Case report

Massive myelomatous pleural effusion: a report of rare manifestation of a patient with multiple myeloma

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Abstract:

Multiple myeloma is a clonal plasma cell disorder with significant symptoms or organ dysfunction. According to the World Health Organisation (WHO) classification of tumours of hematopoietic and lymphoid tissues, myeloma is categorised in a subset of terminally differentiated mature B-cell neoplasms. Patients usually present with anaemia, renal impairment, symptoms of hypercalcemia and bone pain or fractures. Myelomatous pleural effusion is a rare complication and more likely found among multiple myeloma patients with progressive or refractory disease. We present herein a case of a patient with myeloma who developed massive pleural effusion after completing primary myeloma treatment at Thammasat University Hospital, Thailand. The effusion flow cytometry confirmed involvement of myeloma and systemic relapse simultaneously. Second-line therapy with bortezomib-based regimen was commenced; however, the patient's condition rapidly deteriorated after the diagnosis was made. This case report aimed to cover the clinical course of a patient diagnosed with multiple myeloma with myelomatous pleural effusion.

Keywords : ● *Multiple myeloma* ● *Pleural effusion* ● *Myelomatous pleural effusion*

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รายงานผู้ป่วย

ภาวะน้ำในช่องเยื่อหุ้มปอดจากมัยอีโลมา: รายงานภาวะที่พบไม่บ่อยในผู้ป่วยมะเร็งไขกระดูกมัยอีโลมา

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บทคัดย่อ

มะเร็งเม็ดเลือดขาวชนิดมัยอีโลมาเกิดจากการสร้างตัวผิดปกติของพลาสมาเซลล์ องค์การอนามัยโลกได้จัดมัยอีโลมาไว้ในกลุ่มบีเซลล์ที่โตเต็มที่ ผู้ป่วยมักมีอาการในระบบต่างๆ ได้แก่ ซีด ไตวาย แคลเซี่ยมสูง และปวดกระดูกหรือกระดูกหัก ภาวะน้ำในช่องเยื่อหุ้มปอด ที่เกิดจากมัยอีโลมาเป็นภาวะแทรกซ้อนที่พบไม่บ่อย และมักพบในผู้ป่วยมัยอีโลมาที่โรคเป็นมากขึ้นหรือดื้อต่อการรักษา ในราย งานผู้ป่วยนี้ จะนำเสนอผู้ป่วยมัยอีโลมาที่ได้รับการรักษาอย่างครบถ้วน และมีอาการกลับเป็นซ้ำร่วมกับภาวะน้ำในช่องเยื่อหุ้มปอด ที่โรงพยาบาล ธรรมศาสตร์ การส่งตรวจตัวอย่างน้ำในปอดด้วย flow cytometry พบพลาสมาเซลล์ที่ เข้าได้กับน้ำในช่องเยื่อหุ้มปอดที่เกิดขึ้นจากมัยอีโลมาโดยตรง หลังจากนั้นผู้ป่วยได้รับการปรับเปลี่ยนการรักษาเป็น การรักษามุ่งเป้า (bortezomib) ร่วมด้วย แต่ยังพบว่าผู้ป่วยอาการรุนแรง และแย่ลงอย่างรวดเร็วหลังจากการวินิจฉัยโรคที่เป็นซ้ำ รายงานผู้ป่วยนี้มีจุดประสงค์ ที่จะนำเสนอผู้ป่วยโรคมัยอีโลมาที่มีอาการรุนแรง และมีภาวะน้ำในช่องเยื่อหุ้มปอดจากมัยอีโลมา

คำสำคัญ : ● *น้ำในช่องเยื่อหุ้มปอด* ● *มะเร็งไขกระดูกมัยอีโลมา* ● *ภาวะน้ำในช่องเยื่อหุ้มปอดจากมัยอีโลมา*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:259-265.

