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CASE REPORT

Myelomatous Pleural Effusion
Case report and review of the literature

*Khalil Al-Farsi,[1] Ibrahim Al-Haddabi,[2] Nafla Al-Riyami,[3] Rashid Al-Sukaiti,[4] Salam Al-Kindi[1]

الانصباب الجنبي النقوي
تقرير عن حالة ومراجعة أدبيات

خليل الفارسي، إبراهيم الهدابي، نافلة الريامي، راشد السكيتي، سلام الكندي

الملخص: يُعد الورم النقوي بلازماوي الخلايا مرضا غير شائع، وهو ينتشر في أعضاء الجسم المختلفة بالإضافة إلى انتشاره في نخاع العظم بشكل مبدئي، مما يؤدي إلى تنوع مظاهره السريرية. ومع أنّ الانصباب الجنبي قد يحدث في هذا المرض فإن الانصباب الجنبي النقوي نادر جدا. نعرض هنا حالة رجل عُماني (عمره 55 سنة) مصاب بانتكاسة مرض الورم النقوي المتعدد أدى إلى انصباب جنبي نقوي ثنائي الجانب. وقد تم التشخيص بعد معاينة خلايا بلازما غير طبيعية عديدة ووجود معدلات عالية من بروتين أحادي النسيلة في عينة من سائل الانصباب الجنبي. على الرغم من الاستجابة الجيدة الأولية للعلاج، تطور المرض وتوفي المريض بعد ستة أشهر بالإنتان الجرثومي. تشير الأدبيات إلى ندرة مثل هذه المظاهر وأنها علامة تدل على سوء المآل وقصر حياة المريض.

مفتاح الكلمات: وَرَمٌ نِقْوِيٌّ مُتَعَدِّد، خلايا بلازما، انصباب جنبي، تقرير حالة، عُمان.

ABSTRACT: Plasma cell myeloma is an uncommon disease which, besides primarily involving the bone marrow, has a tendency to involve other organs thus presenting with different clinical manifestations. While pleural effusions are infrequent in this disease, true myelomatous pleural effusions are extremely rare. We report the case of a middle-aged Omani man with relapsed plasma cell myeloma who developed bilateral pleural effusions. The diagnosis of myelomatous pleural effusion was made by finding many abnormal plasma cells as well as a high level of a monoclonal protein (IgG κ) in the pleural fluid. In spite of a good initial response to therapy, the patient had progressive disease and died 6 months later with bacterial sepsis. We present a review of the literature that indicates the rarity of such a manifestation and its association with poor prognosis and short survival.

Keywords: Multiple myeloma; Plasma cells; Pleural effusion; Case report ; Oman

Multiple myeloma (now known as plasma cell myeloma) is a malignant disease caused by a proliferation of clonal plasma cells associated with a monoclonal protein or light chain in the serum and/or urine.[1] Patients with plasma cell myeloma commonly present with hypercalcaemia, renal insufficiency, anaemia and/or bony lesions.[2] However, the disease can present with a wide variety of clinical manifestations as a result of the involvement of various organ systems, due to either direct infiltration by plasma cells or the deposition of monoclonal proteins or light chains.[3] Pleural effusions are seen in a minority of patients with myeloma. However, effusions directly related to infiltration of the pleura by plasma cells, i.e. myelomatous pleural effusions (MPE), are extremely rare. In this paper, we report a case of an Omani patient with relapsed myeloma who developed a true myelomatous pleural effusion. We also present a review of the relevant literature.

