Clinical Oncology: Case Reports

Case Report

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Cyclophosphamide, Bortezomib and Dexamethasone (CyBordD) for Multiple Extramedullary Plasmacytomas and Bilateral Myelomatous Pleural Effusion

Leilei Teng, Jennifer R Hewlett, and Khalil I Hussein

Abstract

Multiple soft-tissue Extramedullary Plasmacytomas (EMP) and Myelomatous Pleural Effusion (MPE) are two uncommon manifestations of advanced Multiple Myeloma (MM). The presence of both multiple EMP and MPE in the same MM presentation is very rare. We report the case of an 81-year-old woman who presented with dyspnea on exertion and productive cough. Physical exam found bibasilar rales and multiple soft, subcutaneous, mobile lumps on her bilateral upper extremities. Computed Tomography (CT) of her chest with Intravenous (IV) contrast identified a large mantle of soft tissue surrounding the distal thoracic aorta, a second mass involving the anterior right chest wall, and bilateral pleural effusions. Subsequent biopsy of the right chest wall mass revealed plasma cell neoplasm. Pleural fluid cytology was consistent with plasmacytoid/plasmacytic neoplasm. She was started on Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD). Repeat Positron Emission Tomography (PET)-CT after 11 days of treatment demonstrated excellent response with apparent resolution of the posterior mediastinal mass and right anterior chest wall mass, no activity in thoracic spine, and decreased bone activity. Despite improved disease activity, she acutely decompensated due to aspiration pneumonia and septic shock, and she expired one week later. EMP and MPE individually confer poor prognosis, and the presence of both conditions as the initial manifestations of MM may complicate the diagnostic process and suggest more aggressive clinical features. The experience of our patient suggests the potential for favorable outcomes to CyBorD if complications are avoided.

Keywords: Multiple myeloma; Extramedullary plasmacytomas; Myelomatous pleural effusion; PTEN hamartoma tumor syndrome.

Introduction

Multiple Myeloma (MM) arises from the malignant transformation of plasma cells. As the plasma cells infiltrate into bone marrow and skeleton, anemia, bone pain, renal insufficiency from light chain deposition, and hypercalcemia often result. Although the proliferation of neoplastic plasma cells is highly dependent on the bone marrow microenvironment, extramedullary involvement can occur in advanced stages of MM in the form of plasma cell leukemia or soft tissue Extramedullary Plasmacytomas (EMP). However, soft tissue EMP presenting as the initial manifestation of MM is very uncommon. The incidence of Extramedullary Plasmacytomas (EMP) at the time of MM diagnosis is between 3%-5% and may indicate a more advanced disease at diagnosis and stromal-independent transition [1,2]. EMP usually develops from either local extension of skeletal masses with thoracic wall as the most common affected region, or hematogenous spread with multiple subcutaneous nodules as the most frequently involved sites [3]. Both mechanisms are demonstrated in our case.

Pleural effusion is not rare in MM, and the reported incidence ranges from 11% to 42.7% [4-6]. Myelomatous Pleural Effusion (MPE), however, is a very uncommon cause of pleural effusion in MM with incidence of only 0.8% to 2.65% [7-10]. MPE is due to plasma cell infiltration of the pleura and tends to occur later in the disease course, but in rare cases including ours, MPE can be the presenting manifestation of MM. The pleural involvement can be the result of direct extension or invasion of a nearby lesion, or rarely, primary pleural plasmacytoma [11].

We describe a very atypical presentation featuring both MPE and multiple EMP at the time of diagnosis. A large chest wall lesion was the most likely cause of the MPE, which had to be differentiated from more common and benign etiologies of pleural effusion in MM such as heart failure, renal failure, or concurrent infection. While the concurrence of both EMP and MPE at diagnosis provided mutual corroboration for a more advanced disease stage of MM, the rarity of the combination clouded the initial clinical presentation and prolonged the diagnostic workup, which we highlight in this report. MPE and EMP individually confer poor prognosis, and the combination portended even worse outcome. However, our case suggests the potential for favorable outcomes in response to Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD). As part of our literature review, we collected 18 previously reported cases with our case as the 19th case of both MPE and multiple EMP, and we discuss lessons to be learned [12-15].