Introduction

Plasma cell neoplasm is a spectrum of clonal plasma cell disorders with a wide range of clinical presentations and morphological features. The current World Health Organisation (WHO) classification of tumours of hematopoietic and lymphoid tissues categorises plasma cell neoplasm as a subset of terminally differentiated mature B-cell neoplasm[1]. Multiple myeloma (MM) is a plasma cell neoplasm with significant tumour burden resulting in considerable amounts of paraprotein causing symptoms including bone lysis. Most patients with multiple myeloma present significant chronic bone pain, anaemic symptoms or symptoms of hypercalcemia. Pleural effusion is an uncommon finding among patients with myeloma, occurring approximately in 6% of patients with MM[2]. However, most etiologies of the pleural effusion among patients with myeloma are from hypoalbuminemia, congestive heart failure or pulmonary embolism and are usually present bilaterally. Myelomatous pleural effusion presents in only about 1 to 2% of all cases[3]. Within those cases, 80% involve IgA disease[3]. To date, about 100 cases with myelomatous pleural effusion have been reported. The pathophysiology of myelomatous pleural effusion is believed to have originated from extensions of adjacent plasmacytoma or direct implantation of clonal plasma cells to the pleura. Case reports of MM manifested with massive pleural effusion (MPE) have been shown to indicate an advanced stage of the disease with poor drug response and dismal prognosis[4-6]. The current case report will demonstrate the patient's clinical course from the onset of MM to the development of MPE and outcomes.

Case vignette

A 67-year-old Thai man without significant past medical history, presented to our hospital in June, 2018 with a chief complaint of back pain for three months. The pain occurred spontaneously while he changed his position, without any prior history of trauma. He denied histories of muscle weakness, numbness or radiation of the pain elsewhere. He sought medical attention at a local primary clinic, where he was told that he had lumbar scoliosis and received pain relievers, which were only temporarily effective. The pain worsened when climbing stairs or leaning forward. His pain slowly progressed over the three months until he could no longer perform his daily activities. His appetite also decreased, resulting in weight loss of 12 kg in 4 months (from 76 to 64 kg). His physical examination revealed pale conjunctivae, lumbar hypolordosis, scoliosis and limited range of motion of the lower back. No signs of inflammation were observed while motor and sensory functions remained intact. Other systemic physical examinations were unremarkable, including no palpable masses or skin lesions. Plain radiograph of the lumbar spine revealed an anterior compression fracture of L1 and L3 vertebral body, destruction of endplate regions and diffuse osteopenia. Further laboratory studies are revealed in Table 1. Since the patient presented with hypercalcemia, differential etiologies included PTH-independent hypercalcemia resulting from metastasis of solid cancer, multiple myeloma or tuberculosis of the spine, so CT-guided biopsy of L1 was requested. The pathological report of L1 biopsy revealed the presence of round cell neoplasm, suggestive of small cell haematologic malignancy. No evidence of solid cancer or granuloma was found. At a follow-up visit after the biopsy, the patient still presented with significant asymptomatic hypercalcemia, so he was admitted for correction of this condition. The bone marrow examination revealed hypercellularity with 95% of plasma cells. His serum protein electrophoresis was consistent with hypogammaglobulinemia without any apparent monoclonal spike. Serum immunofixation showed a faint kappa band consistent with possible kappa light chain monoclonal gammopathy further investigation can be seen in Table 1. The diagnosis of kappa light chain multiple myeloma was made, with stage 2 on the international staging system (ISS). At the time of diagnosis, the patient's renal functions remained within normal limits (creatinine 1.15 mg/dL).

Table 1 Investigation results

Initial lab workup
CBC: Hb 8.2 g/dL, MCV 88.2 fL, WBC 2.9 x 10^3 cells/uL, Neu 34.7%, Lymph 56.7%, Plt 140 x 10^3 /uL
Creatinine 1.18 mg/dL, Calcium 11.4 mg/dL, Phosphorus 3.0 mg/dL Parathyroid hormone level 4.9 pg/mL
Total protein 6.37 mg/dL, albumin 4.36 mg/dL, globulin 2.01 mg/dL, total bilirubin 0.98, direct bilirubin 0.18,
AST 44 mg/dL, ALT 21 mg/dL, ALP 60 mg/dL
MM workup
Serum free light chain kappa 639 mg/L, lambda 1.9 mg/L with a K:L ratio of 336.32:1
SPEP no spike at gamma region; IgG 438.5, IgM < 25, IgA < 40 Beta-2-microglobulin was 5.34 mg/L.
Pleural tap profile
RBC 128700, Hct 3%; WBC 23111, Neutrophil 21.6%, Monocyte 78.4%
Fluid albumin 2.67 mg/dL (serum albumin 4.36 mg/dL), Total fluid protein 3.44 mg/dL (serum total protein 6.37 mg/dL),
ADA 17.92 U/L, Sugar 74.51, Fluid LDH 357 (serum LDH 609.93), Gram stain no microorganism, Fluid culture no growth

