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POEMS Syndrome with IgG-λ/IgA-κ Biclonal Gammopathy and Abnormal Serum Free Light Chain Ratio: a Case Report

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Abstract. ***Background.*** POEMS syndrome is a rare paraneoplastic disorder with atypical plasma cell proliferation. Cases of POEMS syndrome presented with either biclonal gammopathy or an abnormal serum free light chain ratio are considered uncommon. The present authors encountered a case of POEMS syndrome with IgG-λ/IgA-κ biclonal gammopathy with dominant κ free light chain and abnormal serum free light chain ratio. ***Case.*** A 56-year-old man with a history of Castleman disease was suspected with POEMS syndrome and admitted for further evaluation for B-cell proliferative disease to rule out multiple myeloma. He also had a sustained tingling sensation on both feet and gait disturbance, which were compatible with diffuse peripheral sensorimotor polyneuropathy with demyelinating features. His laboratory findings revealed hyperlipidemia and hypothyroidism, and he had hypertrichosis. The results of the serum and urine protein electrophoresis seemed normal, except a very weak band at the end of the serum gamma region. Serum immunofixation electrophoresis confirmed IgG-λ and IgA-κ biclonal gammopathy, with an increased serum IgA concentration and normal levels of IgG, IgM, and IgD. Both serum free light chain κ and λ values were increased, and the κ/λ ratio was higher than normal. ***Conclusions.*** The finding of IgG-λ/IgA-κ biclonal gammopathy and abnormal serum free light chain ratio with dominant κ clonality in our case was definitely rare. However, a primary pathogenic role of the different paraproteinemia in POEMS syndrome remains unclear. Further studies to identify better management modalities for POEMS syndrome is needed.

Keywords: Abnormal serum free light chain ratio, Biclonal gammopathy, Castleman disease, POEMS syndrome, Polyneuropathy.

Introduction

POEMS syndrome is a rare multisystem disorder that includes polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. The central feature of POEMS syndrome is plasma cell proliferative disorder, and its incidence is less than 1% of all cases of plasma cell dyscrasia [1]. It is usually associated with osteosclerotic myeloma [2], which contains less than 5% plasma cells. The M-protein is usually of low concentration and is easily mistaken for monoclonal gammopathy of undetermined significance (MGUS) [3]. Moreover, in case of monoclonal IgA that comigrates with normal ß-proteins, it is difficult to detect by using serum protein electrophoresis (PEP). Monoclonal plasma cell proliferative disorder is a major mandatory criteria of POEMS syndrome [4]. Nearly all patients present with λ-restricted monoclonal gammopathy [5-7], although its role in the pathogenesis of POEMS syndrome is not yet fully understood. A vast majority of cases present the IgA-λ or IgG-λ type. Accordingly, it is thought to make an increased concentration of serum free λ light chains, which ultimately produce an abnormal serum free light chain ratio (sFLC-R). However, Wang et al. [8] reported that among 54 patients who showed elevated serum free λ light chains with POEMS syndrome in their study, only 11 (13%) had an abnormal sFLC-R. Stankowski-Drengler et al. [9] also reported that 82% of patients had normal sFLC-R despite having a documented λ clonal plasma cell disorder. Thus, it is considered to be uncommon that patients with POEMS syndrome present either an abnormal sFLC-R or κ light-chain-dominant clonality.

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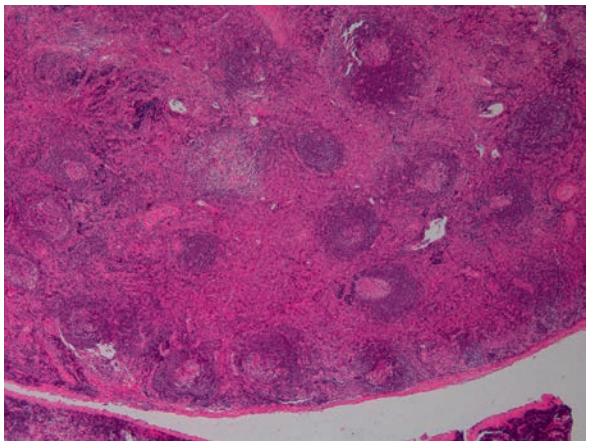

