Fitting the Pieces of the POEMS Syndrome Jigsaw Puzzle-Guillain-Barré Syndrome in a Patient with Refractory Ascites: Case Report

POEMS Sendromunun İki İlginç Belirtisinin Birlikte Görüldüğü Bir Olgu Sunumu: Guillain-Barré Sendromu ve Refrakter Assit

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ABSTRACT POEMS is an acronym for a rare and poorly understood syndrome associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes that usually occurs in the setting of a plasma cell dyscrasia. Elevations of cytokines including vascular endothelial growth factor (VEGF) have all been noted. Enlargement of the lymph nodes and spleen is secondary to changes consistent with Castleman's disease (giant angiofollicular hyperplasia, multicentric plasma cell variant). There is no particular test that establishes the diagnosis of POEMS syndrome with certainty, and a diagnosis is usually made when seemingly unrelated signs and symptoms are linked. We present a case of a 39-year-old man who presented with massive ascites and organomegaly who developed Guillain-Barré syndrome-like neuropathy. He was eventually diagnosed with the POEMS syndrome. The syndrome should be kept in mind in the patients with refractory ascites and compatible clinical picture.

Key Words: POEMS syndrome; Guillain-barre syndrome; vascular endothelial growth factor C; ascites

ÖZET POEMS polinöropati, organomegali, endokrinopati, monoklonal gammopati ve cilt değişikliklerini temsilen kullanılan bir akronim olup sendrom genellikle plazma hücre diskrazisi zemininde görülür. Patogenez tam anlaşılamamakla beraber vasküler endotelyal büyüme faktörü (VEGF) gibi bazı sitokinlerin rol oynadığı düşünülmektedir. Dalak ve lenf nodlarının büyümesi Castleman hastalığına (dev anjiofoliküler hiperplazi, multisentrik plazma hücre varyantı) ikincildir. Tanıyı tek başına kesin olarak koyduran bir test yoktur ve sendrom görünüşte ilgisiz gibi olan belirti ve bulguların bir araya gelmesiyle tanımlanır. Burada masif assit ve organomegali ile başvuran ve izlemde Guillain-Barré sendromu benzeri nöropati geliştiren 39 yaşında bir erkek hasta takdim etmekteyiz. Hasta neticede POEMS sendromu tanısı almıştır. POEMS sendromu refrakter assiti ve uyumlu klinik tablosu olan hastalarda akılda tutulmalıdır.

Anahtar Kelimeler: POEMS sendromu; Guillain-barre sendromu; vasküler endotelyal büyüme faktörü; assit

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POEMS syndrome was first described by Crow in 1956.[1] It is a rare multisystemic disease that occurs in the setting of a plasma cell dyscrasia, and most patients are seen with osteosclerotic myeloma or monoclonal gammopathy of unknown significance (MGUS). The M proteins most frequently found are the immunoglobulin A lambda (IgA-λ) and immunoglobulin G lambda (IgG-λ) light chains.[2] Classic multiple myeloma has not been associated with the disease. The pathophysiologic link betwe-

en the constellation of symptoms and the underlying disease is not well understood; however, elevated levels of cytokines and growth factors have been implicated.[3-5] Because POEMS syndrome is associated with Castleman's disease and angioma formation, the role for human herpesvirus 8 (HHV-8) has been postulated.[6,7] No specific case definition for POEMS exists; however, most authors agree that patients with POEMS syndrome should have three or more of the five features. The polyneuropathy associated with POEMS syndrome is a bilateral symmetric disturbance, involving both motor and sensory nerves, beginning distally, with progressive proximal spread. Cranial or autonomic nerves are not involved. Both demyelination and axonal degeneration are noted.[8]

Herein, we present a case of a 39-year-old male patient who presented with refractory ascites and organomegaly who later developed a Gullian-Barré syndrome (GBS)-like neuropathy and was eventually diagnosed with the POEMS syndrome.

