POEMS Syndrome with Venous Sinus Thrombosis and Visual Failure: A Case Report

Rawiphan Witoonpanich, MD, FRCP*,
Sriphan Phankhian, MD*, Saengsuree Jootar, MD*,
Anuchit Poonyathalang, MD**, Surapon Worapongpaiboon, MD***,
Suchart Phudhichareonrat, MD, FRCPC***, Niramol Chanplakorn, MD***

** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*
*** Department of Ophthalmology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*
**** Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*

POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome is a multisystem disorder associated with plasma cell dyscrasia. Other clinical signs include clubbing of the fingers, edema, papilledema etc. Although papilledema and increased intracranial pressure are common features, their causes or pathophysiology have been uncertain. The authors report here a 16-year-old Thai patient with these features who also suffered from venous sinus thrombosis and visual failure which have never been reported before. The former is considered to be one of the possible causes of the intracranial hypertension and visual failure. MRI of the brain and optic nerve revealed enhancement and swelling of the optic nerve sheaths and optic discs. MRV findings were compatible with chronic veno-occlusive disease. Bone marrow aspiration and biopsy demonstrated an increase of aggregates of intermediate and mature plasma cells. The CSF pressure was markedly elevated. His clinical condition continued to deteriorate and he expired 3 years and 5 months from the onset of his illness. Although, overproduction of vascular endothelial growth factor has been reported and is being considered to be the possible cause of vascular hyperpermeability, the chronic venous sinus thrombosis may play an important role in the pathogenesis of intracranial hypertension and visual failure.

Keywords: *POEMS, Venous sinus thrombosis, Visual failure*

J Med Assoc Thai 2005; 88(5): 690-4
Full text. e-Journal: *http://www.medassocthai.org/journal*

POEMS syndrome is a multisystem disorder which is usually associated with plasma cell dyscrasia and the combination of polyneuropathy, organomegaly, endocrinopathy, M protein (mainly IgG or IgA with a lambda light chain), skin changes (hyperpigmentation, skin thickening and hypertrichosis) and other clinical signs such as clubbing of the fingers, edema, cachexia, fever, telangiectasia, and papilledema[1-6]. Although papilledema and increased intracranial pressure are common features, their causes or pathophysiology have been uncertain. The authors report here a patient with these features who suffered from venous sinus thrombosis and visual failure which have never been reported before.

Correspondence to : Witoonpanich R, Division of Neurology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Rama 6 Rd, Bangkok 10400, Thailand. Phone & Fax: 0-2201-1386, E-mail: rarwt@mahidol.ac.th

Case Report

A 16-year-old Thai young man who initially presented in 1997 with a one month history of distal weakness of both lower limbs and foot drop with occasional headache. On examination, he had bilateral papilledema, predominantly distal weakness of the lower limbs and areflexia. Lumbar puncture was performed with open pressure of 29 cm of water. The CSF was clear with protein of 124 mg/dl, normal cell count and glucose level. Nerve conduction study showed marked slowing of motor conduction velocities in the upper extremities and absence of compound muscle action potentials (CMAP) in the lower extremi-

ties with small sensory potentials in all the nerves tested. He was diagnosed as chronic inflammatory demyelinating polyneuropathy and was treated with prednisolone and intravenous immunoglobulin. His muscle power was only slightly improved after treatment.

Two years later, the polyneuropathy ascended to involve proximal legs and upper extremities both proximally and distally. He was treated with pulse methylprednisolone and oral prednisolone with slight improvement. One year later, the weakness of the upper and lower extremities became worse. At that time, he had severe bilateral papilledema, progressive visual impairment, hyperpigmentation, skin thickening, clubbing of the fingers, white nails, acrocyanosis, lymphadenopathy, hepatosplenomegaly, ascites and peripheral edema. He also suffered from diarrhea off and on with negative stool culture.