Figure 1. Castleman disease, hyaline vascular type. *The lymph node shows follicular hyperplasia with many blood vessels in interfollicular area. The follicles are characterized by the concentric layering of cells, and contain small blood vessels. (Stain, HE; magnification, ×40), HE, hematoxylin and eosin.*

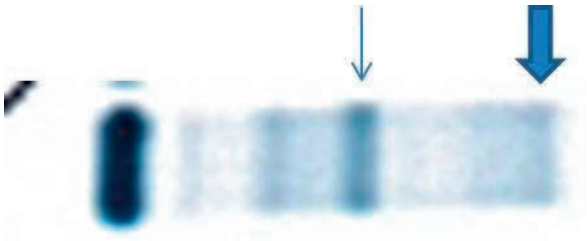

Figure 2. Pattern of serum protein electrophoresis. *Serum protein electrophoresis of the case showing a weak monoclonal band at the end of gamma region (wide arrow). Another monoclonal band (narrow arrow) comigrated with the normal ß proteins.*

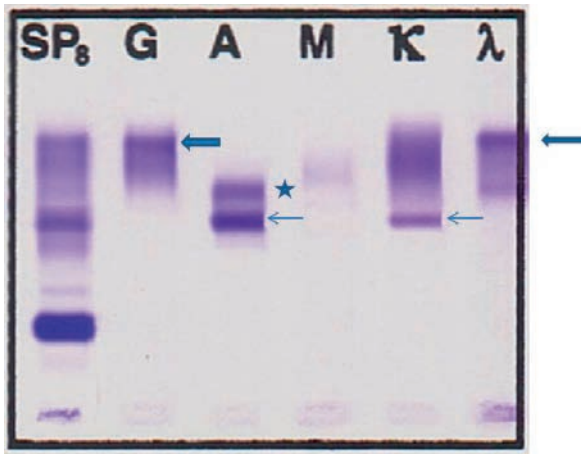

Figure 3. Result of immunofixation electrophoresis. *Serum immunofixation electrophoresis confirmed IgG-λ (wide arrow) and IgA-κ (narrow arrow) biclonal gammopathy. Another band (star) was suspected as an isolated IgA.*

Here, the present authors report a case of POEMS syndrome and IgG-λ/IgA-κ biclonal gammopathy with dominant κ free light chain and abnormal sFLC-R.

Case Report

A 56-year-old man with suspected POEMS syndrome was admitted to the department of internal medicine for further evaluation of B-cell proliferative disease to rule out multiple myeloma. Four years prior, in December 2010, he had an operation for wide-wedge resection of the right middle lobe of the lung and mediastinal lymph node dissection. His postoperative histological diagnosis was lymphoid hyperplasia with suspected Castleman disease **(Figure 1)**. Since then, he has complained of sustained tingling sensation on both feet and gait disturbance, in association with slurred speech and vision impairment. Nerve conduction studies and electrophysiological investigation concluded that his findings were compatible with diffuse peripheral sensorimotor polyneuropathy with demyelinating features. At that time, his laboratory findings revealed hyperlipidemia, with a cholesterol level of 235 mg/dL and triglyceride level of 694 mg/dL, and hypothyroidism with free T4 of 1.4 ng/L and TSH of 6.0 mIU/L. He also had hypertrichosis. He used to visit an outpatient clinic and was also admitted several times for follow-up checkup and management of his condition.

