

## Autologous peripheral blood stem cell transplantation in a patient with POEMS syndrome

Ryszard Pogłód<sup>1</sup>, Maria Kraj<sup>1</sup>, Andrzej Szczepiński<sup>2</sup>,  
Bożena Mariańska<sup>2</sup>, Krzysztof Warzocha<sup>1</sup>

*We report the case of a male patient presenting with polyneuropathy, monoclonal gammopathy, splenomegaly, inconsiderable lymphadenopathy, disseminated sclerotic and single lytic bone lesions, papilledema, leg edemas, discrete hypothyroidism and thrombocytosis. The POEMS syndrome was diagnosed and the patient was initially treated with the VAD regimen. No improvement of neuropathy was observed, but the other disease symptoms did not progress. One year after diagnosis the patient underwent myeloablative treatment, followed by autologous peripheral blood stem cell transplantation (PBSCT). Subjective neurological amelioration, normalization of the platelet count and stabilization of other symptoms was observed.*

### Autologiczne przeszczepienie komórek macierzystych krwi obwodowej u chorego z zespołem POEMS

*U chorego z polineuropatią, gammopatią monoklonalną, splenomegalią, niewielkiego stopnia powiększeniem węzłów chłonnych, uogólnionymi osteosklerotycznymi i pojedynczymi osteolitycznymi zmianami kośćca, obrzękiem tarczy nerwu wzrokowego, obrzękami kończyn dolnych, subkliniczną niedoczynnością tarczycy oraz nadpłytkowością rozpoznano zespół POEMS i rozpoczęto chemioterapię wg programu VAD. Nie uzyskano poprawy neuropatii ale również nie obserwowano progresji innych objawów choroby. Po roku od rozpoznania, chorego poddano leczeniu mieloablacyjnemu i autologicznemu przeszczepieniu komórek macierzystych krwi obwodowej uzyskując subiektywną poprawę neurologiczną, normalizację liczby płytek krwi i stabilizację innych objawów zespołu POEMS.*

**Key words:** POEMS syndrome, multiple myeloma, polyneuropathy, autologous PBSCT

**Słowa kluczowe:** zespół POEMS, szpiczak plazmocytowy, polineuropatia, autologiczne przeszczepienie komórek macierzystych krwi obwodowej

### Introduction

The POEMS syndrome, a multisystemic disorder associated with plasma cell dyscrasia, was first reported by Bardwick et al. in 1980 [1]. They originally established an acronym POEMS and related it to the basic symptoms: polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin lesions (S). The entity is very rare; more commonly reported in Japan, where it is known as the Crow-Fukase syndrome [2]. Recently, the POEMS is being classified as plasma cell tumor – an osteosclerotic form of multiple myeloma, although this plasma cell dyscrasia differs substantially from classic myeloma as it is often associated with disabling polyneuropathy and occurs in younger patients.

At present, a rich syndrome symptomatology is mainly attributed to hypercytokinemia [3, 4]. Inefficacy of treatment, especially in patients who fail to respond to standard chemotherapy, has prompted the search for new treatment approaches. One of the most recent is autologous PBSCT following myeloablative chemotherapy, although experiences with this approach are still very limited.

### Case description

A 38-year-old man was referred to our institution on May 5<sup>th</sup>, 2003 with an initial diagnosis of monoclonal gammopathy. On admission, the patient reported bone pain as well as weakness and numbness of both legs, which he had been observing for at least 6 months. The patient was in a good performance status. Physical examination revealed crural edema, spleen palpable 3–4 cm below the costal margin, small palpable lymph nodes in the right armpit and neck, sensory disturbances and weakened tendon reflexes as well as asymptomatic

<sup>1</sup> Department of Haematology

<sup>2</sup> Department Haematology Cell Transplantation  
Institute of Haematology and Blood Transfusion  
Warsaw, Poland