CASE REPORT

A 39-year-old male patient admitted to our hospital with abdominal distention, loss of appetite, nausea and vomiting with weight loss of 12 pounds in the previous four months. One year earlier he had undergone double vessel coronary bypass surgery. During the past year he had been diagnosed with hypothyroidism and was on levothyroxine at a dose of 100 mcg/day. One month before presentation, he had been hospitalized elsewhere with the diagnosis of tuberculosis peritonitis. He had been administered a combination anti-tuberculosis treatment with isoniazid, rifampicin, and ethambutol. His symptoms failed to resolve despite three weeks of treatment. At presentation, physical examination revealed massive tense ascites, bilateral pretibial edema and generalized lymphadenopathy. The patient was promptly hospitalized for further investigation. A blood work-up on admission revealed serum blood-urea nitrogen (BUN) and creatinine of 111 and 4.7 mg/dl, respectively, with a serum potassium level of 7 mEq/L, for which hemodialysis was initiated. An abdominal and portal system doppler ultrasound showed massive ascites and hepatosplenomegaly. Portal vein dimensions and flow were normal. The kidneys were normal, with no signs of pelvicalyceal system dilatation. After learning that renal function tests during his previous hospitalization were normal, his acute renal failure was attributed to drug toxicity due to rifampicin. Anti-tuberculosis treatment was discontinued citing lack of evidence supporting active tuberculosis infection, and subsequent peritoneal fluid culture results were negative for mycobacterium species and bacterial infections. Microscopic evaluation of peritoneal fluid was unremarkable. His ascites was exudative (serum-ascites albumin gradient: 0.3). A computed tomography scan of the thorax and abdomen revealed enlarged paraaortic lymph nodes, with hepatosplenomegaly and findings consistent with renal lymphocytic infiltration. Upper and lower gastrointestinal tract endoscopic findings were normal, and peritonoscopy failed to ascertain any lesions on the peritoneal surface. No signs of lymphoma involvement were observed in the bone marrow aspirate and biopsy specimen. An estimated ejection fraction of 50-55% was observed on transthoracic echocardiography. No pericardial fluid was detected. The patient remained oliguric requiring hemodialysis support twice a week, with unexplained hypotension (mean arterial pressure between 50-60 mmHg). The patient then started complaining of numbness and progressive weakness of the lower extremities. Neurologic examination revealed bilaterally decreased muscle strength and deep tendon reflexes as well as bilateral papilledema on examination of the fundi. Citing possible malignant infiltration of the spinal cord, prednisolone was initiated at a dose of 1 mg/kg. Electromyography (EMG) findings were consistent with a demyelinizing polyneuropathy involving both sensory and motor nerves. Lumbosacral and cranial magnetic resonance imaging scans were normal. The presence of acellular cerebrospinal fluid, with elevated protein level (237 mg/dl), along with neurological examination and EMG findings prompted a preliminary diagnosis of Guillain-Barré syndrome (GBS) for which 0.4 mg/kg/day intravenous immunoglobulin G (IVIG) as administered over 5 days. After initiation of prednisolone treat-

ment, the patient's urinary output progressively increased, and his serum creatinine level eventually decreased to 0.8 mg/dl without further need for hemodialysis. Similarly, abdominal distention decreased dramatically. However, despite treatment, weakness subsequently involved the upper extremities, a finding thought to be consistent with ascending symmetrical demyelinization. When all the seemingly disperse symptoms and signs were mulled upon, the possibility of the POEMS syndrome was considered. Attempts to determine an M-protein uncovered a peak on serum protein electrophoresis. It was confirmed to be due to an increase in monoclonal IgA-λ and IgA-κ on immunofixation electrophoresis. Histopathological findings of the right axillary lymph node biopsy revealed findings consistent with hyaline vascular type Castleman's disease. A diagnosis of the POEMS syndrome was made. A treatment plan of six cycles of cyclophosphamide, vincristine, and prednisolone chemotherapy was decided upon, and the first cycle was administered without vincristine, taking into account the underlying peripheral neuropathy. The patient's paraparesia gradually decreased during the following week, and after being placed on a rehabilitation program, he was once again able to walk with support. He was eventually discharged to complete his rehabilitation in his home town.