Case Report

An 81-year-old woman with prior history of surgery to remove symptomatic left cavernous hemangioma 15 years ago in Guatemala complicated by residual dysphasia presented with productive cough and dyspnea on exertion of 4 weeks duration. Initial vital signs were: temperature 97.2°F, heart rate 98 beats per minute, blood pressure 168/76 mmHg, respiratory rate 20 breaths per minute, and oxygen saturation 92% on room air. Physical exam found multiple soft, subcutaneous, and mobile lumps on bilateral upper extremities (Figure 1). Chest auscultation demonstrated bibasilar rales, bilateral end expiratory wheezing, and significantly decreased breath sounds over right lower lung field. Labs revealed serum protein 7.7 g/dL, albumin 3.2 g/dL, Serum Lactate Dehydrogenase (LDH) 152 U/L, corrected calcium 9.9 mg/dL, and negative respiratory virus Polymerase Chain Reaction (PCR). Complete blood cell count with differential, creatinine, liver function tests, lactic acid, troponin I, procalcitonin, pro-BNP, blood cultures, and electrocardiogram were unremarkable. Chest x-ray was notable for cardiomegaly, edema, and bilateral pleural pulmonary effusions.

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Computed Tomography (CT) of the chest with Intravenous (IV) contrast additionally identified a large mantle of soft tissue surrounding the distal thoracic aorta measuring 8.0 cm × 7.4 cm × 8.5 cm (Figure 2A) that also involved the T10 vertebral body. Also identified was a mass involving the anterior right chest wall measuring 4.5 cm × 2.5 cm × 4.6 cm (Figure 2B). Magnetic Resonance Imaging (MRI) of the brain found non-specific enhancing lesions in the right parietal calvarium. Full-spine MRI found T4 and T10 body enhancement with right epidural extension, abnormal bone marrow signal throughout the spine, and vertebral hemangiomas. Transthoracic echocardiogram was unremarkable.

Thoracentesis drained 1200 mL of serosanguinous fluid with pleural protein 4.9 g/dL, glucose 105 mg/dL, LDH 132 /L, and amylase 23 U/L, consistent with an exudative effusion. Pleural fluid cultures returned negative. Cytology of the fluid was consistent with plasmacytoid/plasmacytic neoplasm andflow cytometry found involvement by an abnormal lymphoplasmacytic population consistent with surface lambda light chain-restriction. In situ hybridization testing of pleural fluid for Human gammaherpesvirus 8 (HHV-8) and Epstein-Barr Virus (EBV) returned negative, which excluded primary effusion lymphoma.

Biopsy of right chest wall mass showed plasma cell neoplasm, and protein and immunoelectrophoresis showed lambda light chain-restricted and positive IgA lambda light chain gammopathy. Serum

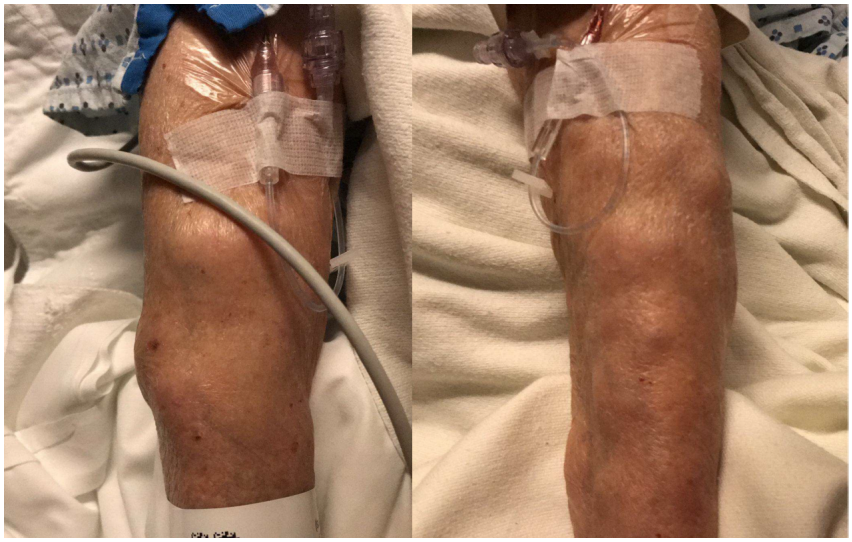

Figure 1: Multiple subcutaneous mobile soft lumps at bilateral upper extremities.