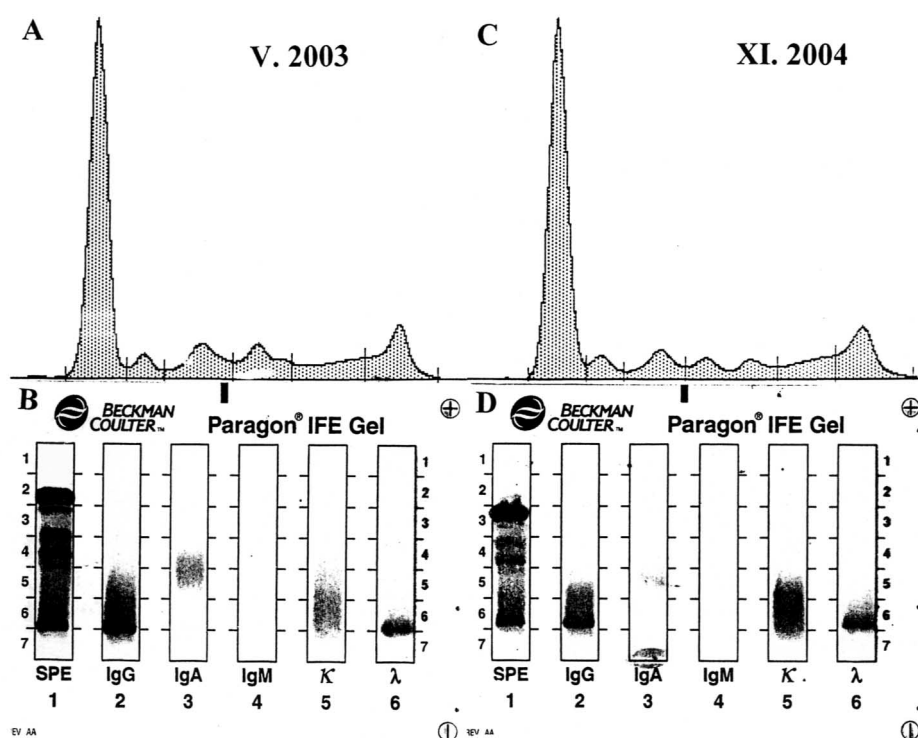
**Table I. POEMS syndrome manifestations in reported case: at diagnosis, after VAD chemotherapy and after myeloablative treatment followed by autologous PBSCT**

Parameter	At diagnosis	After 6 VAD courses	After auto PBSCT (5.5 mo)
Hb g/dL	12.5	10.5	10.7
Platelet count x 10 <sup>9</sup> /L	587.0	554.0	191.0
Polyneuropathy	+	+	+
Demyelination and axonopathy (electromyography test)		+	+
Splenomegaly (long axis in mm)	165	170	155
Cervical and axillary lymphadenopathy	+	+	+
Serum M-protein g/dL	0.80	0.72	0.81
Serum $\beta_2$ microglobulin mg/L	2.17		2.31
Bone marrow plasma cell rate (trephine biopsy)	<10%	5%	1-3%
Osteosclerotic and osteolytic bone lesions	+	+	+
TSH level ul/mL		7.89	6.15
Papilledema	+	+	+
Oedema	+	+	-
Ascites and pleural effusion	-	-	+

papilledema in ophthalmoscopy. The prostate was normal on rectal examination.

Laboratory studies (Table I) disclosed average anemia and thrombocytosis (572 x 10<sup>9</sup>/L), normal white blood cell count and their differential count, elevated ESR (63 mm). Routine blood chemistries, LDH, alkaline and acid phosphatase levels, liver and renal tests as well as  $\beta_2$  microglobulin concentration were within normal values. A small spike in serum electrophoresis was identified as M component IgG $\lambda$ , at a concentration of 0.8 g/dL (Figures 1A,B). Urinalysis showed inconsiderable

proteinuria – 0.2 g/24h. HIV, hepatitis B and C markers were negative. PSA was normal. The X-ray examination of the skeleton revealed numerous mixed osteosclerotic and osteolytic lesions, with an evident predominance of the former ones within the skull, the ribs, the cervical and lumbar vertebra, the humerus, the femur, the pelvis and the sacrum (Figure 2). Ultrasound examination of the abdomen disclosed splenomegaly (165 mm) with no abnormalities in other organs such as the prostate and lymph nodes and no signs of ascites. Ultrasonography of the thyroid gland and cervical lymph nodes did not reveal



**Figure 1.** Patient's serum agarose gel electrophoretic protein pattern (A) and immunofixation (B) at diagnosis and after auto PBSCT (C,D) showing M-protein of IgG $\lambda$ .



