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FULMINANT EVANS SYNDROME AND SPLENIC INFARCTION AS INITIAL MANIFESTATIONS OF POEMS SYNDROME WITH MONOCLONAL KAPPA LIGHT CHAIN RESTRICTION: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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ABSTRACT

Introduction: Autoimmune cytopenias have been very rarely reported in conjunction with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome). To the best of our knowledge, there is no reported case in the existing literature of an association of Evans syndrome with POEMS syndrome.

Case description: A 55-year-old female patient, with a medical history of well-controlled dermatomyositis, developed fulminant autoimmune haemolytic anaemia with immune thrombocytopenic purpura, thus fulfilling the diagnosis of Evans syndrome. To control the disease, acute management required supportive measures in the intensive care unit, repeated transfusions of red blood cells and platelets, high- dose intravenous corticosteroids, a bolus of cyclophosphamide, and splenectomy. Three days post-splenectomy, the patient developed, subacutely, full-blown POEMS syndrome. Therefore, the diagnosis of coexisting secondary Evans syndrome and POEMS syndrome was made. Notably, the monoclonal kappa light chain restriction and multiple splenic infarctions were distinctive features in our patient. Due to procurement issues of lenalidomide, we opted for monthly parenteral cyclophosphamide and autologous stem cell transplantation was programmed.

Conclusion: This case highlights that severe secondary Evans syndrome can coexist with POEMS syndrome, leading to challenges in diagnosis and management.

KEYWORDS

Evans syndrome, POEMS syndrome, Coombs test, splenectomy, splenic infarctions

LEARNING POINTS

- Severe secondary Evans syndrome can coexist with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein,

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and skin changes) syndrome.

- High doses of corticosteroids required for the acute management of Evans syndrome may artificially lower the genuine value of serum vascular endothelial growth factor in the context of associated POEMS syndrome.
- In atypical circumstances like in our case (associated Evans syndrome, kappa light chain restriction), the nerve biopsy is critical to exclude differential diagnoses and confirm typical characteristics of POEMS syndrome- related polyneuropathy.

INTRODUCTION

Evans syndrome (ES) is a rare autoimmune disorder characterized by the presence of two or more cytopenias, typically including autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP), with or without immune neutropenia. ES is generally regarded as an idiopathic condition; however, when secondary, it has been linked to various diseases, including systemic lupus erythematosus (SLE), common variable immunodeficiency, autoimmune lymphoproliferative syndrome, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and viral infections (such as human immunodeficiency virus - HIV, hepatitis C virus - HCV)[1].

To our knowledge, there have been no reported cases of secondary ES occurring in association with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome in the existing literature. In this report, we describe an atypical case of POEMS syndrome that presented concurrently with fulminant ES in a middle-aged female patient. Notably, our patient presented other distinctive features associated with POEMS syndrome, including monoclonal kappa light chain restriction and splenic infarctions.

CASE DESCRIPTION

A 55-year-old menopausal female with a medical history of a dermatomyositis (DM) for the past 10 years. The DM was well-controlled via azathioprine (100 mg/day) and oral prednisolone (10 mg/day). The patient was asymptomatic for the previous 7 years. Two months prior to hospitalization, the patient was admitted to the emergency department for evaluation of asthenia, abdominal pain, and regenerative normochromic macrocytic anaemia (7 g/dl). Abdominal ultrasonography revealed hepatomegaly (HPM) and splenomegaly (SPM). Although haematology consultation was requested, the patient was lost to follow-up.

Two months later, the patient was hospitalized in our department due to the worsening of asthenia, dyspnoea and marked jaundice. The full blood count revealed a severe drop of haemoglobin to 3.2 g/dl, hyperleukocytosis at 27,100/ mm^3 (68.8% of neutrophils) and platelets at 103,000/mm^3. The regenerative nature of anaemia was confirmed with reticulocytes at 156,330/mm^3. C-reactive protein was increased at 190 mg/l (reference range <6 mg/l) with negative procalcitonin.

