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Case Report

POEMS syndrome with renal plasmacytoma and classic polyarteritis nodosa: a case report

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Abstract

POEMS syndrome is a rare conglomeration of disorders associated with plasma cell dyscrasia. The acronym POEMS is derived from main features of the syndrome namely 'polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions'. Other clinical features include presence of sclerotic bone lesions, Castleman's disease, papilledema, pleural effusion, edema, ascites, erythrocytosis and thrombocytosis. Myeloma is the most common plasma cell dyscrasia associated with POEMS syndrome. Renal involvement is rare and renal biopsy is characterized by glomerular involvement with membranoproliferative glomerulonephritis and endothelial injury. We report a case of a 67-year-old male who presented with clinical features satisfying the diagnostic criteria of POEMS syndrome and had rapidly progressive renal failure. Renal biopsy showed extensive interstitial infiltration by plasma cells and concomitant presence of classic polyarteritis nodosa. Although association with small-vessel vasculitis has been reported in patients with POEMS syndrome, to the best of our knowledge, this is the first report of POEMS syndrome associated with medium-sized vessel vasculitis.

Keywords: classic PAN; POEMS syndrome; renal plasmacytoma

Background

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-band and skin changes) syndrome is a rare paraneoplastic disease with multisystem involvement, seen in association with plasma cell dyscrasia. It is also known as Crow–Fukase syndrome or PEP syndrome (plasma cell dyscrasia, endocrinopathy and polyneuropathy) or Takatsuki syndrome. The acronym POEMS was coined by Bardwick *et al.* [1] in 1980, to characterize polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes. The diagnosis of POEMS syndrome is made by the presence of two major criteria (polyneuropathy and monoclonal plasma proliferative disorder) in conjunction with at least one minor criteria (sclerotic bone lesions, Castleman's disease, organomegaly, edema, endocrinopathy, skin changes and papilloedema) [2, 3]. Renal involvement in POEMS syndrome has been described and the clinical presentation can vary from acute kidney injury to chronic renal insufficiency (RI) with mild proteinuria. Renal biopsy usually shows prominent glomerular changes characterized by mesangial proliferation and thickening of the capillary wall with double contour on light microscopy suggesting membranoproliferative glomerulonephritis (MPGN) pattern, without any immune or complement deposits [4, 5]. Association of POEMS with small vessel vasculitis has been described but not with medium vessel vasculitis.

Case report

A 67-year-old male patient, a known case of type 2 diabetes mellitus since 15 years, presented with history of fever on and off since 18 months. He had tingling and numbness of both the lower limbs for a period of 3 months, subsequently had progressively increasing weakness in both lower limbs and later developed progressive weakness in both lower limbs and eventually had bilateral foot drop. He had severe anemia requiring repeated blood transfusions and also had pedal edema for 2 months.

On examination, he had anemia, bilateral pitting pedal edema, raised jugular venous pressure and there was no lymphadenopathy. Systemic examination revealed bilateral reduced breath sounds in lung bases and hepatomegaly. Nervous system examination revealed reduced sensations in lower limbs with bilateral foot drop.

His investigations revealed an increase in serum creatinine to 4.6 mg/dL (406.64 μmol/L) from baseline value of 1.5 mg/dL (132.6 μmol/L) 6 months back. Urinalysis showed trace proteinuria without active sediments; hemoglobin was 6.9 g/dL (69 g/L) despite receiving multiple blood transfusions in recent past, and peripheral smear showed microcytic hypochromic anemia with rouleaux formation. ESR was 32 mmHg per first hour. The bone marrow aspiration revealed reactive marrow with 9% plasma cells and there were focal collections of plasma cells on bone marrow biopsy. Light chain studies performed by immunohistochemical method did not demonstrate light chain

