Pachymeningeal involvement in POEMS syndrome: dramatic cerebral MRI improvement after lenalidomide therapy

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POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare multisystemic disease associated with plasma cell dyscrasia and increased serum or plasma vascular endothelial growth factor (VEGF) levels, the latter likely responsible for several POEMS syndrome manifestations. Whereas peripheral neuropathy is the main neurological feature and a mandatory diagnostic criterium, central nervous system involvement is less common except for papilledema and stroke. We recently reported the frequent occurrence at brain MRI of cranial pachymeningeal involvement in a series of POEMS syndrome patients. Meningeal histopathology revealed hyperplasia of meningothelial cells, neovascularization, and obstructive vessel remodeling without inflammatory signs pointing to a role of VEGF in the meningeal manifestations. Here, we report the dramatic pachymeningeal improvement in patients undergoing lenalidomide therapy. These findings support the therapeutic role of lenalidomide and might shed further light on the pathophysiology of the disease.

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare plasma cell disease with multiorgan involvement [1]. Vascular endothelial growth factor (VEGF) seems to play a pathogenic role and is responsible for several manifestations of POEMS syndrome including ascites, papilledema, peripheral edema, and nerve damage [2]. VEGF serum or plasma levels not only represent a major diagnostic criterium, but do also correlate with response to therapy [1,2]. Although peripheral neuropathy is the main neurological feature and one of the mandatory diagnostic criteria of POEMS syndrome, central nervous system involvement is rarely reported except for papilledema [3] and stroke [4]. We recently described the cranial pachymeningeal involvement in 9 out of 11 patients with POEMS syndrome and no central neurological symptoms or known cause of pachymeningitis [5]. Meningeal histopathology showed hyperplasia of meningothelial cells, neovascularization, and obstructive vessel remodeling, without signs of inflammation, pointing to a possible role of VEGF in the pathogenesis of meningeal remodeling. Consistently, VEGF and VEGF receptor were strongly coexpressed on endothelium, smooth muscle cells of arterioles, and meningothelial cells.

Of our cohort of 9 patients with POEMS syndrome and pachymeningeal involvement [5], three (one of whom, patient #1, had undergone meningeal biopsy) are currently on first line therapy with lenalidomide and dexamethasone [6] as part of a prospective, multicentric, nonrandomized trial with lenalidomide currently ongoing in Italy. Lenalidomide 25 mg/day is given for 21 days in association with weekly dexamethasone 40 mg until tolerated or progression. Of the three patients, two had been previously treated with steroids only. They all had clinical and hematological improvement [7], and serum VEGF levels decreased accordingly (Table I). The M protein decreased to undetectable levels in all the patients 3 months after starting lenalidomide and was absent (at immunofixation) in patient #3 after 12 months therapy. Patient #2 had a concurrent dorsal paravertebral Castleman's disease that greatly improved at neuroimaging control after 5 cycles of lenalidomide.

With regard to the neurological manifestations, strength (measured with the MRC score) as well as the sensory symptoms and signs (assessed with INCAT sensory sum score) steadily improved already after three cycle in patients # 2 and 3; an after 6 cycles in patient #1. The overall neuropathy limitations scale remained stable. Besides hematological and neurological improvement, our patients presented also a dramatic MRI improvement of the cerebral pachymeningeal involvement (Fig. 1a–d). No significant pachymeningeal improvement was instead observed in two patients treated with high dose dexamethasone only (data not shown) or in patients #1 while on steroids therapy (Fig. 2). Lenalidomide is known to have not only antiangiogenic effects, but also to be immunomodulatory and cytotoxic to the plasma cell clone. Accordingly, another patient of our series with POEMS syndrome associated with a localized D9 vertebral osteolytic myeloma achieved a very good partial remission of the disease with VEGF normalization and improvement of pachymeningeal involvement after local radiation therapy (Fig. 1e,f).

One patient with POEMS syndrome responsive to lenalidomide has first been described by Dispenzieri et al. [8] and improvement in daily performance and hematological and systemic findings started already at the third

TABLE I. VEGF Serum Levels and MRI Pachymeningeal Involvement in Three Patients with POEMS Syndrome at Diagnosis and After Lenalidomide Therapy

Pt#	Onset age/Sex	Serum VEGF at diagnosis (pg/mL)	Pachymeningeal involvement (MRI)	Lenalidomide (months)	Serum VEGF (pg/mL)	Pachymeningeal involvement (MRI)
1	67/M	2101	++++	9	481	+++
2	45/M	2501	+	6	545	−
3	66/W	2922	++	12	428	−

Pachymeningeal involvement is scored as very severe (++++), severe (+++), moderate (++), mild (+), and absent (−). VEGF n.v. < 707 pg/mL.