A severe haemolysis was evident with low haptoglobin <0.1 g/l (reference range: 0.62-1.65 g/l), high lactate dehydrogenase at 560 U/l (normal <247 U/l) and elevated total bilirubin and unconjugated bilirubin at 341.2 mg/l (reference range: 3-11 mg/l) and 217.7 mg/l (normal: 2-10 mg/l) respectively. The direct antiglobulin test (Coombs test) was positive for IgG antibodies, thus confirming the diagnosis of AIHA.

Twenty-four hours after admission, the patient's condition rapidly deteriorated into a comatose state with cardio-respiratory disturbances (hypoxia and bradycardia). After admission to intensive care unit for supportive management, an additional workup revealed normal brain computed tomography (CT) and cerebrospinal fluid (CSF) composition. CT scan of the chest, abdomen and pelvis revealed multiple small abdominal and pelvic lymphadenopathies, homogeneous HPM (hepatic arrow at 19 cm) and SPM (16 cm in long axis) which is heterogeneous due to non-enhancing infarction areas after contrast *(Fig. 1)*. A mild left-sided pleural effusion was also present. Repeated blood count tests revealed the occurrence of thrombocytopenia that worsened from 85,000 to 37,000/

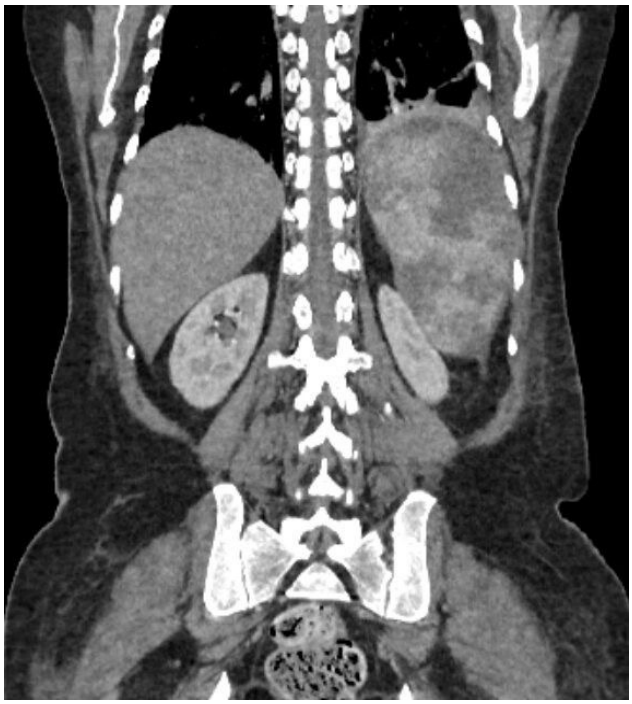


Figure 1. *Contrast-enhanced abdominal computed tomography scan, coronal view: Splenomegaly associated with multiple well-defined, triangular, hypodense areas. These non-enhancing lesions extend from the capsule toward the hilum, typical of segmental splenic infarctions.*



Figure 2. Large vascular purpura in the buttock area.

mm^3. Alongside evolutive thrombocytopenia, a large vascular purpura lesion appeared on the buttocks area *(Fig. 2)*. Therefore, we made the diagnosis of severe ES.

The patient also developed hypoxic hepatitis with increase of aspartate aminotransferase at 720 U/l (normal: 0-45 U/l), alanine aminotransferase at 321 U/l (normal range: 0-45 U/l) and alkaline phosphatase at 127 U/l (reference range: 0-115 U/l). The prothrombin level was moderately low at 60% (normal: >70%). Renal function (urea and creatinine), serum electrolytes, cardiologic evaluation (electrocardiogram and echocardiogram) were unremarkable.

In addition to supportive management of severe hypoxia-related systemic disturbances, repeated transfusions of red blood cells were administered. To manage the severe ES, the patient received an intravenous pulse of high dose methylprednisolone (1 g daily for 5 consecutive days) followed by 1 mg/kg/day of oral prednisolone which had led to the stabilization of haemoglobin between 8 and 10 g/dl and the improvement of consciousness and cardio-respiratory parameters. The hepatic biological disturbances resolved.