Case Report

A 55 year-old man was diagnosed with Durie-Salmon stage IIIA IgG kappa plasma cell myeloma in 2004. He was treated for three months with a combination of thalidomide and steroids-based therapy and achieved a partial response. He was subsequently lost to follow-up and presented again in 2007 with progressive disease with severe anaemia and multiple lytic lesions. He was then treated with four cycles of bortezomib, thalidomide and dexamethasone and achieved complete remission. This was followed by melphalan-based

Departments of [1]Haematology, [2]Pathology, [3]Biochemistry, [4]Radiology & Molecular Imaging, Sultan Qaboos University Hospital, Muscat, Oman.
**Corresponding Author email: khalilf@squ.edu.om*

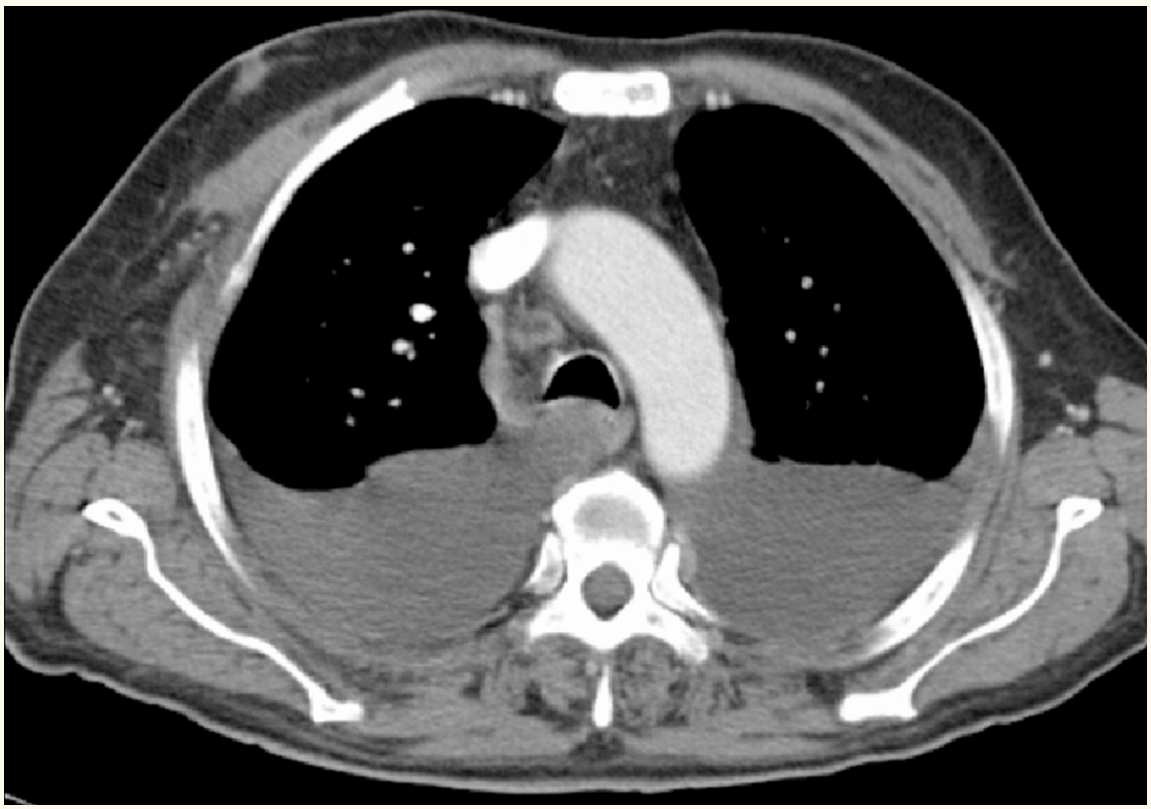

Figure 1: Computed tomography scan of the chest showing bilateral pleural effusions.