Laboratory findings: Hematocrit 34%, WBC 14,000 cell/cumm, N 65%, L24%, M 8%, platelet 59,000/cumm, ESR 34 mm/hr, serum total protein 72 mg/dl (N 64-82), albumin 33.8 mg/dl (N 43.1-53.3), BUN 9 mg/dl, creatinine 0.8 mg/dl, calcium 8.3 mg/dl, phosphate 4.3 mg/dl, PTT 52.2 sec, PT 18 sec (49%), TT 8.9 sec, INR 1.62, TSH 7.2 ug/dl (N 0.4-4.0), FT4 0.9 ug/dl (N 1.0-2.8), T3 < 40 ng/dl (N 90-250), serum testosterone < 0.2 pg/ml (N 2.1-17.3), LH 16.6 mIU/ml (N 1.2-8.6), FSH 24.6 mIU/ml (N 1.3-1.9), prolactin 34.5 ng/ml (N 2.6-13.1), estradiol 29.5 pg/ml (N 2.6-13), cortisol (am., on steroid) 5.9 ug/dl (N 5-25), protein electrophoresis normal, immunoelectrophoresis normal pattern, IgG 23.1 mg/ml (N 6.94-16.18), IgA 3.50 (N 0.68-3.78), IgM 1.46 (N 0.60-2.63), ANA profile negative, anticardiolipin IgM, IgG negative, lupus anticoagulant negative, protein C 59% (N 64-141), protein S 109% (N 61-127), antithrombin III 69% (N 80-128), homocysteine 25.27 umol/l (N 5-15), CSF open pressure 47 cm H_2O, cell 0, protein 70 mg/dl, sugar 80 mg/dl (blood sugar 182), gammaglobulin 20% (N < 10) of total protein.

Roentgenographic bone survey revealed two osteosclerotic lesions in the left proximal femur and left acetabulum. Bone scan was normal. Chest x-ray showed interstitial infiltration. Magnetic resonance image (MRI) of the brain and optic nerve revealed diffuse mild cortical atrophy, enhancement and swelling of optic nerve sheaths and optic discs bilaterally. There was also enhancement and thickening of medial and lateral rectus muscles on both sides with enhancement of the sclera and subcutaneous soft tissue of both orbits. Magnetic resonance venogram (MRV) showed marked irregularity of the right transverse sinus and occlusion of the left transverse sinus. There was also irregular filling defect in the distal part of the superior sagittal sinus and proximal part of the straight sinus with multiple collateral vessels compatible with chronic veno-occlusive disease (Fig. 1). Bone marrow aspiration and biopsy demonstrated an increase of aggregates of intermediate and mature plasma cells. Nerve conduction study showed delayed distal motor latencies, small CMAP, markedly slow motor conduction velocities and prolonged F-wave latencies of median and ulnar nerves bilaterally. CMAP could not be evoked on stimulating tibial and peroneal nerves and sensory action potentials of median, ulnar and sural nerves were absent on both sides. EMG was compatible with neurogenic lesion. Echochardiogram showed slightly reduced left ventricular systolic function with left ventricular enlargement.

Intravenous immunoglobulin (IVIg) was administered without any improvement. As regards his visual function, his visual acuity had never been recorded but his vision became progressively worse from normal activity (being independent on visual task) to hand movement bilaterally in 4 months. Optic nerve sheath fenestration was tried hoping to reduce pressure on the optic nerves but was not successful due to oculocardiac reflex resulting in marked