Nevertheless, despite steroid treatment and repeated platelet transfusions, the thrombocytopenia worsened to 29,000/mm^3. The steroid-refractory thrombocytopenia alongside the difficulty to afford other effective immunomodulatory alternatives (intravenous immunoglobulins, rituximab or plasmapheresis) due to the financial constraints of our national healthcare system, led us to urgently consider 1 g of intravenous cyclophosphamide. Despite this aggressive immunosuppressive therapy, the platelet count did not rise during the following days. To prevent a life-threatening haemorrhage due to persistent severe thrombocytopenia, a splenectomy was performed which allowed a rapid rise of the platelet count to normal values.

Notably, the histopathological study of the spleen confirmed the presence of multiple areas of necrotic and haemorrhagic infarction. No evidence of neoplasm was found. A prophylactic program of vaccinations against pneumococcus, meningococcus and haemophilus influenzae type B with the annual flu shot was initiated. Antibioprophylaxis with daily oral penicillin V for at least 2 years was also started. After the stabilization of the patient's condition, we performed a workup that was initially unconclusive for a secondary cause of ES. Indeed, auto-antibodies of SLE and serologies of infections (Epstein-Barr virus, cytomegalovirus, human herpesvirus 8, HIV, hepatitis B virus, HCV) were negative.

Three days after the splenectomy, the patient developed skin changes with acrocyanosis and oedema of the feet, multiple small angiomas, and areas of localized

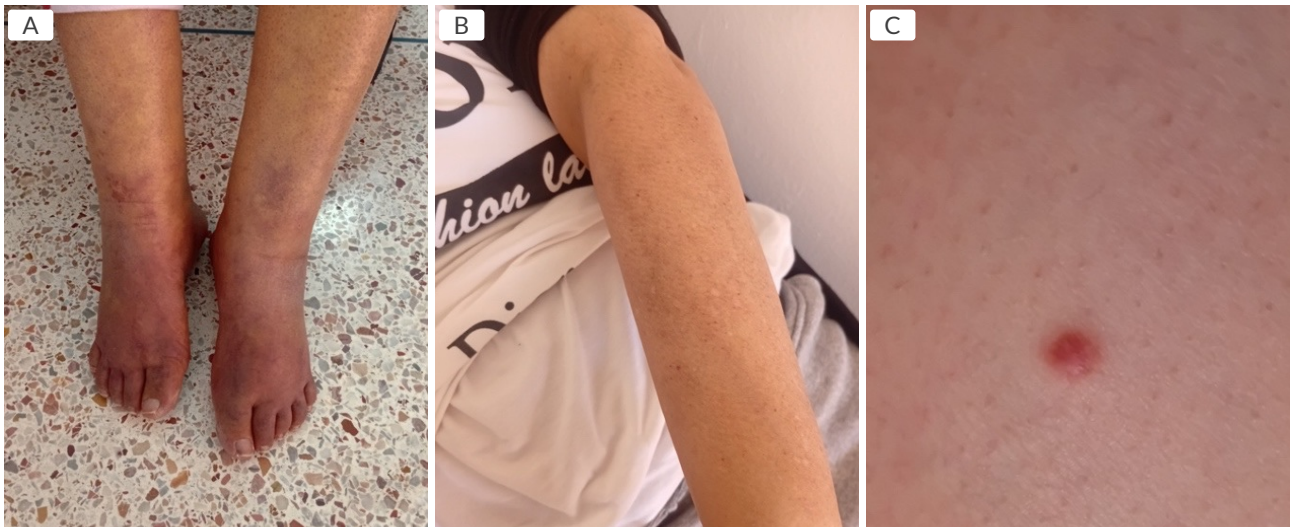


Figure 3. A) Acrocyanosis and edema of the feet. B) Hyperpigmentation on the left forearm. C) Close-up view of a small, well-circumscribed angioma (the right leg).