high dose chemotherapy and autologous stem cell transplantation (ASCT) in April 2008. His disease progressed a year after the transplant and he was treated with lenalidomide and dexamethasone. After five months of therapy, the treatment was interrupted as he developed severe cytopenias. He presented in January 2010 with shortness of breath and dry cough. His temperature was 38.5 °C, pulse was 124/min, respiratory rate was 22 breaths/min, blood pressure was 140/68 mmHg and oxygen saturation 91% on room air. A chest examination revealed decreased breath sounds in both infra-scapular areas with dullness to percussion on both sides. A complete blood count (CBC) revealed a white blood cell (WBC) count of 2.2 x 10^9/L, absolute neutrophil count of 0.5x10^9/L, Hb of 8.7 g/dL and platelet count of 36 x10^9/L. The peripheral blood film showed rouleaux formation and confirmed the thrombocytopenia and neutropenia noted on the CBC. There were no circulating plasma cells or other abnormal cells. Blood chemistry tests showed albumin of 26 g/L, total protein 89 g/L, glucose 5.7 mmol/L, lactate dehydrogenase (LDH) 301 U/L, ß2 microglobulin 12.4 mg/L and C-reactive protein 121 mg/L. Serum calcium, creatinine, uric acid, thyroid stimulating hormone (TSH) and liver enzymes }were normal. Serologies for HIV, hepatitis B and hepatitis C were negative. Serum protein electrophoresis and immunofixation showed a monoclonal IgG κ of 30.9 g/L with normal levels of uninvolved immunoglobulins. The most recent 24-hour urine test showed a total protein of only 0.13 g/24hour. The chest X-ray showed bilateral pleural effusions. A computed tomography (CT) scan of the chest confirmed the presence of bilateral pleural effusions [Figure 1]. It also showed multiple rib, sternal and thoracic vertebral osseous lytic lesions. There were also multiple sub-centimetre mediastinal lymph nodes. There was no evidence of pulmonary embolism. An echocardiography showed no significant abnormalities. The left ventricular ejection fraction was 70%. A thoracocentesis was performed and about 1 L of pleural fluid was drained from the right side. Analysis showed glucose of 6.0 mmol/L, protein of 50 g/L and LDH of 172 U/L. The cytological examination revealed many abnormal plasma cells that constituted around 20% of the total nucleated cell in the pleural aspirate [Figure 2]. Although flow cytometry suggested that these cells were positive for CD38, the results were of poor

