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LETTER TO THE EDITORS

Intracranial hemangiomas in a patient with POEMS syndrome

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Abstract POEMS syndrome is a rare multi-system disease with typical features of polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder and skin changes. We describe a 44-year-old woman with polyneuropathy, hepatomegaly, IgA lambda-plasmacytoma, thrombocytosis, papilledema with elevated protein levels in cerebrospinal fluid and multiple cutaneous hemangiomas who was diagnosed with three intracranial lesions. Histology revealed capillary hemangiomas, one of them displaying partially glomeruloid features.

Keywords POEMS syndrome · Crow-Fukase syndrome · Polyneuropathy · Hemangioma · Vascular endothelial growth factor

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Introduction

POEMS syndrome is a rare multi-system disease, the acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, skin changes) characterizes several dominant findings [10]. For the diagnosis, polyneuropathy and monoclonal plasma cell disorder have to be present; at least one other major criterion (sclerotic bone lesions, Castleman disease, vascular endothelial growth factor (VEGF) elevation) and one minor criterion (organomegaly, edema, endocrinopathy, skin changes, papilledema, thrombocytosis/polycythemia) is required [5]. Therapeutic strategies include irradiation, alkylator-based therapies, corticosteroids and other immune-modulatory drugs as well as high-dose chemotherapy with peripheral blood stem cell transplantation [6]. The criterion of skin changes includes hyperpigmentation, acrocyanosis, skin thickening and multiple hemangiomas. Here, we report the first case of a POEMS syndrome patient with intracranial capillary hemangiomas.

Case report

In 2001, at the age of 39 years, the female patient had been diagnosed with an IgA lambda-plasmacytoma. Further, severe mixed axonal and demyelinating sensomotor

polyneuropathy, essential thrombocythemia and multiple allergies had been found. The plasmacytoma had been treated with four cycles of idarubicine and dexamethasone, cyclophosphamide and stem cell apheresis, and in 2002, high-dose melphalan and subsequent peripheral blood stem cell transplantation. A very good partial response only with monoclonal IgA lambda detected by immunofixation had been noted. Concerning the patient's polyneuropathy, a considerable clinical benefit, but no substantial electrophysiological improvement, had been observed. Controls at regular intervals had shown stable parameters to date.

In 2007, the patient presented herself to a neurologist with transient diplopia. At that time, neurological examination showed the known signs of distally and right accentuated polyneuropathy with grade 3–4/5 lower extremity paraparesis and hypaesthesia without any new symptoms. In particular, no pathologic nystagmus, no ocular muscle paresis and no meningism were detected. The presence of headache was negated. Neither fundoscopy nor measurement of cerebrospinal fluid pressure was performed at that time. An MRI scan revealed three intracranial contrast-enhancing lesions. A tumor close to the dura was resected; histology showed a capillary hemangioma similar to the patient's skin hemangiomas which had been noticed and partially removed around that time. There was no evidence of von Hippel-Lindau disease; the family history was unremarkable. No hemangiomas of other organs were found. Due to benign histology and a lack of clinical symptoms that could be attributed to these lesions, a conservative approach with regular follow-up was taken (Fig. 1a–c).

Nine months later, the patient was admitted to our department with headache, defects of the visual field and blurred vision. Papilledema with reduced visual acuity on