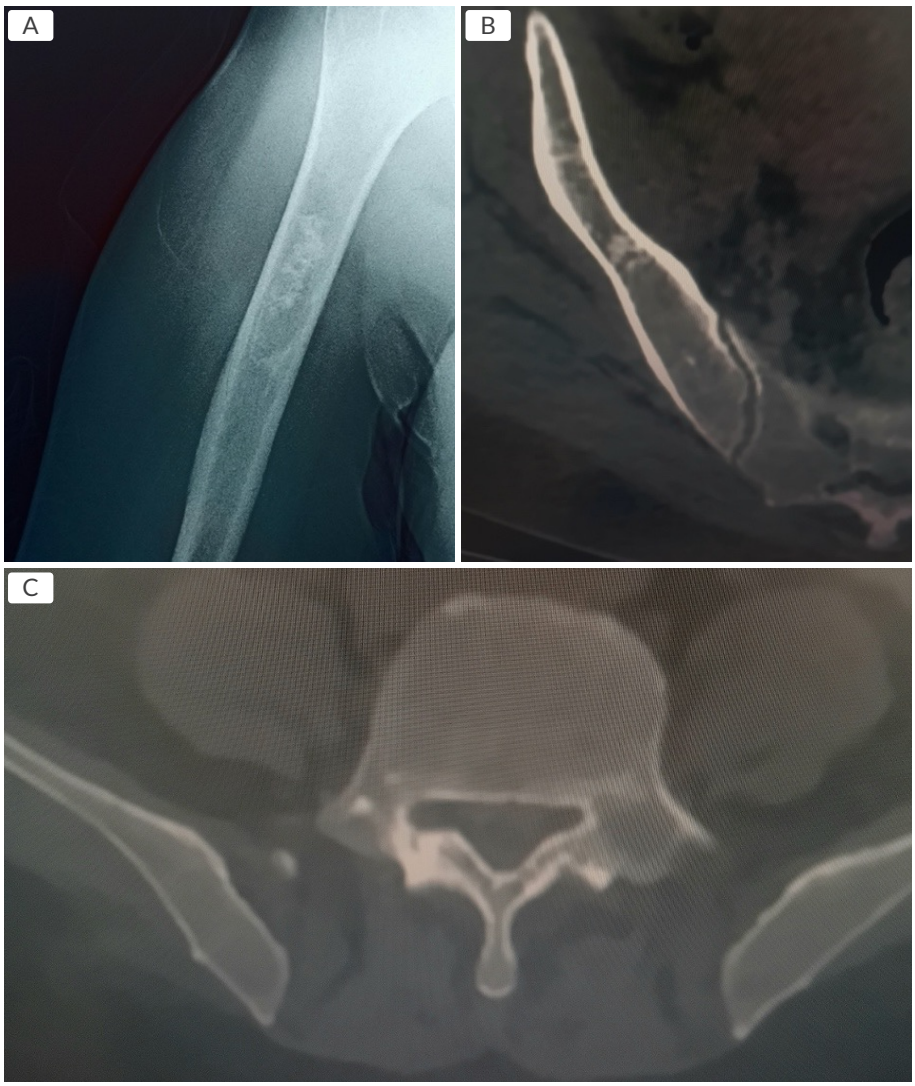


Figure 4. A) Radiographic view of the right humeral diaphysis revealing a localized osteosclerotic area. B) Computed tomography scan of the pelvis, axial view, showing focal osteosclerotic lesions of the iliac wing. C) Computed tomography scan of the lumbosacral spine, axial view, showing osteosclerotic lesions, spiculated bony proliferations of the posterior arc and sclerosis of the lamina and facet joints.

hyperpigmentation *(Fig. 3)*. Moreover, the patient developed subacute paraesthesia, and weakness of the distal parts of the four limbs. Physical examination revealed marked anaesthesia (superficial and proprioceptive modalities) in the 4 extremities with severe, bilateral motor weakness of the dorsiflexors of the feet and hands. The deep tendon reflexes were abolished in the lower limbs and reduced in the upper limbs. Neuropathic postural tremor affecting hands was noticed. Nerve conduction studies demonstrated a mixed pattern of demyelinating and axonal, sensory and motor, length-dependent, peripheral neuropathy of the 4 limbs, which was more severe in the lower extremities. Abundant fibrillation potentials were obvious in the distal muscles of the lower limbs, indicating an active denervation process.