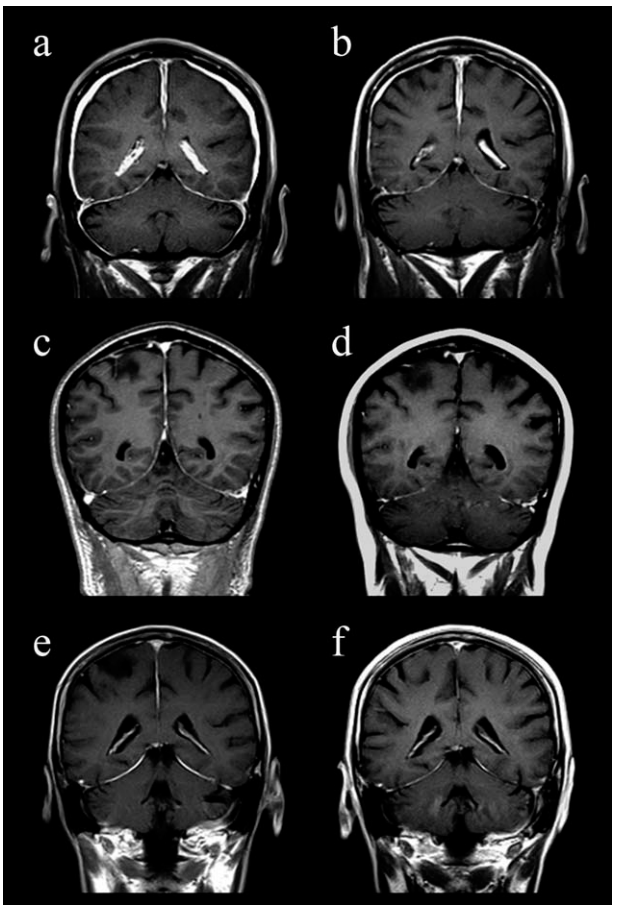

Figure 1. Coronal contrast enhanced T1 images before (left) and after (right) treatment showing improvement of pachymeningeal involvement. Patient # 1 (a,b) and # 2 (c,d) were treated with lenalidomide while the last patient (e,f) underwent local radiation therapy for localized vertebral myeloma at D9 level.

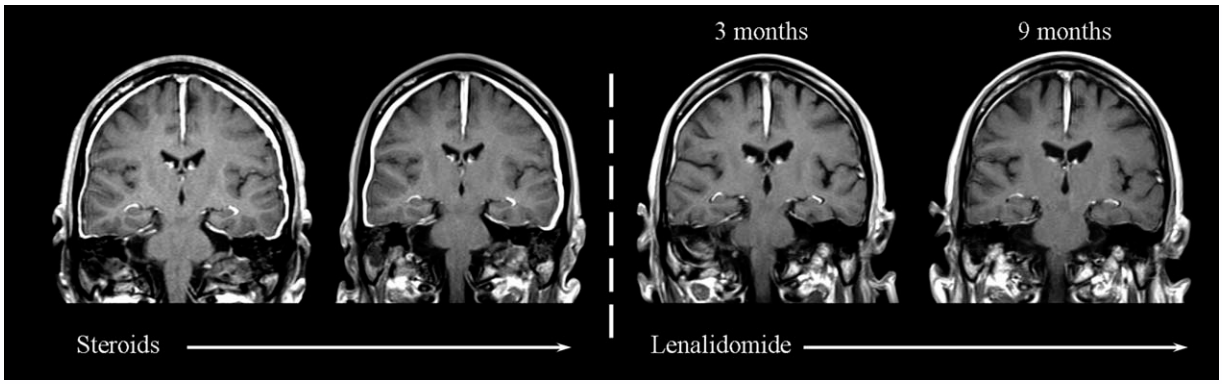

Figure 2. Patient # 1: Coronal contrast enhanced T1 weighted images disclosing increased pachymeningeal involvement during steroid therapy (first two images on the left) and the dramatic and progressive improvement after lenalidomide therapy (last two images on the right).

therapy cycle. Nine POEMS patients treated with lenalidomide have subsequently been reported in an abstract, eight of whom had been previously treated with high-dose chemotherapy with autologous stem cell transplantation (three patients), melphalan-prednisone (three patients), or prolonged steroid (two patients) [9]. Six of these patients were reported to have hematological and clinical improvement. Finally, recent retrospective data from 10 patients treated with lenalidomide as salvage therapy for refractory POEMS syndrome showed a marked improvement of both systemic and neurological manifestations [10], supporting the therapeutic role of lenalidomide, and shedding further light on the pathophysiology of the disease.

The significant MRI changes after "clone-effective" (lenalidomide or radiation) therapy, together with the meningeal histopathological findings, support a role of VEGF in mediating also the pachymeningeal involvement.

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