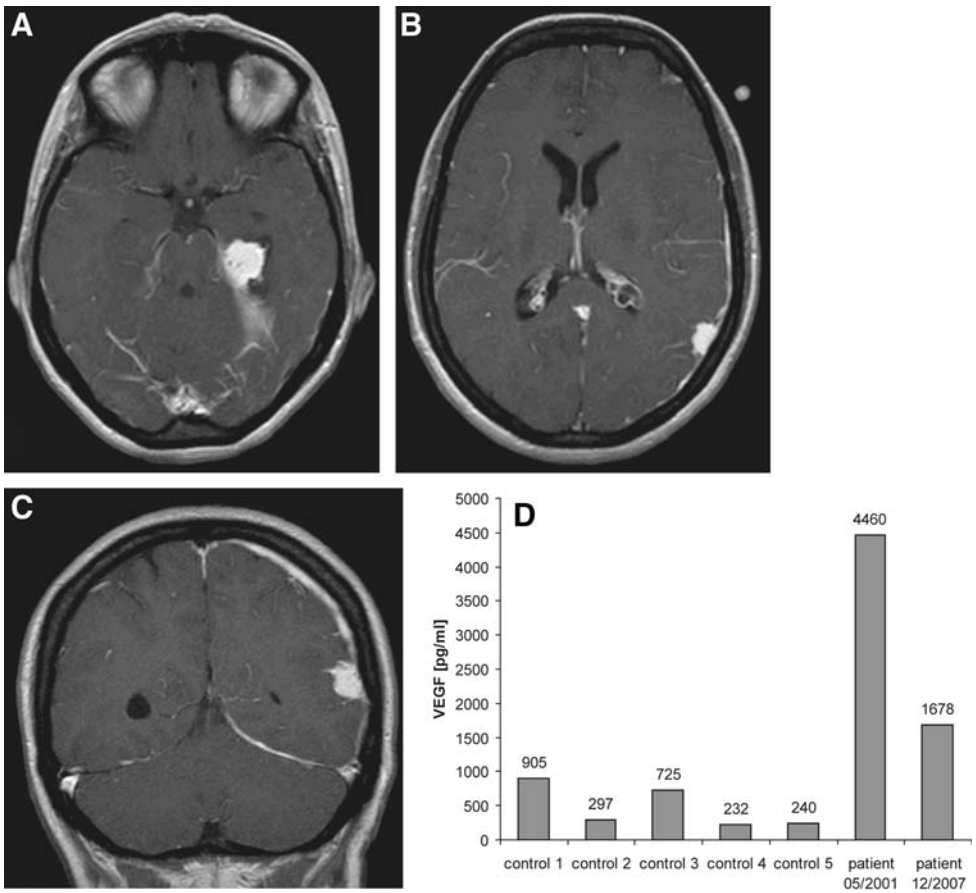

Fig. 1 **a** T1-weighted axial MRI showed a strongly enhancing, extra-axial tumor in the medial part of the left temporal lobe with broad attachment to the tentorial notch. **b** Another extra-axial, equally enhancing tumor was present on the convexity in the dorsal part of the left temporal lobe (T1-weighted MRI after contrast administration). **c** Contrast-enhanced, T1-weighted MRI in coronal plane demonstrated the broad attachment of the temporo-dorsal tumor to the dura and showed a thickening and pathological contrast enhancement of the dura and the subdural space of the left hemisphere. **d** Serum VEGF levels were increased in the POEMS patient: before (05/2001) and five years after (12/2007) chemotherapy with peripheral blood stem cell transplantation, compared to five control patients who were admitted to hospital for classification of polyneuropathy. For the determination of VEGF, a Quantikine Human VEGF ELISA Kit was used (R&D Systems, Minneapolis, MN)

both eyes was detected. MRI showed the intracranial hemangiomas unchanged, a venous sinus thrombosis was excluded. Lumbar puncture revealed an elevated opening pressure of over 50 cm H_2O with increased protein (7.1 g/l). Since no improvement was observed in spite of frequent lumbar puncture and treatment with acetazolamide, a ventriculoperitoneal shunt was placed: pressure normalized and papilledema regressed with normalized bilateral visual acuity. Serum, but not cerebrospinal fluid VEGF levels were elevated in our patient compared to control patients presenting with polyneuropathy (Fig. 1d).

Three months later, the patient developed simple partial seizures. MRI revealed a slight increase in volume of the left parietal lesion. The neoplasm was resected and histopathological examination showed a capillary hemangioma with focal glomeruloid features (Fig. 2a, b). Presence of human herpesvirus-8 (HHV-8) DNA in tumor tissue—an association of HHV-8 with POEMS syndrome had previously been suggested [8]—was ruled out. The third tumor, again a capillary hemangioma displaying few eosinophilic globules which were periodic acid-Schiff (PAS)-positive and showed kappa and lambda light chain deposits (Fig. 2c, d), was removed three months later. Immunohistochemical staining revealed deposition of IgM, IgA and IgG.

Discussion

We diagnosed POEMS syndrome in this female patient with polyneuropathy, IgA lambda-plasmacytoma, thrombocytosis, hepatomegaly, papilledema with elevated protein levels in cerebrospinal fluid and multiple cutaneous and intracranial hemangiomas. The good response of polyneuropathy to immunosuppressive therapy in the patient's past medical history is in line with this diagnosis. Capillary hemangiomas are benign neoplasms very rarely encountered in the central nervous system [1]. So far, intracranial hemangiomas have not been reported in patients with POEMS syndrome. Although a coincidence of two rare diseases cannot be excluded, a relation between cutaneous and intracranial lesions seems probable. All skin lesions and two of the intracranial tumors were capillary hemangiomas; one intracranial hemangioma displayed partially capillary, partially glomeruloid features. The cytoplasmic eosinophilic globules of glomeruloid hemangiomas correspond to polytypic immunoglobulin [17]. In line with these observations, immunohistochemical staining did not show clonal immunoglobulin deposits in our case. Albeit reported in few other patients [7, 15], glomeruloid hemangiomas are considered POEMS-specific [4, 14]. Usually, those hemangiomas are limited to the skin. Recently, a patient with POEMS syndrome with multiple mucosal hemangiomas of the small bowel and colon was described [9]. However, the reason for developing intracranial hemangiomas in this patient remains unclear. One possible explanation could be an innate vulnerability of structures of ectodermal origin to VEGF. Studies on the pathogenetic mechanisms of the common infantile hemangiomas may provide further ideas [3].

