

A Case of Combined POEMS Syndrome and Multiple Myeloma with Positive M protein Only on Immunofixation

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POEMS syndrome is a plasma cell proliferative disorder is characterized by the presence of peripheral neuropathy (P), organomegaly (O), monoclonal gammopathy (M), endocrinopathy or edema (E) and skin change (S). It can be rarely related to multiple myeloma. A 48-year-old man was admitted to our hospital due to paresthesia of both inguinal areas and weakness of both lower extremities. He had a history of Castleman's disease, and showed features of polyneuropathy, multiple osteoblastic lesions, hepatosplenomegaly, pretibial pitting edema, and papilledema. The serum and urine electrophoresis were negative, but urine immunofixation could detect monoclonal protein. Plasmacytoma was confirmed through the biopsy for the osteoblastic lesions. We present a case of combined POEMS syndrome and multiple myeloma with positive M protein only on immunofixation in order to share our experience with physicians and specialists. (*Korean J Hematol* 2008;43:253-257.)

Key Words: POEMS syndrome, Multiple myeloma, Osteoblastic lesion

INTRODUCTION

POEMS syndrome is a paraneoplastic syndrome associated with plasma cell disorder and consists of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin change.⁵⁾ It is one of the conditions that can be related to multiple myeloma, other conditions can also be associated such as radiculopathy and peripheral neuropathy.¹⁾

We have experienced a case of POEMS syndrome and multiple myeloma with minimally detected M-protein only in urine immunofixation. We report a case to share our experience in diagnosis and management with our colleagues.

CASE REPORT

A 48-year-old man was admitted because of paresthesia of both inguinal areas and a burning sensation and weakness of both lower extremities on 13 September 2003. He was diagnosed as Castleman's disease a month before admission at different hospital without any medication history. He appeared alert. The body temperature was 37°C, the pulse was regular at 85 beats per minute, and the respiratory rate was 18 breaths per minute. The blood pressure was 130/76mmHg. On physical examination, bilateral pretibial pitting edema and ascites were present. Enlarged, non-tender lymph nodes were palpated in the

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neck, both axillae, and the inguinal area. Papilledema was also present. The patient reported a 10kg weight loss over one month and complained of impotence.

A complete blood count showed white blood cells (WBC) of $7,700/\text{mm}^3$, hemoglobin of 12g/dL , mean corpuscular volume of 35% , and platelet counts of $207,000/\text{mm}^3$. The PT/aPTT levels were within normal limits, and the peripheral blood smear showed no significant abnormalities. The serum uric acid level was 4.5mg/dL , the serum calcium level was decreased to 7.7mg/dL , and the blood urea nitrogen and creatinine levels were increased to 40.8mg/dL and 1.7mg/dL respectively. The serum total protein and albumin were 6.0 g/dl and 3.3g/dL , respectively, and AST, ALT, alkaline phosphatase levels were 14IU/L , 11IU/L , and 176IU/L , respectively. The serum LDH was 247IU/L , the glucose level was increased to $1,296\text{ mg/dL}$ with HbA1C of 10.3% . Serum electrolytes showed sodium of 126mEq/L , potassium of 5.4 mEq/L , and chloride of 93mEq/L . Thyroid function test showed T3 of 33.6ng/dL (n: $60\sim 181$), TSH of 0.76uIU/mL (n: $0.35\sim 5.5$) and free T4 of 0.78ng/dL (n: $0.89\sim 1.76$), may implicating hypothyroidism or nonthyroidal illness. A 24-hour urine protein was 300.3g/day . A serum β_2 -microglobulin was elevated to 6.2ug/mL , but there was no detectable M peak in serum and urine nor Bence-Jones proteinuria in protein electrophoresis. A serum immunofixation test showed no ab-

normal findings, but lambda chain proteinuria was detected by immunofixation of urine protein. A chest radiograph showed atelectasis of both lower lungs but no pleural effusions. An abdominal CT scan showed multiple osteoblastic lesions at pelvis, sacrum, spines and hepatosplenomegaly. A bone scan showed an uptake at right sacroiliac joint. A nerve conduction velocity showed the finding of a neuromotor polyneuropathy with demyelination. We performed a pelvic MRI (Fig. 1) to confirm multiple osteoblastic lesions which were showed in the ilium on an abdominal X-ray film. An iliac bone biopsy showed sheets of plasma cells filling marrow spaces. The morphology of these plasma cells was not highly anaplastic, but they did destroy regional bone tissue. The immunohistochemical stain for immunoglobulin chains showed positive reaction for lambda light chains (Fig. 2).