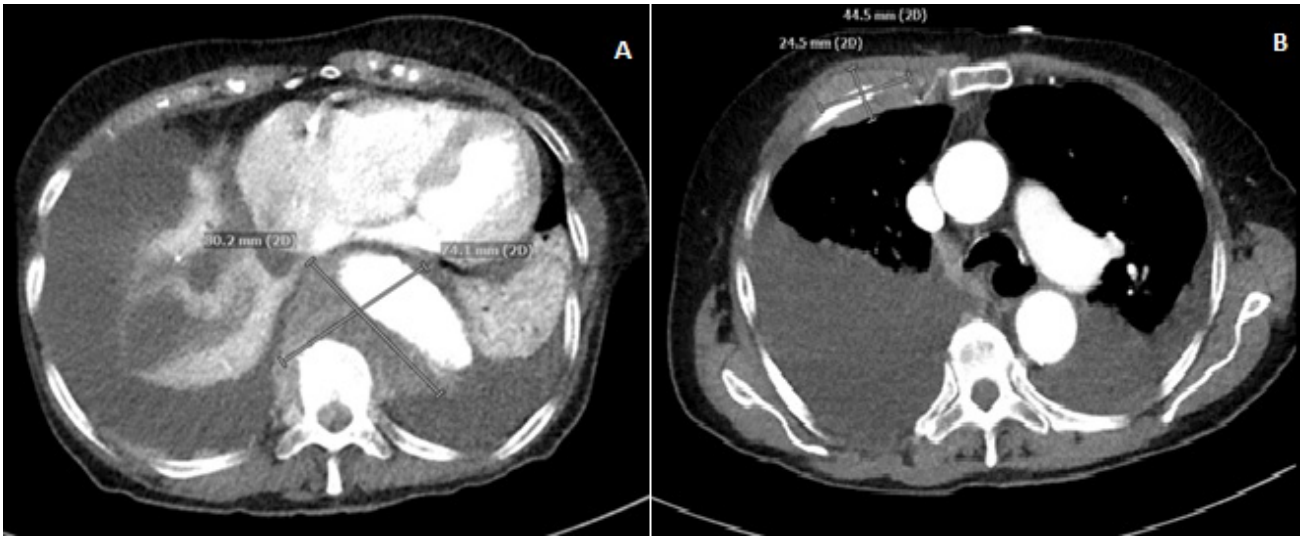

Figure 2: A) Large mantle of soft tissue surrounding the distal thoracic aorta; B) A second mass involving the anterior right chest wall.

protein electrophoresis (SPEP) found abnormal band measuring 1.3 g/dL present in the beta region which was further characterized as IgA lambda on concurrent serum immunofixation electrophoresis. Bone Marrow (BM) biopsy and flow cytometry from BM aspirate were unremarkable.

The patient was started on induction chemotherapy with CyBorD. After 12 days, repeat Positron Emission Tomography (PET)-CT showed excellent response in the posterior mediastinal mass (Figure 3A) and right anterior chest wall mass (Figure 3B) no longer noted (Figure 4), no activity in thoracic spine, and decreased bone activity. One week later, she decompensated due to aspiration pneumonia and septic shock, and she expired.

Literature review

We performed a literature search in PubMed using search criteria [(Multiple Myeloma) and (pleural effusions) and (extramedullary)], which resulted in 41 publications [16-18]. We selected 10 cases consistent with concurrent EMP and MPE by reading the abstracts. We then performed a broader search by the criteria of [(Myelomatous pleural effusion) and (extramedullary plasmacytoma)], which resulted in 19 articles [19]. We then selected additional 7 cases by comparing with the prior list of 10 and excluding the overlap cases. One more case was found by reading the review articles regarding extramedullary disease in Multiple Myeloma in the past 20 years. We included a total of 19 reports of MPE and multiple EMP, 18 from our literature review plus our case (Table 1).