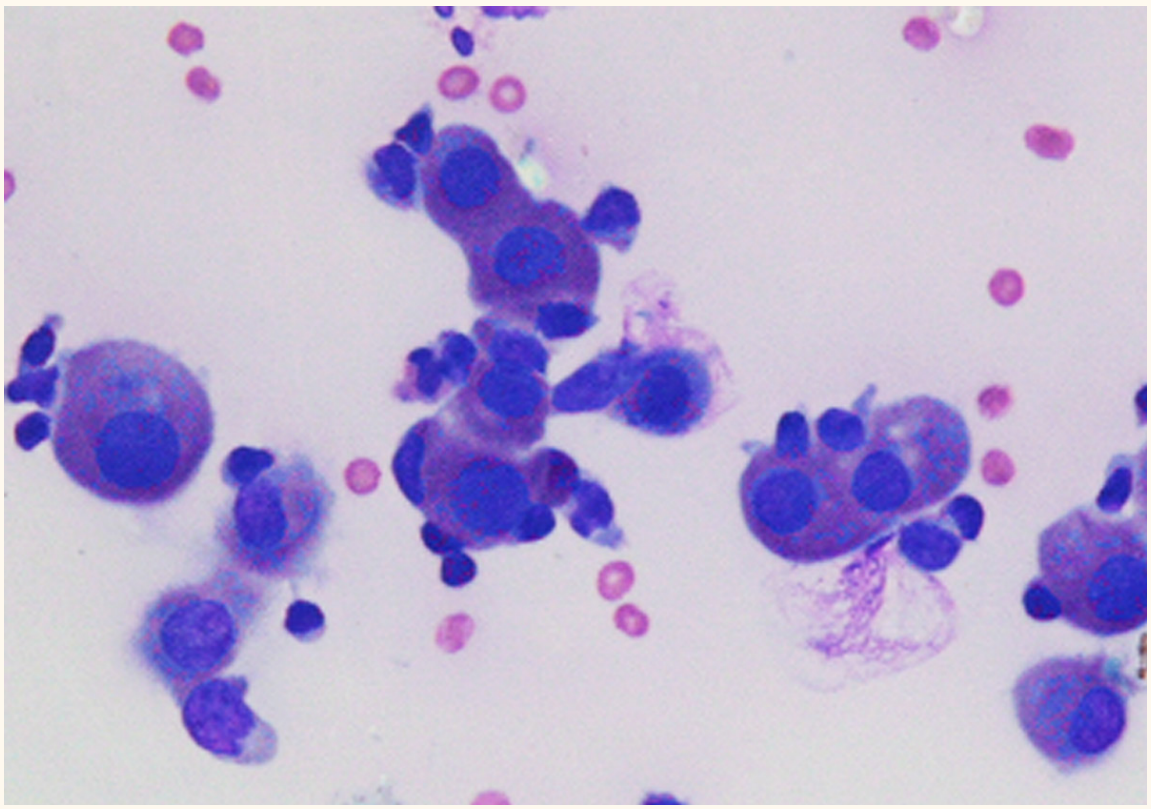

Figure 2: Cytological examination of the pleural fluid showing clusters of abnormal malignant-looking plasma cells.

quality due to the suboptimal quality of the sample and therefore difficult to interpret, especially with regards to light chain restriction. However, protein electrophoresis and immunofixation on the pleural fluid showed 16.7 g/L of IgG κ monoclonal protein [Figures 3 and 4]. A Gram stain, acid fast bacilli (AFB) stain and cultures (bacterial, fungal and TB cultures) were all negative. He was treated with high dose dexamethasone followed by one cycle of a combination of liposomal doxorubicin, bortezomib and dexamethasone. The pleural effusion resolved completely. However, the disease started to progress systemically over the following month, and his performance status deteriorated. He developed refractory cytopenias and became transfusion dependent. The effusions recurred bilaterally within 4 months. He was managed with palliative supportive care and died due to *Escherichia coli* sepsis in the setting of progressive disease in July 2010. A post-mortem examination was not performed.

Discussion

Although plasma cell myeloma is mostly a bone marrow based disease, it can produce a variety of clinical presentations through the involvement of different extramedullary sites. One of these manifestations is pleural effusion. Pleural effusions, caused by several aetiologies, are reported to occur in 6% of patients with myeloma during the course of their disease.[4] Myelomatous pleural effusions are rare and only about 80 cases have been reported in English medical literature.

Pleural effusions in patients with myeloma often results from non-malignant causes, some of which are treatable. The most common cause is congestive cardiac failure due to amyloidosis.[4] Heart failure can also result from hyperviscosity and from cardiomyopathy related to the use of anthracyclines, commonly used in the treatment of myeloma in the past. Other causes include pulmonary embolism, infections, nephrotic syndrome and chronic renal failure.[5] In addition, secondary neoplasms occurring in patients with myeloma, like carcinomas of the breast and lung and mesothelioma, can cause malignant pleural effusions.[6] A detailed systematic approach to investigating pleural effusions, as demonstrated in our case report, is therefore important to exclude these alternative diagnoses.

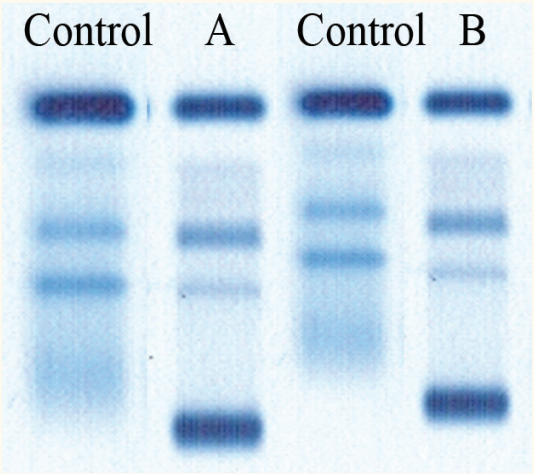

Figure 3: Protein electrophoresis on (A) serum and (B) pleural fluid, both showing a dense monoclonal band in the slow gamma region.

