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Plexogenic pulmonary hypertension associated with POEMS syndrome

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ABSTRACT

Pulmonary hypertension is one of the well-known clinical manifestations of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, occurring in approximately 25–30% of the affected individuals. However, the histopathologic spectrum of pulmonary hypertension associated with POEMS syndrome has not been fully documented in the literature. Herein, we report an autopsy case of POEMS syndrome in a patient whose lung tissues showed histopathology indistinguishable from that of idiopathic pulmonary arterial hypertension with abundant plexiform lesions in the small pulmonary arteries.

1. Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome associated with an underlying plasma cell disorder [1]. It is important to note that not all of the features within the acronym are required to make the diagnosis of POEMS syndrome. Also, there are other important features not included in the POEMS acronym, such as papilledema, extravascular volume overload, sclerotic bone lesions, thrombocytosis/erythorocytosis, elevated vascular endothelial growth factor (VEGF) levels, a predisposition towards thrombosis, and abnormal pulmonary function test [1].

Pulmonary manifestations of POEMS syndrome are protean and include pulmonary hypertension (PH), which has been reported to occur in 27% of unselected patient with POEMS syndrome [2]. VEGF has been reported as the causative factor for PH in POEMS syndrome [3]. This study did not describe the histopathology of PH in their case, however. Since VEGF has been implicated in the formation of plexiform lesions, one can postulate that PH in POEMS syndrome might also have plexiform lesions, one of the most complex types of vascular remodeling invariably associated with severe PH seen in idiopathic and only certain secondary forms of PH [4].

Herein, we report an autopsy case of PH associated with POEMS syndrome showing plexogenic disease, which has not been well documented in the literature.

2. Report of a case

A 56-year-old woman presented with weight loss in December, 2014. Subsequent clinical evaluation revealed an elevated serum creatinine at 2.8 mg/dL (normal range 0.6–1.1). She underwent two renal biopsies in May and October of 2015, both of which were diagnosed as thrombotic microangiopathy. In December, 2015, a monoclonal gammopathy of IgG lambda was detected in her serum, and positron emission tomography (PET) scan revealed a lesion in the left sacrum. The left sacral biopsy was diagnosed as plasmacytoma, lambda light chain restricted, for which she received a radiation therapy during a period from February to March of 2016.

Two weeks after completing radiation therapy, she developed painful skin ulcerations on thighs, abdomen, and breasts, accompanied by retinal hemorrhage, acute renal failure and shortness of breath. PET scan showed persistent sacral plasmacytoma. She also developed bilateral pleural effusions, which were drained. Post-procedural chest x-ray showed clear lung fields without evidence of pulmonary edema. Serum pro-beta-natriuretic peptide was markedly elevated (>60,000 pg/mL; normal <162 pg/mL).

Transthoracic echocardiogram was obtained and was notable for a left ejection fraction of 26% and severe tricuspid valve regurgitation secondary to annular dilatation and incomplete coaptation of the valve leaflets. Mild to moderate mitral valve regurgitation was noted as well. There was mild biventricular enlargement, and moderate decrease in right ventricular systolic function. Estimated

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right ventricle pressure was 37 mmHg, which was thought to be underestimated. Right heart catheterization was not performed due to her clinical condition.

The patient was evaluated by a multidisciplinary team including hematology, dermatology, ophthalmology, cardiology, nonvascular wound, nephrology, and palliative care. The consensus diagnosis of POEMS syndrome was made based on her clinical findings and also supported by the elevated serum VEGF level (697 pg/mL; normal range 31–86), elevated parathyroid hormone (315 pg/mL; normal range 15–65), elevated corticotropin, and multiple serum electrolyte abnormalities. She also had hypocalcemia in the setting of calciphylaxis with painful indurated ischemic plaques on the breast, abdomen, groin and thighs. She developed new onset of biventricular heart failure with severe tricuspid regurgitation. Given the poor prognosis, she was transitioned to comfort care and died in June 2016.