The constellation of subacute polyneuropathy, organomegaly (SPM, HPM, abdominal lymphadenopathies), skin changes (acrocyanosis, hyperpigmentation, angiomas) and extra-vascular liquid overload (oedema of the feet and pleural effusion) strongly indicated a coexisting POEMS syndrome. To confirm this diagnosis, an additional workup disclosed the presence of a small monoclonal protein, IgG Kappa, on serum immunofixation. A small amount of Bence-Jones proteinuria, kappa type, was also present. The serum free light chains revealed a normal ratio, and bone marrow biopsy did not show evidence of an associated myeloma. The re-evaluation of the initial thoracic and abdominal CT scan showed multiple osteosclerotic lesions mainly in the pelvis and spine. Further radiologic assessment of the long bones revealed osteosclerotic lesions in the right humerus bone *(Fig. 4)*.

Serum vascular endothelial growth factor (VEGF) was increased at 710 pg/ml (normal <500 pg/ml). Hormonal tests showed hyperprolactinemia at 49 ng/ml (reference range: 5-35 ng/ml) and menopause range for both estradiol at 9.84 pg/ml (menopausal range <30 ng/l) and follicle-stimulating hormone at 44.77 mUI/ml (menopause range >40 mUI/ml) but abnormally low (for menopause) value of luteinizing hormone at 8.54 mUI/ml (menopause range > 40 mUI/ml). These results indicated pituitary gland dysfunction. The remaining hormonal axes were normal. No papilledema was present on ophthalmic evaluation.

Although nerve biopsy is not mandatory for the diagnosis of POEMS syndrome, we performed sural nerve biopsy due to the presence of atypical features such as the coexistence of ES and monoclonal kappa light chain restriction. The nerve biopsy was analysed using electron microscopy (EM) (in Limoges, France) and revealed moderate and homogeneous

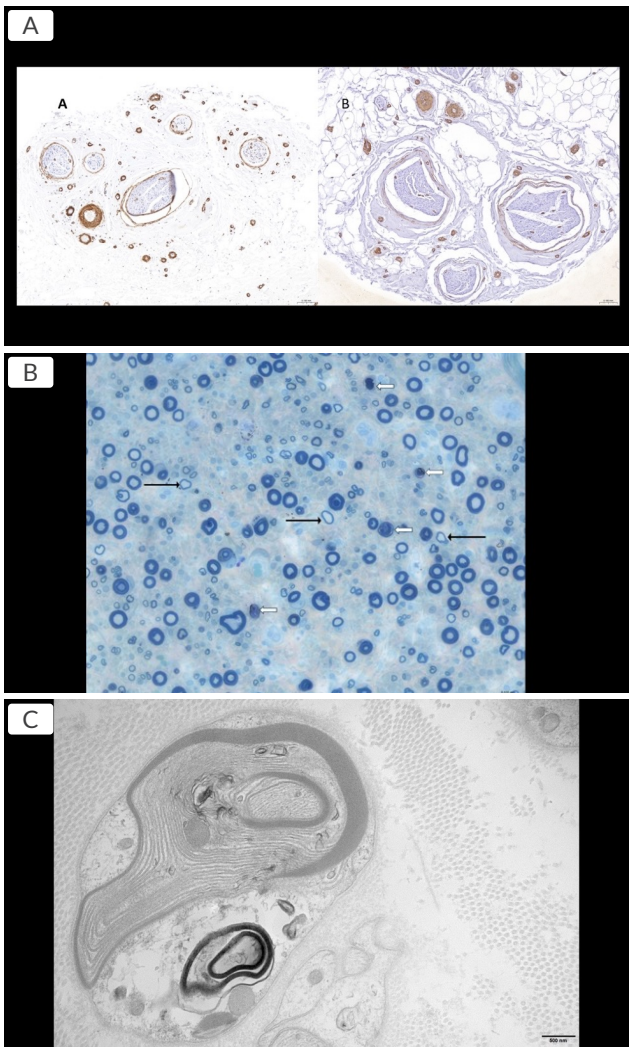


Figure 5. A) Smooth muscle actin paraffin cross sections from our POEMS case (A) and from an idiopathic neuropathy without IgG monoclonal gammopathy (B) nerve biopsies. There is a significant increased number of small epineurial blood vessels in POEMS.