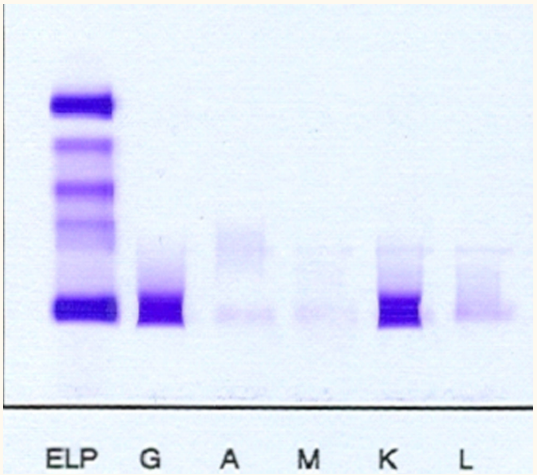

Figure 4: Immunofixation on pleural fluid showing an IgG κ monoclonal band.

Our patient had normal cardiac and renal functions and no evidence of pulmonary embolism or nephrotic syndrome. In addition, there was no evidence of any infective aetiology and no evidence of secondary malignancies.

A true myelomatous pleural effusion is rare and occurs in less than 1% of patients with myeloma.[4,7] It is usually a sign of advanced disease, although there are a few reports of it being the initial presenting feature of myeloma in some patients.[8-10] There are about 80 cases reported in English medical literature. Older reports indicate that most effusions are due to IgA myeloma.[11] However, more recent reports indicate that the majority occur in patients with IgG myeloma, which is the most common type of myeloma, as was the case in our patient.[7,12,13] These recent reviews also indicate that it has an equal gender distribution, is commonly haemorrhagic, more commonly affects the left side and that these patients usually have poor prognostic disease markers.[7,12-14] Our patient had bilateral effusions at a late stage of his relapsed/refractory disease.

The pathogenesis of myelomatous pleural effusion is not well understood, but several possible mechanisms have been proposed. These include: 1) direct extension of the disease to the pleura from adjacent skeletal or lung parenchymal tumors; 2) direct infiltration or implantation of tumour deposits on the pleura, and 3) lymphatic obstruction from mediastinal lymph node inflitration.[4] Extension from a mediastinal extramedullary plasmacytoma has also been suggested as one possible mechanism.[13-16] It is possible that the myelomatous pleural effusion in our patient resulted from extension of his disease from the many lesions in his ribs, sternum and thoracic vertebrae. Whether he had direct infiltration of the pleura is hard to prove as he did not have a pleural biopsy and small areas of involvement might be missed on CT scans.

Diagnostic criteria have been suggested to confirm the myelomatous nature of pleural effusions. The criteria include: 1) detection of atypical plasma cells in the pleural fluid; 2) demonstration of a monoclonal protein on pleural fluid electrophoresis, and 3) histological confirmation using pleural biopsy specimens or autopsy.[11] Our patient had an exudative effusion that had a high level of monoclonal IgG κ as well as many abnormal plasma cells. A pleural biopsy was not done because of his poor general condition and severe thrombocytopenia at that time. In fact, one could argue that a pleural biopsy is not an integral part of the diagnosis. Pleural biopsies are not always done in these patients and when done are not always diagnostic or helpful.[7,12,15,17] The risk associated with the procedure as well as the patchy nature of disease involvement make it less attractive and less reliable as a diagnostic tool.