Postmortem examination was limited to the chest and abdomen. At autopsy, the heart showed mild to moderate biventricular myocardial hypertrophy (heart 533 g, expected 248 g) with organizing fibrinous pericarditis. Hepatomegaly (2480 g; expected 1433 g) and splenomegaly (520 g; expected 143 g) were present with serous ascites (800 mL) in the abdomen.

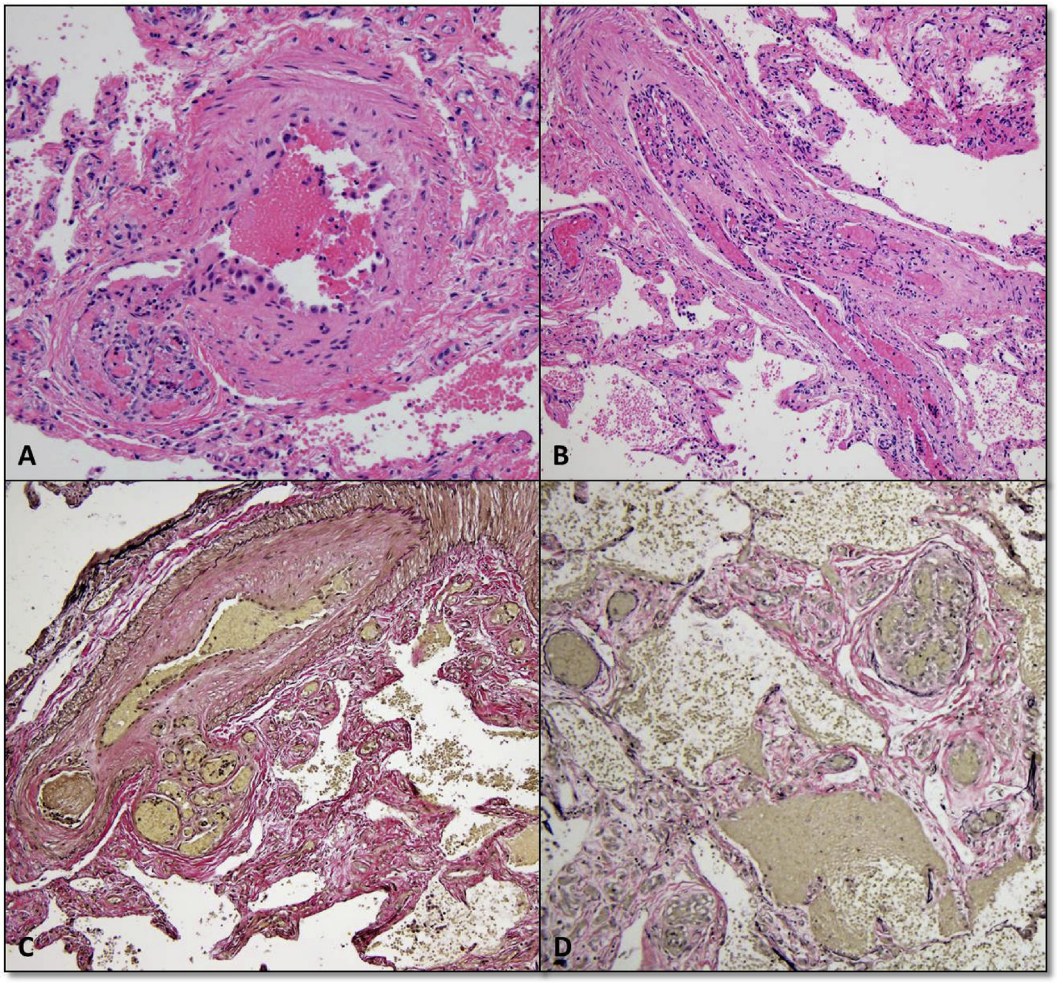

Fig. 1. Hematoxalin and eosin stains of plexiform lesions and recanalizing thrombi (A and B, respectively). *Verhoeff–Van Gieson stain highlights these lesions (C and D).*

Table 1
Diagnostic criteria for POEMS syndrome.