On this admission, his vital signs were stable. Limb weakness with ataxic gait, and hepatosplenomegaly were present on physical examinations. Abdominal computed tomography revealed mild hepatomegaly, moderate splenomegaly, and two or more calcific gall bladder stones with edematous wall thickening. Complete blood cell count and coagulation studies were within their normal limits. Serum creatinine level was also within its normal limit. His follow-up lipid levels and TSH remained high. While anti-nuclear antibody (ANA) was positive with a weak homogenous pattern, results of autoimmune laboratory tests such as anti-DNA antibody, anti-neutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigens, anti-Sicca syndrome A and B antibodies, anticardiolipin antibody, rheumatoid factor, and complements were negative or within the reference intervals. The cerebrospinal fluid (CSF) protein level was increased. The serum PEP seemed normal, except a very weak band at the end of the gamma region **(Figure 2)**. The urine PEP had no abnormal findings. Serum immunofixation electrophoresis (IFE) confirmed IgG-λ and IgA-κ biclonal gammopathy **(Figure 3)**. The serum IgA quantitation result was increased (630 mg/dL), and

Table 1. *The clinical features of the present case which are compatible with the diagnostic criteria.*

Criteria	Features of this case
Major	
Polyneuropathy	Diffuse peripheral sensorimotor demyelinating polyneuropathy
Monoclonal plasma proliferative disorder	Biclonal gammopathy of IgG-λ/IgA-κ
Elevation of serum VEGF levels	Not checked
Sclerotic bone disease	No
Castleman disease	Initially diagnosed as Castleman disease
Minor	
Organomegaly	Hepatosplenomegaly and lymphadenopathy
Edema	Pleural effusion
Endocrinopathy	Hypothyroidism
Skin changes	Hypertrichosis
Papilledema	No
Thrombocytosis/polycythemia	No

VEGF, vascular endothelial growth factor

IgG, IgM, and IgD levels were within the reference limit. Both the serum FLC κ and λ values were increased (288 and 50 mg/dL, respectively), and the κ/λ ratio was higher than the normal limit (5.76). In the bone marrow aspiration examination conducted to rule out multiple myeloma, the plasma cell content was 1.1%, without any morphological abnormality. In the follow-up laboratory test, IgA and sFLC κ were consistently increased and the serum IFE resulted in the same IgG-λ and IgA-κ biclonal gammopathy again. Unfortunately, in this case, the serum level of the vascular endothelial growth factor (VEGF) was not assessed. He received medications with physiotherapy, but his neurological symptoms had gradually worsened.

Discussion

Polyneuropathy and monoclonal plasma cell-proliferative disorder are two mandatory major criteria of POEMS syndrome. In addition, to diagnose POEMS syndrome, at least one other major criterion and one minor criterion are required [7,10]. Because the syndrome is rare and the neuropathic feature in POEMS syndrome is typically demyelinating, it can be misdiagnosed as other neurological disorders such as chronic inflammatory demyelinating polyneuropathy. In addition, it should be distinguished from Castleman disease, which has no clonal change in plasma cells. Although several researchers reported that 11% to 30% of POEMS syndrome patients had coexistent Castleman disease [5,9,11,12], these estimates might be conservative because many patients did not undergo lymph node biopsy. Our patient had several manifestations enough to be diagnosed with POEMS syndrome **(Table 1)**. Interestingly, he showed IgG-λ/IgA-κ biclonal gammopathy in serum IFE.

Although by definition, all patients showed evidence of a monoclonal plasma proliferative disorder, the detectable serum levels of monoclonal proteins in IFE were between 75% and 87% of patients [5,11]. Some patients demonstrated a clonal plasma proliferative disorder only by immunohistochemical staining of bone marrow or sclerotic bone lesion biopsy. In some reports, as in our case, serum monoclonal protein was detected during follow-up for the first time [5,6]. Because the quantity of monoclonal protein is usually small, monoclonal IgA comigrated with normal β-proteins, and rare cases in urine were not detected in serum, it can be easily missed in serum PEP. Thus, if the result of the serum PEP is negative, it is important to perform IFE and sFLC quantitative assays.