B) Semi-thin transverse epon section stained with toluidine blue: moderate diffuse loss of myelinated axons. In this fascicle, a few axonal lesions (ovoids) (white arrows) are associated with rare hypomyelinated axons (black arrows).

C) Electron micrograph, transverse section. This myelinated axon displays uncompacted myelin lamellae typical of POEMS. There is an abnormally widened space between major dense lines.

Abbreviations: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

axonal loss with demyelination. A mild inflammation of the epineurium was present. A significant increase of the number of small vessels in the epineurium was evident (more than 265 epineurial small vessels per transverse section of the nerve). The typical aspect of uncompacted myelin lamellae (UML) affecting approximately 3% of myelinated fibres was also demonstrated via an EM study *(Fig. 5)*. No amyloid deposits, lymphomatous cells, vasculitis, or granulomas lesions were present in the nerve biopsy.

Our patient fulfilled the diagnostic criteria of POEMS syndrome according to Dispenzieri[2], with polyneuropathy and monoclonal plasma cell proliferative disorder as mandatory criteria; increased serum VEGF and osteosclerotic lesions as major criteria; organomegaly, extra-vascular liquid overload, skin changes and endocrinopathy as minor criteria. Thus, we made the final diagnosis of secondary ES coexisting with POEMS syndrome complicated by splenic infarctions.

After 8 weeks of oral prednisolone at the dose of 1mg/kg daily, we initiated a slow tapering until a maintenance daily dose of 10 mg/day. We scheduled 3 cycles of lenalidomide, however due to procurement issues, we opted for monthly cyclophosphamide (CP) 1 g as an alternative.

After 3 boluses of CP, we observed partial clinical improvement mainly of peripheral oedema and with no ES relapse. Nonetheless, the polyneuropathy has not improved. Hence, autologous stem cell transplantation (ASCT) is scheduled to achieve a definitive neurological and haematological response in our patient.

DISCUSSION

POEMS syndrome is frequently associated with thrombocytosis (50%) and to a lesser degree with polyglobulia (15%). Cytopenias are unusual in this syndrome unless Castleman disease is present[2].

Regarding autoimmune cytopenias, we found a unique report describing the association of an AIHA with osteosclerotic myeloma. In this case, the authors have reported the occurrence of an AIHA (positive Coombs test with IgG specificity) during the follow-up of IgA lambda osteosclerotic myeloma with demyelinating polyneuropathy. Although this case did not meet the formal criteria for POEMS syndrome, the term of osteosclerotic myeloma was historically used interchangeably with the acronym POEMS syndrome due to the shared core manifestations mainly the plasma cell proliferative disorder and the osteosclerotic lesions, in addition to the possible evolution of osteosclerotic myeloma into full-blown POEMS syndrome in a subset of patients[3].

Furthermore, we found two case reports of POEMS syndrome associated with ITP. The first report described the occurrence of IgG lambda multiple myeloma (MM) with POEMS syndrome, approximately 3 years after the diagnosis of ITP[4]. The second report described the development of POEMS syndrome 8 months after the diagnosis of ITP. The monoclonal plasma cell proliferative disorder in this case was limited to Bence-Jones proteinuria, kappa type, without detectable M-protein in the serum[5].

ES is a rare cause of autoimmune cytopenia. Non–cross-reacting autoantibodies against antigens specific to red blood cells, platelets, or neutrophils explain the pathophysiology of ES. Though it is usually considered idiopathic (or primary), secondary ES has been noticed to be more severe. Within the group of haematological malignancies, CLL and NHL are the most frequently associated with ES in stark contrast with plasma cell proliferative disorders such as MM or POEMS syndrome.