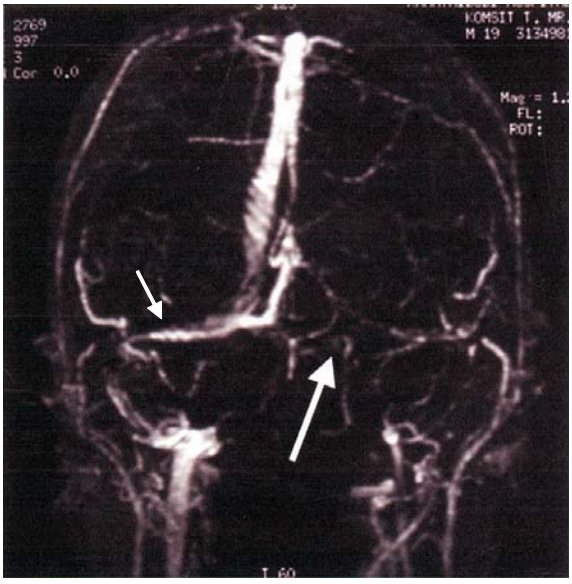

Fig. 1 MRV of the brain showing marked irregular filling defect in the right transverse sinus (short arrow) and occlusion of the left transverse sinus (long arrow) with multiple collateral vessels compatible with chronic veno-occlusive disease

bradycardia and systemic hypotension. Optic nerve sheath was noted to be markedly distended during the operation. He was also treated with a 4-day course of melphalan and prednisolone. Two weeks after treatment, there was slight and transient improvement of his vision, power of muscles of the extremities and transient cessation of diarrhea. However, the weakness in the lower extremities and visual impairment remained quite marked. Unfortunately, the white blood count dropped shortly after the chemotherapy and he suffered from pneumonia which was successfully treated. Anticoagulant was also tried over a short time for venous sinus occlusion in the brain but evaluation of response was impossible due to the short period of administration. Subsequently, his clinical status including his vision continued to deteriorate. His diarrhea persisted and the abdomen became more and more distended but peritoneocentesis failed to obtain any fluid. He was generally weak with progressive decrease in overall muscle power. He was also dyspneic from time to time from pulmonary congestion and had never been well enough to receive another course of chemotherapy. He eventually expired after 3 years and 5 months from the onset of his illness.

At autopsy, extensive studies of peripheral nerves (median, ulnar, sural and femoral nerves) were carried out. The light and electron microscopic examination of these nerves revealed inappropriate thickness of myelin sheaths compared to their axonal diameters, consistent with demyelinating neuropathy. The sections from the right and the left optic nerves demonstrated an increase in glial cells with interstitial and cellular edema. The left optic nerve also showed thickening of arachnoid mater with decreased subarachnoid space. Subdural hemorrhage was found at the left frontoparietal area. The superior sagittal sinus, right and left transverse sinuses did not exhibit thrombus in their lumens. However, hypoxic-ischemic injury with eosinophilic neuronal change of the cerebrum, hippocampal areas and cerebellum was detected.

Both lungs showed diffuse alveolar damage with hyaline membrane formation, interstitial pneumonitis, pulmonary hypertensive change of intra-acinar arterioles and small arteries and chronic adhesive pleuritis. Both testes were atrophic with focal immature spermatogenesis. The skin showed increased basal pigmented keratinocytes with periadnexal lymphocytic infiltration. The bone marrow from the sternum and vertebrae were unremarkable but those from the greater trochanter of the left femur revealed osteosclerotic change of the trabeculae with an increased number of mature plasma cells (approximately 20%). The immunohistochemical study of these plasma cells revealed reactivity to only lambda light chain but not with kappa light chain. Gross and microscopic study of the thyroid gland, parathyroid glands and pituitary gland was unremarkable. The adrenal glands showed generalized cortical hypoplasia with lipid depletion.

Discussion

POEMS syndrome is usually associated with underlying plasma cell dyscrasia and/or extramedullary plasmacytoma (most commonly osteosclerotic bone lesion). The most consistent and earliest feature is predominantly motor or sensorimotor polyneuropathy which usually precedes the development of other clinical features and the discovery of the paraproteinemic state. Monoclonal gammopathy was demonstrable in the majority of the cases provided that immunofixation was done[7]. The presented patient had all the typical features of POEMS syndrome except for the M-protein which was not detected by immunoelectrophoresis and immunofixation was not performed.