DISCUSSION

Bardwick et al first coined the acronym POEMS in 1980 to represent a syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[9] Although there are several series in the literature, controversy exists on the number of features necessary for diagnosis. For example several important entities are not represented in the acronym, including Castleman's disease, ascites, edema, pleural effusion, thrombocytosis and sclerotic bone lesions.[10-12] In an attempt to clarify the definition, Dispenzieri et al. analysed the data of 99 patients with POEMS and suggested two major and at least one minor criterion be satisfied to differentiate the syndrome from neuropathy associated with MGUS, myeloma, and Waldenström's disease.[2] The major criteria were polyneuropathy and clonal plasma proliferative disorder while the minor ones include osteosclerotic bone lesions; Castleman's disease; papilledema; organomegaly, including lymphadenopathy; edema, pleural effusion, or ascites; endocrinopathy; and skin changes.[2] Having polyneuropathy and monoclonal IgA-λ and IgA-κ as evidence of monoclonal plasmaproliferative disorder, our patient fulfilled both major criteria. He had papilledema, ascites, hepatosplenomegaly, enlarged lymph nodes, edema, hypothyroidism, and Castleman's disease as minor criteria. Although there is no question regarding the diagnosis, we believe that two features deserve particular merit; neurologic involvement as GBS and accompanying massive ascites.

Ascites could result from several pathologic conditions in our patient. First of all he had renal failure on admission and when combined with his hypoalbuminemic state one can expect nephrogenic ascites as part of a general hypervolemic state. On the other hand, ascites was a predominant finding in our patient with the absence of pleural effusion, and pulmonary congestion expected with this kind of massive ascites. The ascites did not resolve with intensive hemodialysis. Myxedema ascites is another possibility, but it is a very rare complication of severe hypothyroidism occurring in approximately 1% of cases.[13] Our patient's ascites failed to respond to thyroid hormone replacement, either. Any suspicion of a solid malignancy were dissolved after normal peritonoscopy findings and benign cytologic features of the ascites. Ascites is frequently associated with POEMS, reported as 7[2], 32[8], and 52%[10] in three series. The presence of a hyperpermeability factor was postulated by Takazoe et al. to be responsible for chronic renal failure in POEMS.[14] The same factor may also be related to serositis with massive fluid retention in the syndrome. Vascular epidermal growth factor (VEGF), a potent microvascular permeability enhancing mediator, was shown to have raised levels in patients with POEMS syndrome and is one of the most important candidates for the hyperpermeability factor.[14] The fact that our patient's ascites completely resolved and renal functions returned to nor-

mal, possibly secondary to decreased prerenal component, after prednisolone treatment supports the suggested pathogenesis because steroids are well known for their effect on stabilizing vascular permeability.

Peripheral neuropathy is the dominant clinical picture of the syndrome. All of the patients had a peripheral neuropathy in the three big series.[2,8,10] Our patient developed ascending type of paralysis and hypoesthesia within three weeks of admission. In light of the EMG findings consistent with demyelinizing polyneuropathy involving both sensory and motor nerves he was diagnosed with GBS.[15] The symptoms in our case developed in less than four weeks, as is required by the definition of GBS. In the literature, there is only one case of a GBS-like presentation within the context of POEMS,[16] and to the best of our knowledge our case is the second example. Takakura et al reported the appearance of GBS-like symptoms following a biopsy of a plasmacytoma and the procedure was speculated to induce release of VEGF from plasma cells.[16] VEGF was thought to be responsible for an increase in microvascular permeability affecting the blood nerve barrier and its plasma level was found to be elevated in this patient. In our case, the occurrence of massive ascites and GBS with the common pathogenetic mechanism of increased permeability, lead us to hypothesize that a hyperpermeability factor, possibly VEGF under the light of the current literature, was the mediator. Unfortunately, we were not able to measure VEGF level in our patient.

Our case is the second reported case of POEMS complicated by GBS. Vascular hyperpermeability as the shared pathogenesis for various manifestations of the syndrome such massive ascites and GBS deserves special mention. Steroid treatment may be a good option for those with findings of extracellular volume overload, like massive ascites, Additionally, we experienced that IVIG was very effective for neurologic symptoms, and this supports Takakura et al in the fact that IVIG will be able to be one of the future therapies of the POEMS.[16] Further studies are needed for use of IVIG in all polyneuropathy cases of POEMS.

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