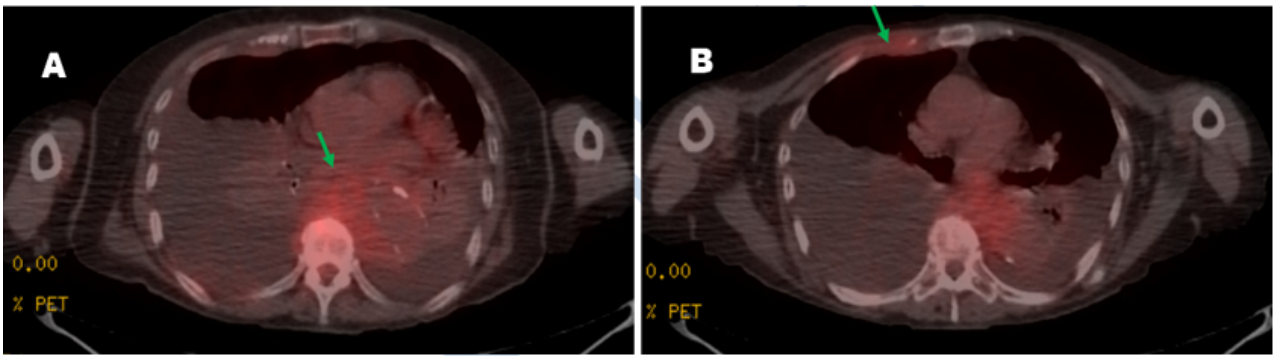

Figure 3: A) PET CT at the beginning of chemotherapy showed activity associated with the soft tissue mass (green arrow) located in the anterior to low dorsal spine extending into the posterior mediastinum; B) activity associated with some soft tissue fullness (green arrow) lateral to the sternum to the right of midline in the chest wall.

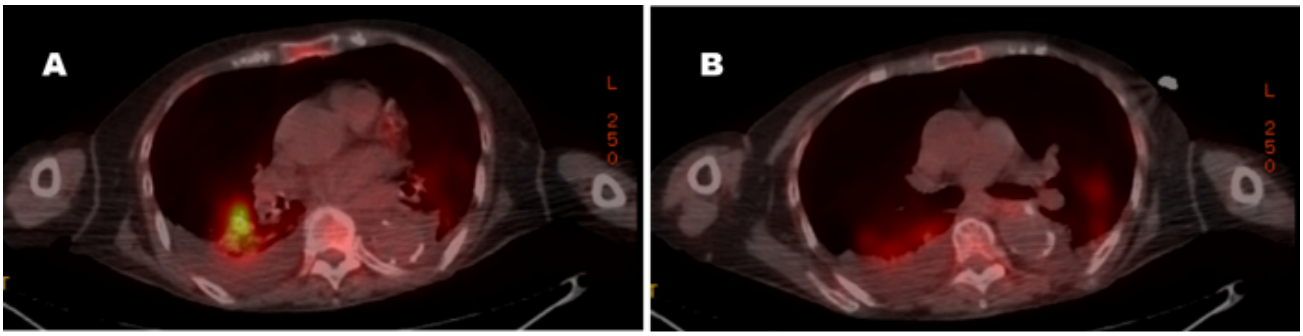

Figure 4: A) PET CT 12 days AFTER starting CyBORD, previously demonstrated abnormal tracer accumulation associated with abnormal posterior mediastinal soft tissue is resolved; B) previously demonstrated abnormal tracer accumulation in right parasternal intercostal soft tissues is resolved.

Table 1: Summary of case reports.

Age (years)	Sex	Onset in the disease course	EMP sites	MPE laterality	Pathology subtype	Management	Outcomes
62	Male	At diagnosis	Para-tracheal mass lesion	Right	Not done	Dexamethasone and lenalidomide	Expired 2 weeks after presentation
68	Male	After diagnosis, exact time not given	Right thoracic and paravertebral	Right	IgA Kappa	PE drainage, pleurodesis by bleomycin instillation, local radiation, systemic therapy for MM (pomalidomide +cyclophosphamide+dexamethasone) resulted in resolution of 2 episodes of MPE	Expired 18 months after the first MPE episode