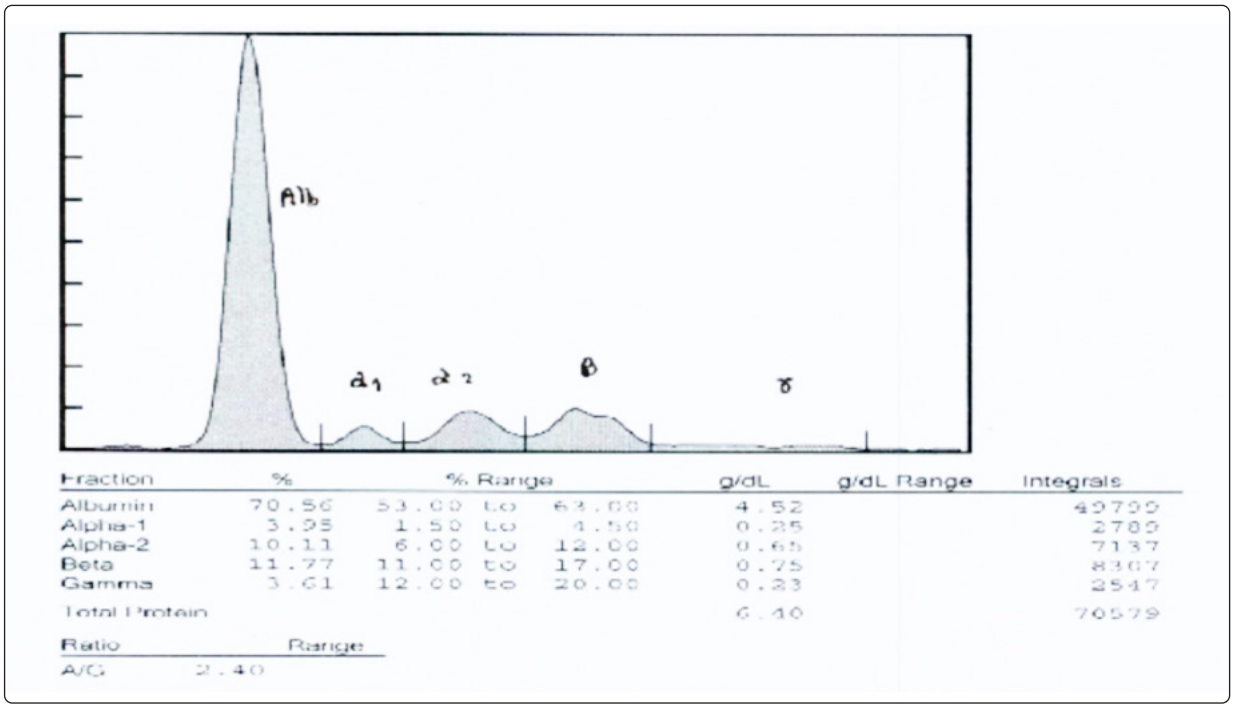

Figure 1 Serum protein electrophoresis

Due to his age and functional status, he was deemed ineligible for autologous stem cell transplantation and received treatment with thalidomide, dexamethasone, zoledronic acid and palliative local radiation therapy to the involved spine for pain control. He completed 12 cycles of thalidomide and dexamethasone in January 2021, along with zoledronic acid with a few minor interruptions due to reversible leukopenia. Disease status was evaluated at the end of the 12th cycle revealing no monoclonal band by immunofixation but persistent hypogammaglobulinemia. Serum free light chain kappa 25.7 mg/L, lambda 10.1 mg/L with a ratio of 2.54 was compatible with complete response of MM. Serum protein electrophoresis re-evaluation can be seen in Figure 1. Systemic treatment was stopped at that time and the patient continued monthly zoledronic acid infusion to completion in two years. Chest X-ray obtained during his regular visits revealed normal cardiac shadow, no pleural effusion, sharp costophrenic angle and no pulmonary infiltration.