restriction. Urine for Bence Jones protein was negative, and electrophoresis showed a normal pattern. Serum electrophoresis showed monoclonal band. Serum for immunofixation was consistent with IgA lambda monoclonal gammopathy. Serum IgA level was 25 200 mg/L, normal range is 600–3300 mg/L. Other immunoglobulin levels were normal. Serum free light chains assay showed lambda level 510 mg/L (normal, 5.7–26.3 mg/L) and kappa chain level 3.8 mg/L (normal, 3.3–19.4 mg/L). Beta-2 microglobulin level was 6.92 mcg/mL (588.2 nmol/L), normal is 229.5 nmol/L. Serum total calcium was 9.0 mg/dL (2.24 mmol/L). Serology was negative for anti-nuclear antibodies and ANCA by immunofluorescence detection. Viral markers including HIV, HbsAg and HCV were non-reactive. Serum TSH, PTH and cortisol levels were normal. Ultrasound of the abdomen showed normal-sized kidneys without any internal lymphadenopathy. High-resolution CT chest did not reveal any positive findings. The magnetic resonance imaging of the spine revealed multiple low signal intensity consistent with sclerotic lesions in dorsal and lumbar vertebrae. The nerve conduction velocity was suggestive of sensory motor neuropathy.

He underwent renal biopsy after two sittings of hemodialysis. Histology included 12 glomeruli of which one was globally sclerosed in a 1.4-cm length of linear core. It revealed multiple nodular infiltrates of plasma cells in the interstitium (Figure 1) (color as Supplementary material), which were monoclonal (lambda light chain restriction on immunohistochemistry). In addition, the arcuate artery showed transmural fibrinoid necrosis indicative of vasculitis (Figure 2) (color as Supplementary material). However, glomeruli were unremarkable and non-proliferative. Lobules did not show mesangiolysis, fibrinoid necrosis or crescent formation (Figure 3) (color as Supplementary material). Immunofluorescence (IgG, A, M, C3, C1q and fibrin) was negative. Congo red stain on renal and bone marrow biopsies was negative for amyloid. The conglomeration of vasculitis and sparing of glomerular capillaries was diagnostic of classic polyarteritis nodosa (PAN). Renal biopsy was reported as renal plasmacytoma with classic PAN.

Patient was treated with a 28 days cycle of dexamethasone and bortezomib combination. He received oral dexamethasone (40 mg/day for 4 days) on Days 1–4, 9–12, 17–20 and intravenous bortezomib (1.3 mg/m^2) on Days 1, 8, 15 and 22 of each cycle. After completion of first cycle of chemotherapy, his symptoms improved remarkably and the hemoglobin increased to 10 g/dL (100 g/L) without any need of further blood transfusion. His renal functions and urine output improved as well, and the dialysis was stopped. His serum creatinine reduced to 3.0 mg/dL (265.2 µmol/L). During the second cycle of chemotherapy, he complained of breathlessness and high grade fever on 12th day (i.e. before scheduled third dose of bortezomib of second cycle). Blood investigations showed leukopenia (total leukocyte count—1400 cells/mm^3) and X-ray chest revealed right-sided pneumonia. He was intubated and mechanically ventilated. Bronchoalveolar lavage grew *Klebsiella pneumoniae*

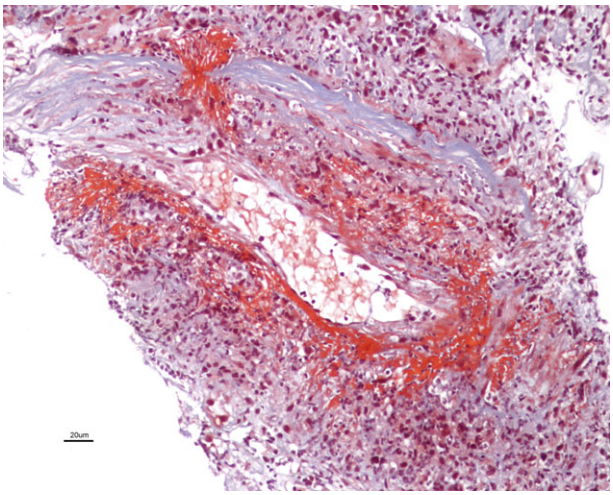

Fig. 2. Arcuate artery revealing diffuse transmural fibrinoid necrosis accompanied with neutrophilic and lymphocytic inflammatory cell infiltrate. Fibrinous material is seen seeping out into the perivascular area (×20, Masson trichrome).

