Monitoring of Vascular Endothelial Growth Factor in POEMS Syndrome

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Abstract: POEMS syndrome is a clinical unit with a very heterogeneous clinical behavior. Its diagnostics as well as monitoring are not easy and depend on clinician’s experience. We present three case reports of patients with POEMS syndrome with different clinical manifestation and course of the disease. Our presentation demonstrates the benefit of the use of biochemical parameter VEGF (vascular endothelial growth factor). Retrospective analysis revealed that VEGF behaved accordingly with the state of the disease, i.e. it increased in active phase and decreased with remission of the disease. We suggest the use of VEGF not only for the diagnostics but also as a potential marker of therapeutic response and for monitoring of the course of POEMS syndrome.

Keywords: POEMS syndrome, disease monitoring, VEGF.

INTRODUCTION

POEMS syndrome (P = polyneuropathy, O = organomegaly, E = endocrinopathy, M = monoclonal gammopathy, S = skin changes) is a rare clinical unit belonging to plasma cell dyscrasias [1]. Unlike multiple myeloma (MM), it is usually manifested in younger patients, and its course is less aggressive [2].

The presenting symptoms include obligatory chronic progressive polyneuropathy and the presence of monoclonal immunoglobulin (almost exclusively with lambda light chain). The other characteristic features of the acronym (organomegaly, endocrinopathy, skin changes) are variably present and sometimes difficult to unveil, and many of the patients are treated as other (usually neurological) disorders.

The previously used diagnostic criteria were too vague and enabled the inclusion of different unrelated conditions solely on the coincidence of the symptoms [3]. The current opinion on this disease has recently changed the criteria into a more coherent panel (Table 1) [4]. Interestingly, one of the major molecules which is thought to be responsible for the pathogenesis of the disease, the vascular endothelial growth factor (VEGF), is nowadays being regarded as one of the major criteria in POEMS syndrome diagnostics [5,6].

We present three different manifestations of the disease with stress placed on the role of VEGF (measured by quantitative sandwich enzyme immunoassay) as an emerging diagnostic tool as well as a possible parameter of the activity of the disease.

METHODS AND RESULTS

Case Report 1

The first patient was a male, age 81, originally led under a neurological diagnosis of CIDP (Chronic Inflammatory Demyelinating Polyneuropathy) and treated using corticosteroids (Prednisone) from 9/1997. When presented at our hematology department in 10/1998, the diagnosis of POEMS was made within one week as majority of the classical symptoms were present.

The polyneuropathy was very serious with both axon and myelin damage (according to electromyography – EMG and electroneurography – ENG), the patient was unable to walk, and the activities of daily living were substantially affected. He had enlarged lymph nodes in his armpits, and the histobiopsy confirmed Castleman’s disease. The endocrinology screening revealed elevated prolactin, FSH, urine cortisol, blood glucose and C-peptide. Bone marrow biopsy confirmed slightly increased number of monoclonal lymphoplasmocytic elements (5.2%), and in both the serum and spinal fluid we found monoclonal protein IgG lambda. Within the physical examination, we saw hyperpigmentation of the chest and back, hypertrichosis, thickening of the skin and several angomas both on the body and the limbs.

The patient presented several accompanying symptoms in the diagnostic criteria [3], such as trombocytosis (485 x10^9/L), the presence of osteosclerotic lesions on the X-ray of his arms, and weight loss.

The patient was treated using radiotherapy aimed at the osteosclerotic lesions of his arms, and by conventional chemotherapy (Melphalan + Prednisone). After treatment, the patient improved with the increase of muscle strength, restitution of walking, and normalization of the size of increased lymph nodes. The values of blood count and endocrine parameters normalized together with the decrease
impairment of glucose metabolism (insulin, C-peptide), normal. The endocrine screening found just a mild due to steatosis, the spleen as well as lymph nodes were ultrasonography described slightly enlarged liver, probably without axon loss or demyelinisation). The abdominal found in the sural nerve biopsy (normal histological finding partly by diabetes, especially when there was no pathology EMG) was therefore thought to be caused by CIDP and 2 diabetes without adequate compensation. The woman was obese with a long lasting type syndrome was one of the differentially diagnostic possibilities. The woman had several co-morbidities, still, the clinical investigation as well as the laboratory findings did not initially support the correct diagnosis although POEMS syndrome was one of the differentially diagnostic possibilities. The woman was obese with a long lasting type 2 diabetes without adequate compensation. The initial polyneuropathy (both sensitive and motor according to EMG) was therefore thought to be caused by CIDP and partly by diabetes, especially when there was no pathology found in the sural nerve biopsy (normal histological finding without axon loss or demyelinisation). The abdominal ultrasonography described slightly enlarged liver, probably due to steatosis, the spleen as well as lymph nodes were normal. The endocrine screening found just a mild impairment of glucose metabolism (insulin, C-peptide), associated with poorly compensated diabetes mellitus. Physical examination revealed a few benign hemangiomas of the body and the limbs. The blood count and biochemistry spectrum were normal. Bone marrow examination (including trephine biopsy) was without the presence of clonal plasmocytes and the X-ray finding was physiological. At this time the plasma cell dyscrasia was described as a monoclonal gammapathy of undetermined significance (MGUS) with no need of hematological treatment. Within one year, however, we could see a continuous worsening of the symptoms with no effect of neurological approach and immunomodulatory therapy. Moreover, the patient had an eruption of several skin hemangiomas. We reassessed the patient with newly present anemia, focal accumulation of clonal plasma cells in the bone marrow, and with several osteolytic lesions of the skull. The conventional 99mTc scintigraphy and CT found a small locus of osteoplastic/osteosclerotic remodelation in the distal sternum. These findings supported the diagnosis of osteosclerotic myeloma, respectively POEMS syndrome.