Therefore, the patient was satisfied the diagnostic criteria for POEMS syndrome, and multiple myeloma, stage IIIA according to Durie-Salmon stage. We started chemotherapy with cyclophosphamide and prednisolon from 26 September and showed 1% of plasma cells from bone marrow aspiration after the second cycle of chemotherapy. He was admitted to hospital again with refractory ascites and diagnosed as the end-stage renal disease on 16 November, and then recieved hemodialysis. During the treatment, serum β_2 -microglobulin was not checked and serum albumin was decreased from 3.3g/dL

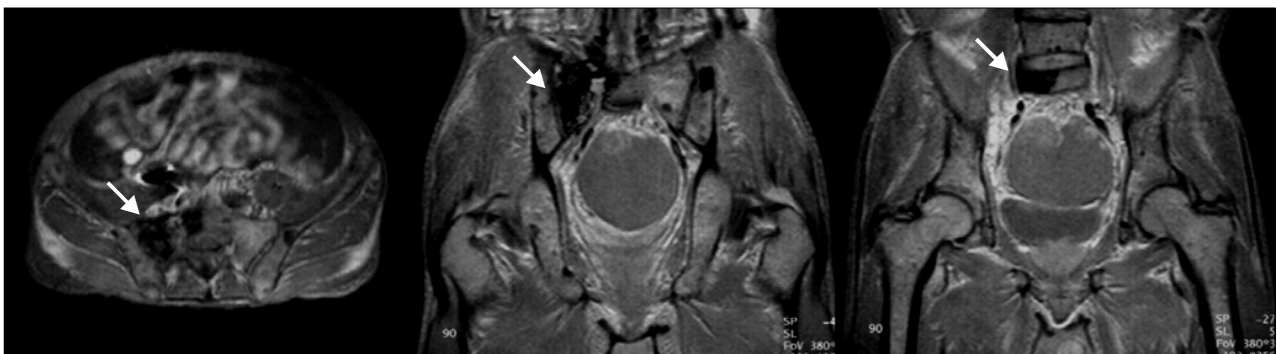


Fig. 1. Pelvic MRI showed multifocal osteoblastic lesions at pelvic bone, sacrum, and L5 (white arrows).

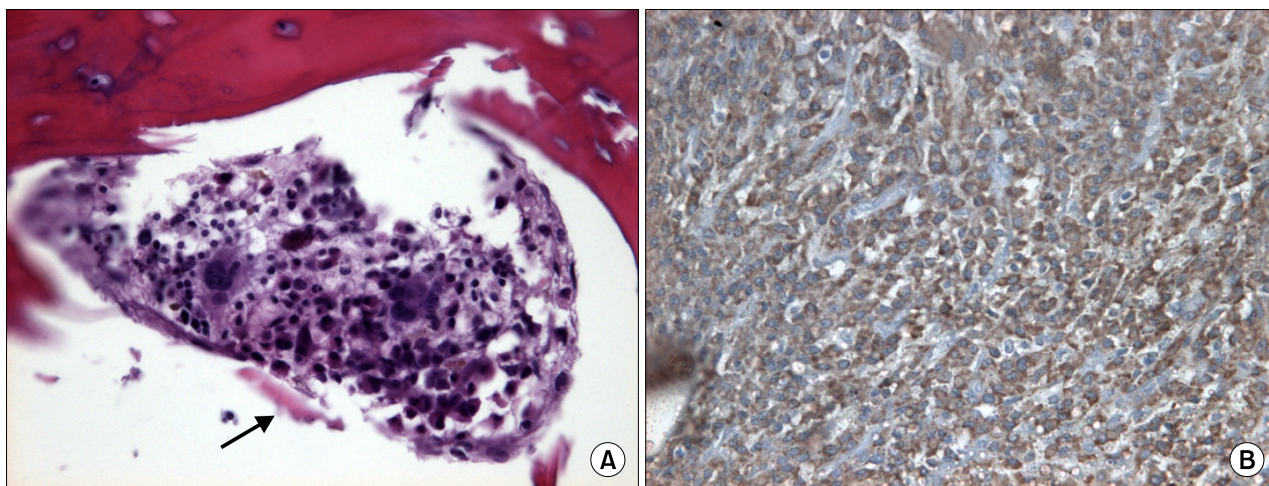


Fig. 2. Eccentrically placed nuclei of neoplastic plasma cells with basophilic cytoplasm and a sequester (black arrow) (Bone biopsy, H&E stain, $\times 400$, A) and positive staining for λ chain ($\times 400$, B).

to 2.7g/dL since hemodialysis. The patient completed the 6th cycle of chemotherapy on 10 February 2004 and one month later, hemodialysis should be discontinued due to hypotension. As a consequence, the patient died due to his poor general condition, uremic encephalopathy, pneumonia complicated with septic shock on 18 March 2004.

DISCUSSION

This is a case of POEMS syndrome with multiple myeloma whose M protein was detected only in urine immunofixation. The pathogenesis of POEMS syndrome is very complex, through hyperestrogenemia,²⁾ and HHV-8³⁾ infection have been hypothesized to contribute to its pathogenesis. Furthermore, the coagulation pathway and its relationship to VEGF,⁴⁾ have been projected to play a role. Unfortunately in this case, serum VEGF was not checked. For a diagnosis of POEMS, polyneuropathy and a monoclonal plasma cell disorder should be present, in addition to at least one other major criterion and one minor criterion.⁵⁾ In order to diagnose multiple myeloma, at least 10% of plasma cells from a bone marrow aspiration or M-protein more than 3g/dL should be detected. But any percentage of

plasma cells in bone marrow or M protein can be allowed to the diagnosis of multiple myeloma if related organ or tissue injury was documented.⁶⁾ In this case, the patient had the features of polyneuropathy, hepatosplenomegaly, pretibial pitting edema, newly diagnosed diabetes mellitus, papilledema and a history of Castleman's disease, and there were osteoblastic bone lesions which was proven as plasmacytoma. Initially we thought of non-secretory multiple myeloma (NSMM) with POEMS syndrome, because of the absence of urine and serum M-protein in electrophoresis until urine immunofixation detected minimal M-protein. Therefore we were able to make a diagnosis of POEMS syndrome with multiple myeloma whose M protein detected minimally only in urine immunofixation.