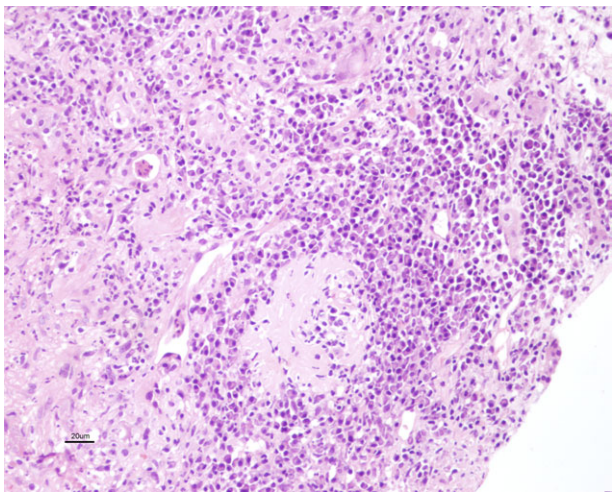

Fig. 1. Intersititium shows predominantly plasma cell infiltration forming an expansile lesion (×20, *hematoxylin and eosin* stain).

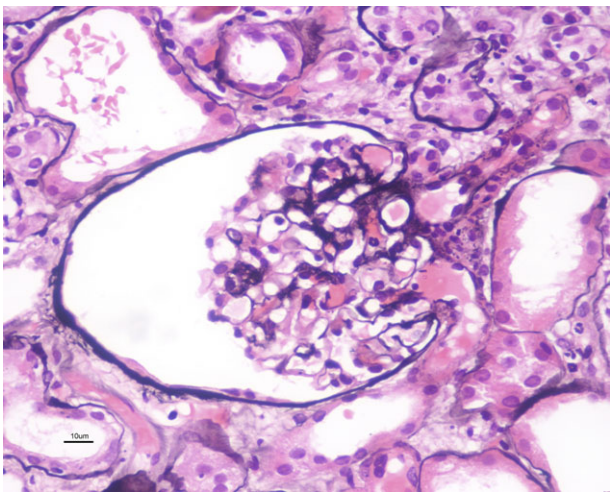

Fig. 3. Glomerulus revealing unremarkable capillary tufts with single contoured basement membrane without any mesangiolysis or fibrinoid necrosis or crescent formation (×40, PASM).

(count > 100 000 cfu/mL) after 72 h. Blood culture did not show any organisms after 48 h. He was treated with appropriate intravenous antibiotics but succumbed to sepsis and multiorgan failure after 5 days of hospital stay.

Discussion

One of the first descriptions of POEMS syndrome was given by Schneiker, in 1938, in an autopsy case of a 39–year-old man who had a solitary plasmacytoma, sensorimotor polyneuropathy and localized patches of thickened and deeply pigmented skin on the chest [6]. Later, Crow described two patients with osteosclerotic plasmacytomas with neuritis and features including clubbing, skin pigmentation, white fingernails, lymphadenopathy and ankle edema [7].

The diagnosis criteria for POEMS are polyneuropathy and evidence of monoclonal plasma proliferative disorder (two major criteria) and osteosclerotic bone lesions, Castleman's disease, organomegaly or lymphadenopathy, endocrinopathy, features of volume overload, such as edema, ascites and effusions and papilledema (seven minor criteria). The diagnosis requires the presence of both the major and any one of the minor criteria [3]. The revised diagnostic criteria include elevated vascular endothelial growth factor levels [2].