Indeed, the association of MM with ES is very rare with only a few published cases[1,6].

To the best of our knowledge, there is no reported case in the existing literature of an association of ES with POEMS syndrome. Pro-inflammatory cytokines, such as VEGF and interleukin (IL)-1β and IL-6, play a pivotal role in the pathogenesis of the various manifestations of POEMS syndrome. Thus, the significant aberrations in the microenvironment and cytokine imbalance in POEMS syndrome may lead to the development of autoimmune cytopenias of ES by increasing the activity of antigen presenting cells[3]. In our case, we could not confirm that the M-protein (IgG kappa) was responsible for the haemolysis based on the IgG positivity of the Coombs test (same IgG type). However, this could be a possibility since one study demonstrated that M-protein and the immunoglobulins directed against erythrocytes were of the same type and subtype (IgG1kappa) in a patient with MM and AIHA[6].

The light chain in the M-protein of POEMS syndrome is almost always lambda, nevertheless, in rare, published cases of this disease there was kappa light chain restriction[7]. We could not find a particular shared pattern of these cases (such as clinical manifestations, severity, response to therapies) due to the extreme scarcity of POEMS syndrome with kappa light chain restriction. In such instances, the rigorous exclusion of differential diagnoses is critical. Indeed, despite our patient fully met the diagnostic criteria of Dispenzieri for POEMS syndrome, the atypical features (coexisting ES, kappa light chain restriction, splenic infarctions) led us to perform the histopathological study of nerve biopsy.

The histopathological study not only excluded the main differentials (such as amyloidosis, lymphomatosis, granulomatosis, and vasculitis) but also demonstrated characteristic features of POEMS syndrome-related polyneuropathy. In addition to the expected mixed pattern of demyelination and axonal loss, ultrastructural study revealed UML; a finding considered nearly pathognomonic for the disease. Indeed, typical UML were observed in 19 of 22 patients with POEMS syndrome studied in France and this abnormality affected 1-16% of the myelinated fibres[8].

Moreover, due to the effect of VEGF on nerves, the highly suggestive pattern of increased neovascularization in the epineurium in POEMS was highlighted by some studies. Indeed, the authors of a Mayo clinic study have suggested that more than a cutoff of 120 epineural small vessels (per transversal section of the nerve) is very useful to differentiate POEMS syndrome from chronic inflammatory demyelinating polyradiculoneuropathy[9]. In our case, more than 265 small epineurial blood vessels (per transversal section of the nerve) were revealed, further corroborating the diagnosis through this significant neovascularization pattern.

In POEMS syndrome, patients are at increased risk of arterial and venous thrombosis with an estimated incidence of 30%. Among arterial events, cerebrovascular complications are well-documented, with strokes occurring in approximately 10% of patients. Key risk factors include thrombocytosis, bone marrow plasmacytosis, and aberrations in the coagulation cascade. However, splenic infarction remains an exceptionally rare vascular complication of POEMS syndrome, with only a few cases reported in the literature[2].

Notably, in addition to POEMS syndrome, ES is increasingly recognized as a prothrombotic condition with cases of massive splenic infarction leading to rupture and hemoperitoneum, have been mentioned in the literature[10]. Thus, it is highly plausible that ES contributed to the severity of the splenic infarctions observed in our patient.

While ASCT is considered as the gold standard of care for eligible patients with disseminated forms of POEMS syndrome, this procedure may also represent an effective therapeutic strategy for ES, particularly in cases that are refractory to or intolerant of first-line immunosuppressive therapies[2].

In conclusion, our report reveals that secondary and fulminant ES can coexist with POEMS syndrome, posing significant diagnostic and management challenges.

Of note, the requirement for high-dose corticosteroids and aggressive immunosuppressive therapy to control ES may artificially lower serum VEGF levels. This can create a potential risk of masking a key major diagnostic criterion, thereby leading clinicians to overlook a concomitant diagnosis of POEMS syndrome.

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