In July 2021, the patient developed progressive dyspnea on exertion along with orthopnea and dry cough for one month. He developed functional class change from class one to three. Physical examinations included pitting oedema on both legs and fine crepitations of the right lower lung. Chest X-ray revealed blunting costophrenic angles of both lungs and increased right pleural effusion without trachea shift. Chest ultrasound demonstrated right pleural effusion, no left pleural effusion and collapsed inferior vena cava. Electrocardiography was within normal limits. He was admitted at a local hospital to treat acute decompensated heart failure responding to diuretics therapy. However, after being discharged, his dyspnea progressed, and he became bedbound. He further developed leg edema, frothy urine, back pain, weight loss, orthopnea and mucous diarrhea within one week. He was re-admitted in September 2021 for acute decompensated heart failure and further investigations. Echocardiographic study revealed preserved ejection fraction (62.3%), no regional wall motion abnormalities and diastolic dysfunction grade II without significant chamber wall thickening. Further complications during this admission included acute renal injury (creatinine 2.8 mg/dL) most likely drug induced, relapsed multiple myeloma or cardiorenal syndrome. Cardiac magnetic resonance imaging with viability protocol was requested to evaluate the cause of his congestive heart failure but postponed due to renal instability. His chest X-ray revealed new massive right pleural effusion (Figure 2). Computerised tomography scan of the patient's chest revealed subsegmental atelectasis at both lower lobes, no definite focal mass or lesion, minimal pleural effusion and diffuse osteolytic lesion at the thoracic spine. Bone marrow biopsy revealed plasma cells at 60% with kappa restriction along with increasing serum free light chain of kappa 49.1 mg/L, lambda 3.55 mg/L and a K:L ratio of 13.42, compatible with relapsed MM. Thoracentesis revealed serosanguinous exudative effusion with polymorphous lymphoid cells, without fungus or bacteria. The pleural tapping profile can be seen in Table 1. The patient's pleural effusion was sent for adenosine deaminase (ADA) to rule out pulmonary tuberculosis. Because ADA was 17.92 U/L, polymerase chain reaction for tuberculosis was not performed. Flow cytometric analysis of pleural fluid revealed CD38/CD138- positive plasma cell events with monotypic kappa light chain restriction. As the patient relapsed within one year after stopping primary therapy for MM and with renal failure, treatment was switched to a bortezomib-based regimen, namely, cyclophosphamide bortezomib-dexamethasone. However, the patient's condition deteriorated rapidly despite receiving two cycles of chemotherapy leading to cardiopulmonary collapse and mortality.

Discussion

Pleural effusion in MM can be caused by many different mechanisms, mostly secondary to the disease complications, e.g., congestive heart failure, hypoalbuminemia or pulmonary embolism, rather than from the plasma cell infiltration of pleura[7,8]. Pleural effusion secondary from disease complication commonly presents