To our knowledge, the presented patient is the youngest to be reported. In two large series by Nakanishi et al and Dispenzieri et al, their youngest patient was 27 and 30 years respectively[1,7]. The presented patient initially presented with predominantly motor polyneuropathy in the form of bilateral foot drop. The only other physical sign was bilateral papilledema. Nerve conduction study (NCS) showed changes consistent with mixed axonal and demyelinating process. At that time, a diagnosis of chronic inflammatory demyelinating polyneuropathy was made although he was not a typical case in view of the NCS and the fact that only the lower extremities were affected. The CSF pressure and protein were slightly elevated. It took some time for the full syndrome to develop. Therefore, the authors would agree with Dispenzieri et al that this syndrome should be suspected or diagnosed in a patient with polyneuropathy and monoclonal plasmaproliferative disorder plus one other feature well known in this syndrome[7]. Early detection should lead to early initiation of treatment with probably better outcome. In the case of absence of monoclonal protein (with or without immunofixation), the authors had to rely on the clusters of the familiar clinical features and the osteosclerotic bone lesion detected by bone survey.

One of the striking features in the presented case is the increased intracranial pressure resulting in severe papilledema and progressive visual failure. Pseudotumor cerebri with raised CSF protein and papilledema were reported in about 60-90% of the patients[1,2]. However, visual failure has never been mentioned or documented. The causation of intracranial hypertension, papilledema and visual failure may be multifactorial. Overproduction of vascular endothelial growth factor (VEGF) has been reported by several investigators and is being considered to be the possible cause of vascular hyperpermeability[8-10]. Hyperpermeability of cerebral vascular endothelium may lead to increased intracranial pressure as well as pressure in the optic nerve sheath as observed during the operation. The pathological finding of interstitial and cellular edema of the optic nerves is interesting and might be related to hyperpermeability. Another interesting and less- recognized feature is the venous sinus thrombosis which was demonstrated in the MRV together with decreased protein C and antithrombin III and increased homocysteine level in the presented patient. These may play an important role in the pathogenesis of intracranial hypertension and visual failure. The cerebral venous sinus thrombosis has never been reported before although arterial obliteration has been documented[11,12]. Anticoagulant could be given just briefly to the presented patient in view of various intervention and for fear of the bleeding diathesis. Therefore, the effect of it could not be evaluated.

Treatment for patients with this syndrome has not been successful to date because of the uncertainty of pathogenesis. Many regimens of chemeotherapy have been tried with only transient improvement and most patients eventually died. Local radiation for a solitary lesion or resection of an extramedullay plasmacytoma resulted in the same outcome[1]. A recent report showed that radiation to an isolated plasmacytoma was effective in stabilizing or improving the systemic features and neuropathy in at least half of the patients[7]. For chemotherapy, melphalan and prednisolone appear to be the most often used combination yet clinical response occurred in only 22-56% of the patients[7]. If this combination fails, other regimens may have to be tried. Cyclosporine and azathioprine were ineffective if given alone without combining with prednisolone. Plasmapheresis and intravenous immunoglobulin were also ineffective[7]. High dose chemotherapy with autologous stem cell transplantation has been reported with dramatic improvement[7,13]. However, this means of treatment can only be given to patients with good general condition and in specialized units.