Mandatory major criteria	1. Polyneuropathy 2. Monoclonal plasma cell-proliferative disorder
Other major criteria	1. Castleman disease 2. Sclerotic bone lesions 3. VEGF elevation
Minor criteria	1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 2. Extravascular volume overload (edema, pleural effusion, or ascites) 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic) 4. Skin changes (hyperpigmentation,hypertrichosis, glomeruloid hemangiomata,plethora, acrocyanosis, flushing) 5. Papilledema 6. Thrombocytosis/polycythemia
Other symptoms and signs	Weight loss, hyperhidrosis, pulmonary hypertension, thrombotic diathesis, diarrhea

On microscopic examination of the lungs, the airways were unremarkable and the alveolar architecture was well preserved without significant interstitial fibrosis or inflammatory infiltrate. The small muscular pulmonary arteries showed multiple plexiform lesions (Fig. 1). Some small pulmonary arteries contained organizing thrombus. There was no significant alveolar hemosiderosis or pulmonary venous/venular occlusion on hematoxylin and eosin and Verhoeff-Van Giesen stainings. No significant alveolar capillary engorgement or pulmonary capillary hemangiomatosis-like reaction was noted.

The overall pulmonary vascular findings were consistent with pre-capillary hypertensive pulmonary vascular disease of plexogenic type, occurring in a background of otherwise unremarkable lung tissue, except for superimposed acute pneumonia in the lower lobes.

Of note, there was zone 3 congestion and hepatocyte necrosis in the liver, in keeping with the presence of severe PH. No evidence of plasmacytoma was identified either in the lung or any other organ.

3. Discussion

We report a case of PH in a patient who had characteristic clinical and laboratory features of POEMS syndrome. Postmortem examination of the lung showed many plexiform lesions, indicative of the plexogenic form of pulmonary arterial hypertension. It is of note that plexogenic disease has the same histopathologic appearance regardless of whether it is of idiopathic or secondary type. Although the patient also had a left heart failure, no features of secondary pulmonary venous hypertension were found on the lung sections.

The precise mechanism of development for plexiform lesion is not fully understood. Plexiform lesions are best known in idiopathic pulmonary arterial hypertension (formerly primary pulmonary hypertension) but can be seen in several types of secondary PH such as congenital heart disease with high volume left to right shunt, human immunodeficiency virus infection, liver disease and some collagen vascular diseases.

POEMS syndrome is a rare disease characterized by mandatory, major, and minor criteria (Table 1). The diagnosis is made when both mandatory, one major, and one minor criteria are met. Individuals with POEMS syndrome are at risk of developing PH, with a prevalence of 27–36% [1,2]. Those who have PH have poorer overall survival, with a median survival of 54 months in one study and hazard ratio of 3.99 in another [1,5]. Development of pleural effusion is also deleterious [5]. PH improved with treatment of the underlying plasma cell disorder in 88% of individuals undergoing either medical therapy including melphalan and steroids or autologous transplant [1,6]. Melphalan based treatment is superior to steroids alone. Improved pulmonary function and right ventricular pressure after radiation treatment for plasmacytoma has been reported [7].

Elevated serum VEGF is common in POEMS syndrome. VEGF increases microvascular permeability leading to volume overload, stimulates endothelial proliferation, induces endothelial dysfunction and activates vascular smooth muscle [8–11]. VEGF is strongly expressed in plexiform lesions in primary and secondary PH [12–14]. VEGF also plays a role in the development of renal thrombotic microangiopathy, a form of vascular remodeling, which was found on the premortem renal biopsies as well as on the postmortem examination of the kidney tissues.

