distal
Autonomic involvement	Yes, early	Yes	Yes, early
Coasting effect ²	No	Yes	Yes
Nerve conduction studies	Length-dependent, axonal	Length-dependent, axonal	Length-dependent, axonal
Mechanism of neuro- toxicity	Unknown Dorsal root ganglia main target of dysfunction	Unknown Angiogenesis inhibition, immunomodulation	Dysfunction of cellular and axonal transport mediated by micro- tubules
Risk factors	Pre-existing PN (associated with more severe PN) Prior vincristine treatment MM recurrent Twice-weekly schedules	Pre-existing PN (more severe) Lower baseline β2-micro- globulin	Hereditary PN Hepatic insufficiency Age, poor nutritional status
Pharmacogenomics	RDM1, CASP9, ALOX12, LSM1 (associated with early PN) ERCC3, ERCC4, IFNGR2, MRE11 (PN at cycles 2–3) CTLA4, CTSS, GJE1, PSMB1, TCF4, and DYNC11	ABCC1, DPYD GSTT1 lower frequency of PN	ABCC1, ABCC4, ABCC5, associated with early PN
Evolution/Prognosis	Reversible, 60-% PN resolution at a median of 6 months	Partially reversible, slow recovery	Partially reversible, recovery may take up to 2 years
Special considerations	Retreatment is not associated with a higher risk	Combination of thalidomide with bortezomib is associated with a higher risk of PN	Fulminant neuropathies described with underlying Charcot-Marie-Tooth neuropathy

PN: Peripheral neuropathy; ¹ Grade of neuropathy according to NCI.CTCv (2 or 3); ² coasting effect is described as worsening of the neuropathy the first months after stopping the treatment

non-fluorinated glucocorticoids, such as prednisone. Importantly, it can often affect respiratory function even when proximal limb muscles remain strong [56].

Finally, encephalopathy and seizures in MM patients, apart from the metabolic disturbances detailed above, can also be associated with treatment with high-dose melphalan, commonly used as an induction to stem cell transplantation; reversible posterior leucoencephalopathy syndrome induced by bortezomib has rarely been reported [57].

Concluding Remarks

- Neurological complications associated with multiple myeloma and plasmacytoma are commonly observed in clinical daily practice. Early diagnosis and intervention in the most frequent complications can prevent disabling outcomes in many cases.
- Neurological complaints can involve the peripheral and central nervous system, secondary to direct or remote effects of the plasma cell neoplasm.
- The spectrum of complications associated with the PO-EMS syndrome has grown in recent years to include meningeal thickness and an increased relative risk of stroke.
- Nerve conduction studies are useful in distinguishing neuropathy associated with MM and POEMS, and can also be helpful in early differentiation between chronic immune demyelinating neuropathy and POEMS-related polyneuropathy.
- The high rate of peripheral neurotoxicity induced by firstline therapies used against MM and POEMS syndrome makes neurological monitoring advisable in order to minimize the risk of severe and disabling neuropathies.

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Conflict of Interest

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