Figure 2. Osteosclerotic and osteolytic lesions in the femur

any abnormalities within the thyroid gland and confirmed the presence of slightly enlarged (up to 10 mm in diameter) cervical lymph nodes located along blood vessels. Gastroscopy and colonoscopy results were normal. The rate of plasma cell infiltration within the bone marrow was below 10%. After negative screening for entities other than plasma cell tumor the POEMS syndrome was diagnosed and the patient started treatment according to the VAD regimen. In the course of the third chemotherapy cycle he developed symptoms of venous thrombosis of the right forearm, confirmed by ultrasonic Doppler flow examination. We commenced treatment with low molecular weight heparin. Between June 2003 and April 2004, six VAD cycles were administered. The patient reported diminishing bone pain after each chemotherapy course, but with no essential improvement of the neurological status. M protein remained stable at low levels (not exceeding 1.0 g/dL) and the platelet counts were below  $700.0 \times 10^9/L$ . The patient's physical examination after six VAD courses (Table I) revealed bone pain, neurological abnormalities and leg edema. Peripheral neuropathy was confirmed in the course of electromyographic examination (EMG) which showed signs of mixed demyelinating and axonal

degenerative neuropathy in the upper and lower extremities. Additionally discrete hypothyroidism with increased TSH and normal T3 and T4 concentrations was found. Bone marrow plasma cell rate was 5%. No progression of bone lesions was observed. Lymphadenopathy, splenomegaly, papilledema and thrombocytosis remained at the same level as at the onset of treatment.

Due to the lack of significant improvement, especially regarding the polyneuropathy symptoms, the patient underwent autologous PBSCT. Following G-CSF stimulation,  $502 \times 10^6$  of CD34+ cells were collected. After myeloablative treatment with Melphalan 200 mg/d i.v. for two days, the autotransplantation of  $2.3 \times 10^6$  CD34+ cells/kg was performed. Due to absence of haemopoiesis regeneration on day +12 and septicemia (*Staphylococcus epidermidis*) the patient received G-CSF and was transplanted with  $2.0 \times 10^6$  CD34+ cells/kg on day +14. The platelet count was  $>20 \times 10^9/L$  on day +21 and  $>50 \times 10^9/L$  on day +27, while the white blood cell count exceeded  $1.0 \times 10^9/L$  with the absolute neutrocyte count  $>0.5 \times 10^9/L$  on day +17. The patient was discharged from the Transplantation Ward with features of hematopoietic recovery. Control tests performed during his hospitalization in the Transplantation Ward and out-patient observation showed normalization of platelet count, persistence of serum M protein and splenomegaly, and appearance of a small amount of fluid in both the peritoneal and the pleural cavities. No relevant abnormalities were found in the course of echocardiography.

Status assessment performed 5.5 months after autologous PBSCT (Table I) showed the patient in good clinical condition, with diminishing bone pain, regression of leg edema and some subjective amelioration of motor functions. However, the EMG test did not show any improvement of the sensory and motor neuropathy within the extremities. Small palpable lymph nodes could also be discerned in the neck and the left axilla, with maintained splenomegaly and papilledema. Laboratory tests showed normal platelet count, slightly decreased leukocyte count ( $3.4 \times 10^9/L$ ), mild anemia and normal  $\beta_2$  microglobulin level. Serum M protein concentration was 0.8 g/dL (Figures 1CD). A small amount of monoclonal protein IgG $\lambda$  (42 mg/dL; total 0.53g/24 h) was detected in urine by immunofixation. Plasma cell rate in bone marrow biopsy was 3%. Thyroid hormone profile showed elevated TSH concentration. No progression of osteosclerotic and osteolytic lesions was found in X-ray examination of the skeleton. Abdominal ultrasonography disclosed splenomegaly of 155 mm and a small amount of fluid in the peritoneal cavity. Since the time of auto PBSCT, the patient has remained without systemic treatment.

## Discussion

The diagnosis of the POEMS syndrome may be difficult because in order to pronounce it seemingly separate symptoms must be combined into one entity. Moreover,

POEMS patients present a remarkable diversity of symptoms, hence there exist controversies as to the minimal criteria for diagnosis [1, 2, 5]. One of the most recent suggestions concerning minimal diagnostic criteria includes the presence of two main symptoms i.e. polyneuropathy and monoclonal plasmacproliferative disorder combined with at least one of the minor symptoms, such as sclerotic bone lesions, organomegaly, endocrinopathy, Castleman's disease, skin lesions, edema and effusions, papilledema [5]. The patient fulfilled both four main acronym criteria (P,O,E,M) and a number of minor ones.

A leading POEMS symptom is symmetrical, usually sensory-motor, polyneuropathy of a mixed axonal and demyelinating type. In the case of our patient it was the main disorder present during the entire observation period, and one which had only subjectively improved after autologous PBSCT. The POEMS patients manifest a wide spectrum of polyneuropathy intensity – from paresthesias to generalized paresis and wheel-chair bound disability. Neuropathy symptoms progress slowly and usually resistant to standard treatment [1, 2, 5, 7, 8].