NSMM can be classified as non-producer or producer type by production of M-protein from plasma cells.⁷⁾ In the non-producer type, the disorder originates from reticular cells rather than the plasma cells and seems to block the protein production process from plasma cells.⁸⁾ In other words, the possible mechanism is considered as a defect of the production process or transport system of immunoglobulin. Immunoglobulin can be seen in the cytoplasm in the producer type; such patients produce, but are unable to se-

crete.⁹⁾ It is still not certain about the mechanism of the defect of immunoglobulin transport, but a transportation defect is usually seen among incomplete immunoglobulins,⁵⁾ and the differential diagnosis should be done with pseudo-non-secretory type. In the pseudo-nonsecretory type, the proteins are secreted, but dissolved quickly and deposited to the tissues, and are not found in serum and urine.¹⁰⁾ It caused severe proteinuria and chronic kidney disease because of deposition of light chains in the kidneys.

Recently, there is a report of a serum free light-chain assay which is useful for diagnosis and monitoring of many patients with NSMM.¹¹⁾ According to Drayson et al, increased concentrations of either κ or λ free light chains were detected in 19 of 28 patients with NSMM by using the serum free light-chain measurement.¹²⁾ Therefore, we expect a decrease in the incidence of NSMM in the future. The direct immunofluorescence test can be useful for identifying the subtypes, and presence of immunoglobulin, but we could not perform any of these tests in this case.

The treatment options for multiple myeloma are systemic pulse steroid therapy, combination chemotherapy with alkylating agents (melphalan, cyclophosphamide) and prednisolone, or VAD (vincristine, adriamycin and dexamethasone), thalidomide, bortezomib, and autologous or allogeneic stem cell transplantation. Radiotherapy is effective for localized osteoblastic bone lesions in POEMS syndrome,¹³⁾ but chemotherapy and peripheral blood stem cell transplantation should be considered in patients with diffuse osteoblastic bone lesions.¹⁴⁾ In our case, we had limited treatment options because of the patient's poor economic status and osteoblastic bone lesions. The patient and his family declined the high dose chemotherapy followed by stem cell transplantation and oral melphalan. Therefore, we treated the patient with cyclophosphamide and prednisolone.

The prognosis of multiple myeloma is poor

with a median survival of three years for patients receiving conventional chemotherapy.¹⁵⁾ However, the average survival of POEMS syndrome is more than a decade in contrast to multiple myeloma and the number of features does not affect the survival.⁵⁾ In this case, the patient survived for only seven months. We think the accompanying renal failure and infection might have played a role in shortening the survival.

The diagnosis and treatment were difficult in this case because of the negative M protein from serum and urine electrophoresis and the low socioeconomic status of the patient. In addition, there were no correlation between the treatment effect and prognosis. Therefore, if patients are having unexplained polyneuropathy, the serum VEGF level and symptoms or signs of POEMS syndrome should be determined, these two methods are the best ways to distinguish POEMS from other entities such as chronic inflammatory demyelinating polyneuropathy, Guillain-Barre, monoclonal gammopathy associated peripheral neuropathy and AL amyloidosis.⁵⁾ Further, the serum free light chain assay, a bone marrow aspiration and biopsy, skin and lymph node inspection, and examination of the endocrine system should be considered.⁶⁾ Further studies for better treatment modalities of the POEMS syndrome with multiple myeloma must be pursued.

요 약

POEMS 증후군은 형질세포질환의 하나로 말초신경병증 (P), 장기비대증 (O), 내분비병증 (E), 단클론감마병증 (M), 그리고 피부변화 (S)를 특징으로 한다. 이는 다발성 골수종과 연관되어 나타날 수 있으며 진단이 힘들고 드물게 발생한다. 48세 남자가 양측 서혜부의 타는 듯한 이상 감각과 양측 하지의 약화를 주소로 내원하였다. 환자는 캐슬만병의 과거력이 있었고, 입원 당시 말초신경병증, 뼈형성병변, 간비장종대, 하지 부종, 유두 부종이 보였다. 다발성 골수종을 의심하여 혈청 및 소변 전기영동 검사 시행하였으나 음성이었으며 소변 전기영동면역고정법에서만 M 단백이 관찰되었다. 그러나, 뼈병변에 대해 조직검사 결과 형질세포종 확인되어 다

발성 골수종으로 진단되었다. 환자는 POEMS 증후군과 다발성 골수종으로 진단되었고 진단과 치료 과정의 경험을 공유하고자 증례를 보고한다.

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