Our patient satisfied two mandatory major criteria (polyneuropathy and monoclonal IgA gammopathy) and osteroosclerotis lesions; minor criteria (volume overload and organomegaly). The case fulfilled the diagnosis of POEMS syndrome associated with IgA plasma cell myeloma and medium size vessel vasculitis (classic PAN) in the kidney. Renal involvement in POEMS syndrome has been reported in different case series. The renal pathology is characterized by glomerular involvement in the form of an MPGN-like picture on light microscopy, however, without immune/complement deposits. Sub-endothelial lucent spaces have been described ultrastructurally suggesting endothelial injury [5, 8, 9]. Sharabi *et al.* [10] reported a case of POEMS syndrome presenting with vasculitic skin lesion. Singh *et al.* [11] also reported a minor association between POEMS syndrome and vasculitis in their retrospective study of 14 cases over a period of 8 years at a tertiary center. Vasculitides associated with multiple myeloma are paraneoplastic in nature with cutaneous leukocytoclastic vasculitis i.e. small vessel vasculitis in all of them [12, 13]. Hence, we believe in our case that the association of medium vessel vasculitis and POEMS syndrome/myeloma as 'temporal'.

'ANCA' test and 'glomerulonephritis' play a pivotal role in distinguishing medium-sized vessel vasculitis from pauci-immune small vessel vasculitis. Approximately 90% of patients with active untreated microscopic polyangiitis and Wegener's granulomatosis are associated with ANCA [14]. The Chapel Hill Nomenclature System excludes a diagnosis of PAN if there is evidence for concurrent small vessel vascultitis, such as glomerulonephritis or pulmonary alveolar capillaritis [15]. Microscopic polyangiitis is a systemic necrotizing vasculitis with few or no immune deposits affecting predominantly capillaries, venules and arterioles; however, necrotizing arteritis involving small and medium-sized arteries may be present [15, 16]. Wegener's granulomatosis has granulomatous inflammatory reaction in addition to necrotizing vasculitis [16]. The diagnosis of medium-sized vasculitis i.e. classic PAN was made in the index case due to lack of pulmonary symptoms; absence of proteinuria, hematuria and active urine sediments; negative ANCA; unremarkable glomeruli in an adequate kidney biopsy coupled with widespread transmural fibrinoid necrosis of arcuate artery. Extensive transmural fibrinoid necrosis is most commonly seen in PAN than in any other form of vasculitis [17].

RI occurred in six patients (6%) with POEMS syndrome, in which four developed as pre-terminal event [3]. RI developed pre-terminally (6–8 weeks before) in our case. The cause for RI is multifactorial: widespread sheets of plasma cell infiltrates, active tubulointerstitial nephritis and medium-vessel vasculitis. The bone marrow biopsy showed 9% plasma cells, which is not typical of a myeloma of medullary origin. At the same time, the renal biopsy showed sheets of plasma cell infiltration in the kidney with light chain restriction suggesting myeloma of extramedullary origin (renal plasmacytoma). The index case had severe anemia and RI coupled with significantly elevated serum IgA levels.

The response to treatment is better in POEMS than in classic myeloma. The treatment regimen similar to myeloma has been tried. In addition to chemotherapy, radiotherapy has been tried for those with osteosclerotic lesions [3]. The single osteosclerotic lesion usually responds well to radiotherapy. For those with widespread osteosclerotic lesions, chemotherapy is used [3]. The options of chemotherapy are melphalan, dexamethasone, combination chemotherapy (such as VAD and CHOP regimen) and cyclosporine and azathioprine (in combination with corticosteroids). Plasmapheresis and intravenous immunoglobulin have been tried without appreciable response. Treatment with bortezomib and lenalidomide has been described with good benefit [3]. Favorable response has been seen after hematopoietic cell transplantation in young patients with multiple osteosclerotic lesions. Our patient responded favorably to treatment with oral dexamethasone and intravenous bortezomib initially and there was significant improvement in his clinical symptoms as well as anemia and renal functions. But, during the second cycle of chemotherapy, he developed right lobar pneumonia, sepsis and multiorgan failure leading to his death.

The association of renal plasmacytoma with POEMS is very rare. In addition, the presence of concomitant medium vessel vasculitis without any glomerular capillary involvement was diagnostic of classic PAN. This association of POEMS with renal plasmacytoma and classic PAN has not been reported earlier. Early diagnosis has important therapeutic and prognostic implications although disease or treatment-related mortality and morbidity is still high.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.

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