Despite the proposed criteria, the diagnosis of myelomatous pleural effusions can be challenging. Reactive plasma cells may be seen in effusions secondary to cardiac surgery, tuberculosis, viral infections, connective tissue diseases, Hodgkin's lymphoma and carcinomatosis.[16,18] In addition, malignant plasma cells have a wide spectrum of appearances in fluid specimens and may be missed

as being of plasmacytic origin, especially if low in number. Furthermore, due to *in vivo* and *in vitro* degeneration and changes during sample processing, the morphology can be significantly altered leading to further difficulties in recognising these cells as malignant plasma cells.[7] The characteristic clock-faced condensed chromatic pattern is absent in these cases. Instead, the nuclei of these cells are round to oval or pleomorphic and have a coarse and irregular chromatin pattern with prominent nucleoli. These malignant cells also have dense cytoplasm with absent or inconspicuous perinuclear hof.[19,17] Pleural biopsies might not be feasible and are not always diagnostic. It has been suggested that flow cytometric studies should be used to supplement the diagnosis.[7] It has been shown, however, that in some instances flow cytometry might not be helpful due to poor specimen quality causing non-specific light-chain staining.[17,19] It has also been suggested that cytogenetic analysis be done on the pleural aspirate to support the diagnosis as an abnormal cytogenetic karyotype in the pleural fluid can provide unequivocal evidence of malignancy;[7] however, this is not always possible. The diagnosis in most of the reported cases relied mainly on finding abnormal plasma cells and a monoclonal protein in the pleural fluid.

The lack of alternative diagnosis and the presence of malignant-appearing plasma cells in the pleural fluid support the diagnosis of myelomatous pleural effusion in our patient. In addition, the lack of circulating plasma cells in his peripheral blood, while there were many in his pleural fluid, argues strongly against the monoclonal protein in his pleural fluid being the result of contamination with peripheral blood. Flow cytometry was attempted, but the suboptimal quality of the sample precluded interpretation of the results. The pleural fluid was not subjected to cytogenetic analysis in our patient. Such analysis is not necessary for routine diagnosis.[7] In addition, cytogenetic studies in myeloma patients can be difficult because few mitoses are often obtained.[18,20] Overall, with the clinical presentation and the findings on pleural fluid analysis, there is no doubt that our patient had a true myelomatous pleural effusion.

The diagnosis of myelomatous pleural effusion carries a poor prognosis despite aggressive treatment. The literature suggests that the median survival of these patients is about 4 months. Several treatments have been tried including different combinations of systemic chemotherapy,[7,12,21] as well as intra-pleural injections of different agents like adriamycin and interferon.[19,20,22,23] Despite some reported responses, the majority of these were transient and recurrences were common. There seems to be no added benefit from salvage chemotherapy followed by high dose therapy and ASCT in these patients.[7] There appears to be some hope, however, with the use of novel agents. Bortezomib, a novel proteasome inhibitor which has been shown to overcome some of the poor prognostic factors in myeloma, has proven to be safe and effective in patients with relapsed/refractory myeloma, especially if combined with other novel agents like liposomal doxorubicin.[21,24] Some have reported encouraging responses to systemic as well as intra-pleural bortezomib.[22,23,25,26] Our patient was exposed to all available novel drugs including thalidomide, lenalidomide and bortezomib and did have a good response to systemic treatment with bortezomib, liposomal doxorubicin and dexamethasone. As his effusions resolved, no intra-pleural therapy was given. Unfortunately, the response was transient and he was not able to tolerate further therapy. He eventually died within 6 months of developing the myelomatous pleural effusion.

Conclusion

Pleural effusions in patients with multiple myeloma result from different aetiologies, each requiring a different type of treatment. Due to the important therapeutic and prognostic implications of finding a myelomatous pleural effusion, diagnostic throracocentesis with careful cytological examination and protein electrophoresis with immunofixation should be performed whenever possible. Supplemental studies with flow cytometry and cytogenetics should also be considered.

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