Although a λ light chain with (most commonly) an α heavy chain (IgA-λ) is the main isotype in monoclonal gammopathy in POEMS syndrome, monoclonal gammopathy of IgG-κ, IgG-λ, IgA-κ, and rarely, IgM-κ or an isolated α heavy chain have also been reported [1,6,9,13-16]. Because the finding of IgG-λ/IgA-κ biclonal gammopathy in our case is rare, we reviewed many articles and case reports; however, only three such cases have been reported to date. Levinson [3] identified low concentration of double IgA-κ M-proteins by IFE, Stankowski-Drengler et al [9] reported a case of biclonal gammopathy (IgA- λ and IgG-κ type), and one case of IgG-κ, λ biclonal gammopathy was included in the study of Jang et al [17]. Levinson, Stankowski-Drengler et al, and Jang et al did not describe any distinct characteristics of patients with biclonal gammopathy in POEMS syndrome; therefore, we could not highlight the differences or similarities between our case and the previously reported ones. Furthermore, our case presented a normal course of disease progression. As the reason of our case's biclonal gammopathy, two different mechanisms can be considered. Two independent B cell clones are the most likely to produce the two immunoglobulins. But there is also a rare possibility of a single B cell clone with specific IgH rearrangement in which a subclone undergoes isotype switching and different light chain use. However, we unfortunately could not confirm this unlikely possibility.

In addition to biclonal gammopathy, the abnormal sFLC ratio with dominant κ clonality was another interesting feature of our case. Stankowski-Drengler et al [9] proposed an association between restricted IgA heavy chain and more disseminated or active disease status in POEMS syndrome. They reported that POEMS syndrome patients with IgA monoclonal gammopathy were more likely to show diffuse bone marrow involvement of the paraprotein than were patients with IgG monoclonal gammopathy. This finding is consistent with reports that IgA myeloma shows poorer prognosis than IgG myeloma. However, the present case did not show diffuse bone marrow involvement of monoclonal plasma cells, in spite of increased serum IgA level and the occurrence of an IgA monoclonal band in serum IFE. Because large group studies for POEMS syndrome are few owing to the rarity of the disease, we could not find more information about the frequency of various types of monoclonal gammopathies, differences in disease progression under biclonality, and clinical or prognostic characteristics of POEMS syndrome based on the specific monoclonal gammopathy.

When our patient was diagnosed with Castleman disease and peripheral polyneuropathy, his serum or urine PEP results were unremarkable. During follow-up serum PEP, we found only a very weak monoclonal band at the end of the gamma region, but missed a band comigrating with normal beta proteins. Finally, we confirmed IgG-λ and IgA-κ biclonal gammopathy on serum IFE. His urine PEP showed no abnormal band. The serum IgA level was elevated, the serum IgG level was within the reference limit, and both sFLC κ and λ levels were elevated, with an abnormal κ/λ ratio. Monoclonal plasma cell disorders can lead to abnormal concentrations of serum κ or λ FLC, resulting in an abnormal sFLC-R, which also reflects the clonality of the disease. Despite that most cases of POEMS syndrome had λ light chain clonality, their sFLC-R were reported to be within the reference intervals. Their serum κ light chain levels were also increased, likely because of impairment of their renal function or the activation of polyclonal activation of medullary and extramedullary plasma cells. In our case, the fact that the patient's kidney function was normal and the serum κ FLC level was much greater than the serum λ FLC level likely contributed to the abnormal sFLC-R. Dispenzieri [10] recommended minimal follow-up laboratory tests, including serum PEP, IFE, and affected immunoglobulin quantitative assay, initially every 3 months and then yearly. Our patient has so far shown the same IFE pattern, and no remarkable change was observed in the immunoglobulin and sFLC quantitation results in the follow-up, despite several therapeutic efforts.

Evidence for a primary pathogenic role of different isotype monoclonal gammopathies in POEMS syndrome remains elusive. Thus, further larger studies for evaluation of its prognostic impact and better management modalities based on different features of POEMS syndrome must be pursued.

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