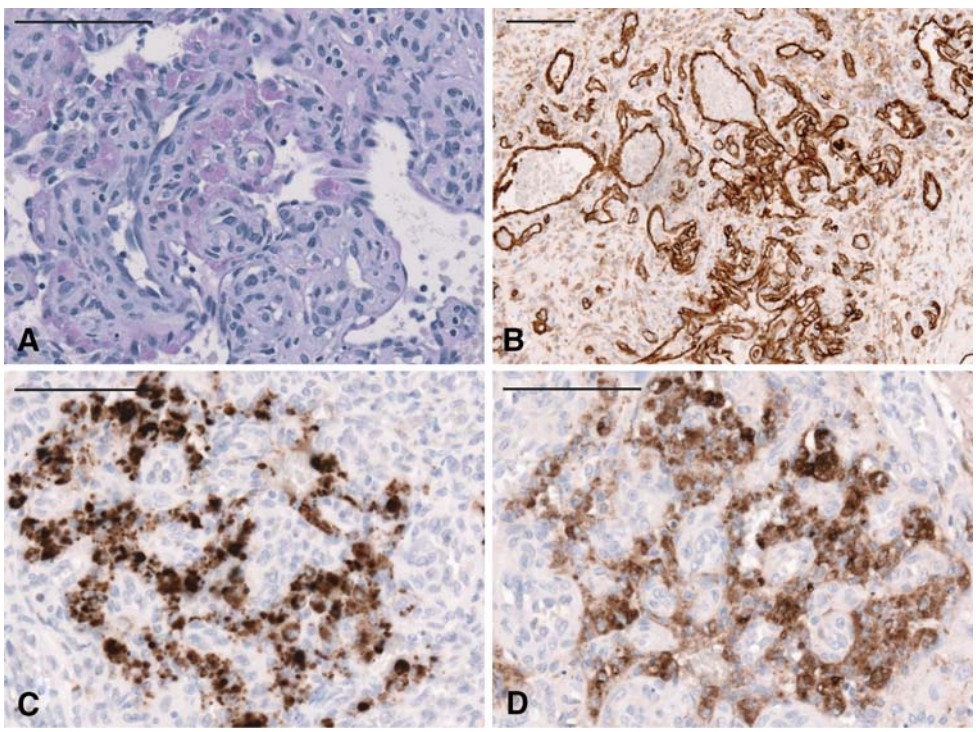

Fig. 2 **a** Hematoxylin-eosin staining displaying glomeruloid inclusions in the hemangioma of the left parietal lobe. **b** CD34-immunostaining demonstrating numerous capillaries in the tumor. The PAS-positive eosinophilic globules showed kappa (**c**) and lambda (**d**) light chain deposits. *Scale bar* 100 μm

Symptoms of intracranial hypertension (headache, visual symptoms, papilledema) with elevated opening pressure and increased cerebrospinal fluid protein sometimes appear in patients with POEMS syndrome for unknown reasons. However, such severe intracranial hypertension requiring ventriculoperitoneal shunting, as found in our patient, is not common in POEMS syndrome. There is no evidence that there is any association of these symptoms with the intracranial hemangiomas.

Although the pathogenesis of POEMS syndrome is complex and unclear, VEGF appears to be an essential cytokine in this multi-system disease. Serum VEGF elevation in patients with POEMS syndrome and a correlation with the activity of the disease has been reported [12, 16]. Compared to our patient's situation before chemotherapy with peripheral blood stem cell transplantation, when she was wheelchair-bound because of her neuropathy, her general condition had clearly improved. Nevertheless, a still-elevated VEGF suggests an active disease, also reflected by the appearance of hemangiomas and intracranial hypertension. In consideration of different clinical reports focussing on experimental therapeutic strategies such as anti-VEGF antibodies (bevacizumab, with contradictory results, [2, 11, 13]), further investigation concerning the role of VEGF in this complex disease is needed and will provide valuable information towards a better understanding of its pathophysiology.

Conflict of interest statement The authors report no conflicts of interest.

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