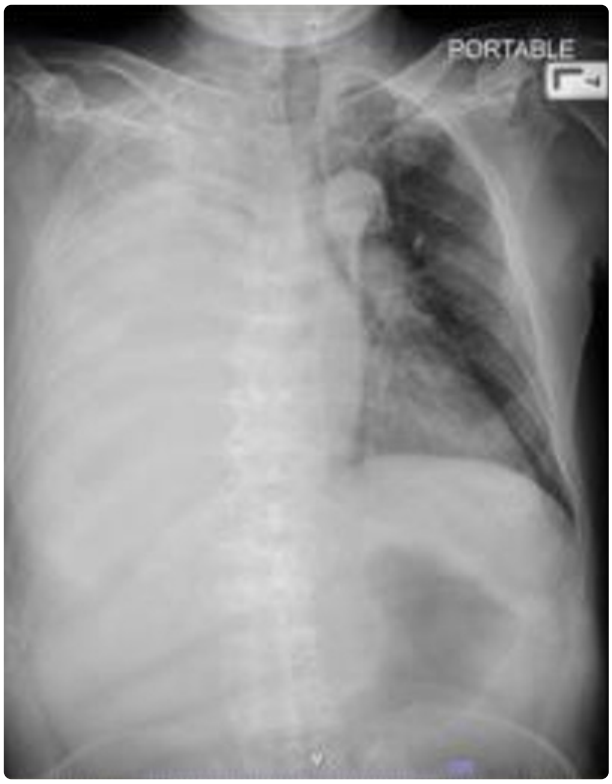

Figure 2 Chest X-ray showing massive right pleural effusion

bilaterally having a transudative profile, while pleural involvement of myeloma usually presents with unilateral exudative effusion. However, large amounts of serum immunoglobulins sometimes present with bilateral pleural effusion[6]. This patient presented unilateral exudative effusion. Thus, the differential diagnosis would include parapneumonic effusion, tuberculous effusion, metastatic effusion and rarely, myelomatous effusion. MM renders the patient immunocompromised, so opportunistic fungal or atypical bacterial infection are common. Metastatic effusion is as likely but would imply a primary site of metastasis which showed no evidence in any previous investigations. In this case, immunophenotypic findings and pleural tapping profile (Table 1) of said pleural effusion is compatible with myelomatous pleural effusion. The current patient's course of disease is in concordance with other reported cases including initial complete response of MM followed by relapses of the disease with myelomatous effusion and mortality shortly afterwards[5,9]. Other patients received similar treatments including immunomodulators and corticosteroids, then bortezomib based regimen once MM relapsed with extramedullary involvement[9-11]. Extramedullary symptoms are indicative of high mortality and poor prognosis[4,5,10].

Ghorbel, I.B., et al. compiled five case studies of MM with MPE, each with a similar clinical course[5]. Of the five presented cases, two were IgG kappa, one IgA, one IgG lambda and one lambda light chain. The patients receiving melphalan-based chemotherapy proved to be initially effective but worsened after the onset of MPE. Nonetheless, treatment provided was proven futile because the patients' condition deteriorated. Evidence of other treatment options including adriamycin, vincristine and dexamethasone also were futile[4].

Iqbal N. et al.[9] reported a similar case of MPE who developed acute respiratory distress. Investigations revealed right unilateral pleural effusion with cytologic results of atypical plasma cells consistent with MPE. The patient received a combination treatment of lenalidomide, dexamethasone and bortezomib together with multiple thoracocentesis yielding effective results. Afterwards, the patient's chest X-ray revealed the complete resolution of MPE. In contrast to the presented case where similar combinations of drugs were used, but the patient experienced a poor outcome. This could have been due to the patient receiving early and aggressive treatment whilst the presented case received directed therapy late, but further evidence is required to cement a recommendation.

Lang K. J., Lidder S. and Aitchison R. reported a case of successful treatment of MPE from IgG kappa MM[2]. The presented case was treated with bortezomib and dexamethasone with complete resolution of MPE seven days after initiating therapy. The study anecdotally recommended a two-step management involving initial thoracocentesis for symptomatic alleviation and early diagnosis by cytology. The second step included early systemic chemotherapy to slow disease progression.

Al-Farsi K., et al. presented a case of IgG kappa MM with bilateral MPE. The patient was initially treated with high dose dexamethasone followed by one cycle of liposomal doxorubicin, bortezomib and dexamethasone[12]. The patient's MPE resolved completely and his clinical signs improved. However, his disease still progressed and MPE recurred bilaterally within four months. This eventually led to cytopenia and sepsis, resulting in the patient's demise. The study proposes a criterion to diagnose MPE involving three parameters - atypical plasma cells in pleural fluid, monoclonal protein demonstration on protein electrophoresis and histological confirmation. However, said criteria needs refinement because parameters are compatible with other differential diagnoses including reactive plasma cells secondary to pulmonary tuberculosis, carcinomatosis and Hodgkin's lymphoma.

No clear consensus remains concerning the treatment of myelomatous pleural effusion besides standard MM treatment and supportive care[6]. The onset of MPE often begins in the latter stages of the disease and can present unilaterally or bilaterally. The presentation of

MPE includes insidious onset and sudden worsening of clinical signs similar to other documented cases[4,11].

Myelomatous pleural effusion is suggestive of poor prognosis and late stage of the disease[4,5]. Additionally, MPE should be considered a part of extramedullary presentation of MM[9]. Due to its rarity and rapid mortality, a specific treatment has not been agreed upon. The current best recommendation is early diagnosis and management that can result in complete resolution of MPE[2,12]. We report a case of a patient with relapsed MM with rapidly progressive MPE who experienced poor treatment outcome and review other cases to compare.

Pleural effusion is a rare complication found among patients with multiple myeloma with progressive and refractory disease. This report presented myelomatous pleural effusion and reviewed other complications of multiple myeloma. Early diagnosis of pleural effusion and its etiology provide insights that might lead physicians to prepare a second line therapy to achieve a successful outcome.

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