To our knowledge, a single case report describes pulmonary findings in an autopsy performed on a 49-year-old woman who died of complications of pulmonary hypertension in the setting of POEMS syndrome [15]. A prominent plasmacytic infiltrate was present within vessels causing stenosis, and in some vessels recanalization. No plexogenic arteriopathy, or thrombi were noted in contrast to this case.

4. Conclusion

In summary, we documented the presence of well-developed plexiform lesions in PH associated with POEMS syndrome that has not been well illustrated in the literature to our knowledge. Elevated VEGF level might be related with the development of plexiform lesions in POEMS syndrome.

References

[1] A. Dispenzieri, POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management, Am. J. Hematol. 89 (2) (2014 Feb) 214–223.
[2] J. Li, Z. Tian, H.Y. Zheng, et al., Pulmonary hypertension in POEMS syndrome, Haematologica 98 (3) (2013 Mar) 393–398.
[3] H. Niimi, K. Arimura, M. Jonosono, et al., VEGF is causative for pulmonary hypertension in a patient with Crow-Fukase (POEMS) syndrome, Intern Med. 39 (12) (2000 Dec) 1101–1104.
[4] N.F. Voelkel, R.W. Vandivier, R.M. Tuder, et al., Vascular endothelial growth factor in the lung, Am. J. Physiol. Lung Cell. Mol. Physiol. 290 (2) (2006 Feb) L209–L221.
[5] C. Wang, X.F. Huang, Q.Q. Cai, et al., Prognostic study for overall survival in patients with newly diagnosed POEMS syndrome, Leukemia (2016 Jun 24), http://dx.doi.org/10.1038/leu.2016.168.
[6] S. Chandrashekaran, A. Dispenzieri, S.S. Cha, et al., Pulmonary morbidity improves after autologous stem cell transplantation in POEMS syndrome, Respir. Med. 109 (1) (2015 Jan) 122–130.
[7] M.J. Brewis, A.C. Church, A.J. Peacock, et al., Pulmonary hypertension in POEMS syndrome: resolution following radiotherapy, Pulm. Circ. 4 (4) (2014 Dec) 732–735.
[8] O. Watanabe, K. Arimura, I. Kitajima, et al., Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome, Lancet 347 (9002) (1996) 702.
[9] O. Watanabe, I. Maruyama, K. Arimura, et al., Overproduction of vascular endothelial growth is causative in Crow-Fukase (POEMS) syndrome, Muscle Nerve 21 (11) (1998) 1390–1397.
[10] M. Soubrier, C. Sauron, B. Souweine, et al., Growth factors and proinflammatory cytokines in the renal involvement of POEMS syndrome, Am. J. Kidney Dis. 34 (4) (1999) 633–638.
[11] M. Scarlato, S.C. Previtali, M. Carpo, et al., Polyneuropathy in POEMS syndrome: role of angiogenic factors in the pathogenesis, Brain 128 (Pt8) (2005) 1911–1920.
[12] R. Geiger, R.M. Berger, J. Hess, et al., Enhanced expression of vascular endothelial growth factor in pulmonary plexogenic arteriopathy due to congenital heart disease, J. Pathol. 191 (2) (2000 Jun) 202–207.
[13] S. Hirose, Y. Hosoda, S. Furuya, et al., Expression of vascular endothelial growth factor and its receptors correlates closely with formation of the plexiform lesion in human pulmonary hypertension, Pathol. Int. 50 (6) (2000 Jun) 472–479.
[14] R.M. Tuder, M. Chacon, L. Alger, et al., Expression of angiogenesis-related molecules in plexiform lesions in severe pulmonary hypertension: evidence for a process of disordered angiogenesis, J. Pathol. 195 (3) (2001 Oct) 367–374.
[15] C. Katsuya, F. Yasunori, Severe pulmonary hypertension caused by smoldering plasma cell myeloma: an autopsy case of POEMS syndrome, Case Rep. Med. (2012 Nov), http://dx.doi.org/10.1155/2012/836893.