The patient was treated with radiotherapy of the sternum and high-dosed chemotherapy followed by autologous stem cell transplantation. Chemotherapy led to a partial remission of the disease with normalization of blood count, decrease of monoclonal immunoglobulin and bone marrow plasma cell involvement, still with persistent neuropathy of the lower limbs. Therefore, after a 2-month recovery period following the transplant, we continued with conventional chemotherapy regimen (Melphalan plus Prednisone and later Cyclophosphamide plus Dexamethasone). Novel drugs (thalidomide and bortezomib) were not used for the treatment due to severe peripheral neuropathy.

Within the knowledge of VEGF being suspect of the disease onset, we traced its levels in the course of the disease. The highest level, 1960.2 ng/L (normal range 62-707 ng/L) was observed at diagnosis, followed by its slow decrease corresponding to the treatment response, and an increase within the relative activation of the disease after 2-month treatment withdrawal (Fig. 1). Within the next course,
following the chemotherapy, the VEGF level decrease continued, and it finally attained the normal range.

At the moment the patient is slowly progressing with the eruption of skin hemangiomas and the increase of paraprotein. The progression is accompanied by the elevation of VEGF.

**Case Report 3**

A 25-year old man had an 8-month history of polyradiculoneuritis. After the initial treatment with Azathioprine and Methylprednisolone (due to poor response to Methylprednisolone alone) at the neurological department, he improved and started rehabilitation with the interruption of immunosuppressive treatment. This was complicated by the development of a severe condition with polyserositis (lower limb edema, ascites), dyspnea (pleural and cardiac effusions), and paraparesis of lower limbs. He lost 25kg in 8 months. The initial screening for possible infectious, malignant or systemic cause was negative. Except thrombocytosis $1016 \times 10^9/L$ and the presence of monoclonal immunoglobulin IgG lambda, there was no other impairment in laboratory findings. Repeated analyses showed normal biochemistry including CRP, total protein, albumin, creatinine, BUN. Infectious disease screening was negative, screening for onkomarkers showed no alteration, immunological screening and endocrine tests were physiological.

Except of ascites, pleural and cardiac effusions, there was no alteration in parenchymatous organs, the tests of the aspirate of both pleural effusion and ascites confirmed transudate with no biochemical or cytological pathology. Assessment of liquor was negative and the results of bone marrow trephine biopsy including immunophenotyping were normal.

The suggestion of POEMS syndrome was supported by vast imaging findings (with no complimentary symptoms), including mixed osteolytic-osterosclerotic lesions of proximal femur, ribs, vertebral bodies and clavicles on X-ray, MRI and PET/CT. The definitive diagnosis was confirmed by the finding of compact infiltrate of monoclonal plasmocytes from the targeted biopsy of one of the larger lesions (right clavicle).

The patient was treated using radiotherapy aimed at two larger osteosclerotic lesions of left femur and right clavicle, and using high-dosed chemotherapy with preparation for autologous stem cell transplant. The stem cell harvest was, however, unsuccessful (twice in 2 month interval), with severe neutro and trombocytopenia, probably due to long-time nonspecific pretreatment. The recovery period after the attempts at the harvest was followed by the reactivation of the disease. The following therapy consisted of conventional chemoterapeutics (Melphalan plus Prednisone), and led to the disappearance of effusions and improvement of overall condition including slow improvement of peripheral neuropathy, recaclification of the osteolytic lesions, normalization of blood count, and restitution of normal walking.

The plasma level of VEGF measured at the time of diagnosis was over the measurable range (more than 2000 ng/L). After diagnosis, the patient was treated with high-dosed chemotherapy, which led to a short-term stabilization of the disease and a decrease of VEGF into normal levels (505,3 ng/L). Within the course, there were two unsuccessful attempts at stem cell harvest followed by a recovery period without chemotherapy, and thus by the reactivation of the
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At present, the patient is in remission with no concurrent therapy.