References

1. Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E**,** et al. The Crow-Fukase syndrome: A study of 102 cases in Japan. Neurology 1984; 34: 712-20.
2. Bardwick PA, Zvaiffler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes: the POEMS syndrome. Report of two cases and a review of the literature. Medicine (Baltimore) 1980; 559: 311-22.
3. Witoonpanich R, Jootar S, Vejjajiva A, Chuahirun S, Nitiyanant P. The POEMS (Crow-Fukase) syndrome: a case report. J Med Assoc Thai 1988; 71: 406-11.
4. Miralles GD, O'Fallon JR, Tally NJ. Plasma-cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. N Engl J Med 1992; 327: 1919-23.
5. Intragumtornchai T, Phanthumchinda K, Lerdlum S, Sumpathanukul P, Sakulramrung R. POEMS syndrome: a case with proliferative vasculopathy and a review of cases in Thailand. J Med Assoc Thai 1993; 76: 585-90.
6. Gherardi RK, Belec L, Soubrier M, Malapert D, Zuber M, Viard JP, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood 1996; 87: 1458-65.
7. Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR**,** et al. POEMS syndrome: definitions and long-term outcome. Blood 2003; 101: 2496-506.
8. Watanabe O, Arimura K, Kitajima I, Osane M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet 1996; 347: 702.
9. Soubrier M, Dubost JJ, Serre AF, Ristori JM, Sauvezie B, Cathebras P, et al. Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. Arthritis Rheum 1997; 40: 786-7.
10. Watanabe O, Maruyama I, Arimura K, Kitajima I, Arimura H, Hanatani M, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve 1998; 21: 1390-7.
11. Lesprit P, Authie FJ, Gherardi R, Belec L, Paris D, Melliere D, et al. Acute arterial obliteration. A new feature of the POEMS syndrome? Medicine (Baltimore) 1996; 75: 226-32.
12. Soubrier M, Guillon R, Dubost JJ, Serre AF, Ristori JM, Boyer L, et al. Arterial obliteration in POEMS syndrome: possible role of vascular endothelial growth

factor. J Rheumatol 1998; 25: 813-5.
13. Hogan WJ, Lacy MQ, Wiseman GA, Fealey RD, Dispenzieri A, Gertz MA. Successful treatment of POEMS syndrome with autologous hematopoietic progenitor cell transplantation. Bone Marrow Transplantation 2001; 28: 305-9.

ภาวะหลอดเลือดดำในสมองอุดตันและตาบอดในผู้ป่วยกลุ่มอาการโพเอมส์: รายงานผู้ป่วย 1 ราย

รวิพรรณ วิทูรพณิชย์, ศรีพรรณ พันธุ์เขียน, แสงสุรีย์ จูฑา, อนุชิต ปุญญทลังค์, สุรพล วรพงษ์ไพบูลย์, สุชาติ พุทธิเจริญรัตน์, นิรมล ฉันพลากร

กลุ่มอาการโพเอมส์เป็นภาวะที่เกิดร่วมกับความผิดปกติของเซลล์พลาสมา ผู้ป่วยมีอาการของปลายประสาทผิดปกติ ตับม้ามโต ความผิดปกติของต่อมไร้ท่อ การเปลี่ยนแปลงของผิวหนังและมีโมโนโคลนัลโปรตีน นอกจากนี้ยังมีอาการบวมตามตัว แขนขาและที่ประสาทตา อาการหลังร่วมกับความดันสูงในสมองพบได้บ่อยแต่พยาธิสรีรวิทยายังไม่เป็นที่ทราบแน่ ได้รายงานผู้ป่วยภาวะนี้ 1 รายซึ่งมีภาวะหลอดเลือดดำในสมองอุดตัน และตาบอดซึ่งไม่เคยมีการรายงานมาก่อน เชื่อว่าภาวะหลอดเลือดดำอุดตันนี้น่าจะเป็นสาเหตุหนึ่งของความดันสูงในสมอง การตรวจสมองด้วยคลื่นแม่เหล็กพบว่าประสาทตาบวมและการตรวจหลอดเลือดดำด้วยการฉีดสีและคลื่นแม่เหล็กพบการอุดตันของโพรงหลอดเลือดดำบางจุด ไขกระดูกมีเซลล์พลาสมาตัวอ่อน ปานกลางเพิ่มมากกว่าปกติ ความดันน้ำไขสันหลังสูง อาการของผู้ป่วยทรุดลงเรื่อย ๆ และผู้ป่วยเสียชีวิต 3 ปี 5 เดือนหลังจากเริ่มมีอาการ แม้ว่าปัจจัยที่ทำให้เอนโดทีเลียมของหลอดเลือดเพิ่มมากขึ้นอาจเป็นสาเหตุของการซึมมากผิดปกติของผนังหลอดเลือด ภาวะหลอดเลือดดำอุดตันน่าจะเป็นสาเหตุหนึ่งที่ทำให้ความดันสูงในสมองและตาบอด