An array of plasma cell dyscrasia in the course of the POEMS syndrome may range from a monoclonal gammopathy of unknown significance to overt myeloma with osteosclerotic or mixed sclerotic and osteolytic bone lesions [1, 2, 5, 6, 8]. In some rare situations this syndrome is associated with other lymphoplasmacytic neoplasms, such as Waldenström macroglobulinaemia [10]. During the 18-month treatment our patient demonstrated low and stable serum M protein IgG $\lambda$  concentrations and low or normal plasma cell rate in the bone marrow. Auto PBSCT did not allow to decrease the M protein level. Low M protein concentration with a significant (up to 95% of cases) prevalence of the  $\lambda$  light chain type and low bone marrow plasmacytosis (considered non-diagnostic for myeloma) are common in POEMS [2, 5, 6, 8, 9]. Contrary to typically observed myeloma bone lesions, the patient presented with disseminate osteosclerotic lesions. In approximately 1% of multiple myeloma patients osteosclerotic changes are found [11], while single, but more often disseminated, osteosclerotic or mixed – osteosclerotic and osteolytic bone lesions are observed in almost all POEMS patients. On pathological examination plasma cell infiltrates may be discerned [2, 5, 6, 8].

Limited splenomegaly and lymphadenopathy did not regress during treatment, as well as during the post autologous PBSCT observation. Organomegaly, especially splenomegaly, is found in 30-50% of cases, while the less common lymphadenopathy – in 25% of patients. Biopsy usually shows features of Castleman's disease [2, 5].

Subclinical hypothyroidism was another feature observed in our patient; this abnormality together with disturbances of the gonadal axis may be considered to be the most frequent endocrinopathies observed in the course of the POEMS syndrome [2, 5].

Extravascular volume overloading is also a typical feature of POEMS, initially in our patient it manifested

itself only as leg edema and asymptomatic papilledema, but was later followed by slight ascites and pleural effusion. According to recent views these and other symptoms result from the overproduction of a number of cytokines such as IL-6, IL-1 $\beta$ , PDGF, TNF $\alpha$  and VEGF, which in turn is brought on by altered interactions between tumor plasma cells and their microenvironment [3-5, 8, 9]. Of these the VEGF seems to be causative for microangiopathy, increased vasopermeability, neovascularisation and the formation of skin angiomas, while its serum concentration correlates with symptom severity and response to treatment [4, 12].

Generally, the treatment of POEMS mimics that administered in the case of plasma cell tumors. In localized tumors, such as single bone plasmacytoma, the removal of the lesion or the administration of radiotherapy result in long-term remission, including polyneuropathy regression [5, 8]. In systemic disease, various chemotherapy programs are used. Some authors report on the efficacy of prednisone, or mephalan and prednisone, and other combined anti-myeloma chemotherapy regimens, with most recent reports concerning the administration of thalidomide. There also exist reports concerning the application of other treatment modalities, such as plasmapheresis, intravenous immunoglobulins, immunosuppressive drugs although these have shown to have limited or no efficacy [5, 9]. A relatively long survival with a median of 165 months in responding patients has been reported lately [5].

The inefficacy of systemic chemotherapy, especially in the case of patients with widespread osteosclerotic lesions who were suffering from neurological complications, prompted the search for new treatment methods. Beginning with the year 2001, the authors of first reports on autologous bone marrow or PBSCT in POEMS patients following myeloablative treatment (sometimes preceded by total body irradiation or the application of the bone seeking isotope Samarium) had emphasized a significant long-term improvement, reaching even some 10 years, often associated with a dramatic regression of neurological symptoms and the disappearance of monoclonal protein [6-8, 12]. However, in the most recent and, so far, the largest single institution study on 16 patients undergoing auto PBSCT after previous unsuccessful treatment, the authors have reported one death during the peritransplant period, one case of long-term mechanical ventilation maintenance and five cases of respiratory failure requiring intubation. Thus the authors stress both the efficacy and the significant morbidity of this therapy [13]. In the case of our patient the initial VAD treatment did not result in neurological improvement. In turn, his peritransplant period was free from severe, life threatening events. The majority of POEMS symptoms persisted, but did not progress. It suggests that the entire treatment did not result in essential improvement but, rather, resulted in disease stabilization.

The rarity of this particular syndrome, the lack of established treatment methods and the limited experience

with myeloablative treatment followed by autologous PBSCT has prompted us to report this case.

**Ryszard Poglód MD, PhD**

Department of Haematology  
Institute of Haematology and Blood Transfusion  
Chocimska 5, 00-957 Warszawa, Poland  
e-mail: rpoglod@wp.pl

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