DISCUSSION

POEMS syndrome represents a very complex disease with variable presence of accompanying symptoms. Except for characteristic polyneuropathy and monoclonal gammopathy, the other associated symptoms might not be evident at the onset of the disease. Or, similarly as in the case report 2, they might be obscure and related to other concomitant diseases. It is therefore necessary, that the assessment is carried out by an experienced physician, and every polyneuropathy associated with monoclonal gammopathy (especially with the presence of light chain lambda) should be investigated for the signs of POEMS syndrome. Recent studies aim at the biology of the disease with the expectation of possible molecules specific for the disease.

The pathogenesis of POEMS syndrome has been intensively studied. It is supposed to be caused by the imbalance between pro-inflammatory cytokines, IL-1β, IL-6 and TNFα. The actual impulse responsible for the onset of the disease is thought to be the elevation of vascular endothelial growth factor - VEGF.

VEGF is reckoned to be responsible for majority of the symptoms. Increasing microvascular permeability leads to edema of neural tissue, increased endoneural pressure and exposure of myelin to serum cytokines which cause demyelination [7,8]. Increased vascular permeability and angiogenesis are thought to cause organomegaly, edema and skin hemangiomas, as seen in our patients [7]. The pathogenesis, on the other hand, is more complex as the symptoms might not be present in all patients. Even our small cohort showed different manifestations from nearly physiological findings (except of peripheral neuropathy) in case report 2, to the „wet form” of POEMS syndrome with severe edema of the limbs, pleural and cardiac effusions and ascites.

VEGF is highly expressed in blood vessels and some nonmyelin forming Schwann cells [9]. One of the major sources are thought to be the platelets [10]. This idea is in accordance with increased levels of thrombocytes in majority of patients, and thrombocytopenia might be the reason for the lack of VEGF elevation in some patients [11]. On the other hand, even patients with low platelet count present elevated VEGF levels. The possible other sources of VEGF are osteosclerotic lesions, plasma cells, tumor cells and endothelial cells [12,13].

The levels of VEGF in POEMS syndrome are usually higher than in patients with other plasma cell dyscrasias such as MGUS and multiple myeloma [1,14,15]. On the other hand, they might be affected by other conditions, such as the presence of solid tumor, inflammation, estrogen levels, hepatic disorders or even some reparative physiological processes, which make VEGF less specific for differential diagnosis. The complicated role of VEGF in the pathogenesis of POEMS syndrome has been underlined by several reports on the treatment of the disease using an anti-VEGF antibody, bevacizumab [16-18]. In the study of Badros et al., a patient with POEMS syndrome was...
successfully treated with bevacizumab with the decrease of VEGF, resolution of edema and vanishing of the neuropathy pain [16]. Contrary to this experience, in the report of Strasume et al. and Samaras et al., the patients after short-term improvement developed refractory edema and died, suggesting the impact of increased apoptosis of motor neurons and endothelial cells due to rapid decrease of VEGF [17,18]. Nevertheless, the investigation of VEGF in POEMS syndrome has a great potential to unreveal the actual causes of the disease and to choose the optimal treatment target.

Evaluation of the course of POEMS syndrome is often very not easy and dependent on subjective assessment of the physician. There are no standard means of remission or progression of the disease, and even the values of paraprotein might not be always helpful. Remission and/or progression are therefore usually defined as the normalization or re-appearance of clinical symptoms (edema, skin lesions, lymph nodes, worsening of neuropathy) together with laboratory abnormalities (endocrine spectrum, hemoglobin levels, etc.). Our findings suggest VEGF as an emerging tool for routine assessment of the course of POEMS syndrome. There have not been many studies monitoring VEGF in the course of the disease. Kuwabara reported the normalization of VEGF levels in 4 patients with POEMS syndrome treated by autologous stem cell transplantation [19], some other authors described recently case reports with sequential VEGF monitoring [20-22], still, there has not been a larger cohort study which would confirm the presented findings.

We acknowledge the limitations in the retrospective analysis, and the small number of patients precludes statistical analysis. The levels of VEGF were not evaluated in standardized intervals, and the time between drawing of the sample and the analysis of VEGF levels differed. All of the samples were first frozen and then analyzed together, usually in a 2-3 month interval so the degradation as well as other external influences might have affected the final result. Studies with longer follow-up and larger number of patients will be needed to determine whether the role of VEGF in POEMS syndrome maintains only its diagnostic value or might have the potential to predict the course of the disease and become the marker of the stability and/or the activity of the disease.

CONCLUSION

Our paper contributes to the assessment of POEMS syndrome by the suggestion of longitudinal monitoring of VEGF levels in the course of the disease. The levels of VEGF behaved in accord with the activity of the disease and predicted the course of the disease better than the evaluation of paraprotein and subjective symptoms. If confirmed by larger studies, VEGF has the potential to become a pivotal marker of the disease activity and a predictor of its behavior or, at least as a surrogate marker of successful treatment of this rare disease.

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REFERENCES