50	Female	Not available	Ovaries, uterus, pancreas	Right	Not available	At the presence of MPE, 4 courses of the bort ezomib+lenalidomide+dexamethasone regimen, partial response was achieved; 2 courses of daratumumab+lenalidomide+dexamethasone (DLd) regimen achieved complete response; followed by autologous peripheral blood stem cell transplantation +additional 4 courses DLd regimen; maintenance therapy containing daratumumab and dose-reduced lenalidomide	Maintained relapse-free survival for two years with maintenance therapy
67	Female	EMP at 14 years and MPE at 19 after diagnosis	Right chest wall	Right	IgA Kappa	Chemotherapy, autologous hematopoietic stem cell transplantation, and local radiation therapy at the presence of EMP; chemical pleurodesis with talc, local radiotherapy and chemotherapy (pomalidomide–dexamethasone–cyclophosphamide) at the presence of MPE	Achieving clinical remission that lasted 6 months after diagnosis of the MPE.
39	Female	4 years after diagnosis	Pericardial, cardiac tamponade	Left	IgA Lambda	4 cycles of PAD (bortezomib+adriamycin+dexa methasone)+ Zoledronic acid resulted complete remission for 2 years; at the 1st relapse, 4 cycles of Lenalidomide+dexamethasone, loss of response, VCD chemotherapy (bortezomib, cyclophosphamide, and dexamethasone) achieving a second complete remission; reduced-intensity conditioning regimen followed by fully matched sibling hematopoietic stem cell transplantation to consolidate response; at 2nd relapse, 2 cycles of VCD, switched to VBCMP/VBAD chemotherapy (vincristine, carmustine, cyclophosphamide, melphalan, prednisone/vincristine, carmustine, doxorubicin, and high-dose dexamethasone), achieving a third complete remission; at presence of MPE, 18th cycle of carfilzomib+dexamethasone	Remained complete remission 19 months after MPE
68	Male	4 months after diagnosis	Left chest wall mass	Bilateral	IgA Kappa	MPE appeared after two cycles of chemotherapy using bortezomib and dexamethasone; required intubation at the presence of MPE	expired 12 hours after extubation for comfort measures only
74	Female	at diagnosis	Mediastinal mass; right posterior paraspinal mass	Right	IgG Kappa	Hospice	expired within a month of diagnosis
62	Female	3 months after diagnosis	Subcutaneous	Right	IgA Kappa	three cycles of thalidomide and dexamethasone induction + local radiation resulted in remission of MM; local radiation leading to complete regression of the subcutaneous nodule; VAD (vincristine, doxorubicin and dexamethasone) started at the presence of MPEsubcutaneous nodules	expired 12 month after the first clinical presentation
52	Female	7 years after diagnosis	Abdominal lymphadenopathy; renal mass	Right	IgG Kappa	Thalidomide and dexamethasone resulted In complete remission of MM; thalidomide+zoledronic acid maintenance for 5 years; at 5th year's progression, lena lidomide+dexamethasone+zoledronic acid resulted in partial response; new pelvic lesion, palliative radiotherapy, 3 cycles of VRD (bortez omib+lenalidomide+dexamethasone) regimen followed by VRD maintenance ; at 7th years presence of EMP, 1 cycle of PAD (bortezomib+doxorubicin+dexamethasone) regimen, followed by metronomic therapy (cyclophosphamide+prednisolone+thalidomide	Expired 3 months after the presence of MPE
53	Male	At the diagnosis	Bilateral pleural nodules	Bilateral	IgG Kappa	2 cycles of VTD (bortezomib, dexamethasone and thalidomide)	By the time of case reported, overall condition of the patient is good (clear time course not given).
65	Male	At the diagnosis	Anterior mediastinal mass	Bilateral	Lambda light chain restriction	Two courses of induction chemotherapy intravenous (thalidomide+cyclophosphamide + dexamethasone), radiotherapy	Long term outcomes not given
76	Male	At diagnosis	Bilateral pleural and chest wall masses; extraosseous soft-tissue masses on lumbosacral spine	Bilateral	IgG Lambda	Not reported	Expired 4 weeks after presentation
70	Male	at diagnosis	Mediastinal mass; numerous pleural-based nodules	Right	IgG Lambda	Velcade, melphalan, and prednisone	Not reported

66	Female	1.5 years after diagnosis	Pleural thickening	Right	Igg Kappa	8 months of CTD (cyclophosphamide+thalidomide+dexamethasone) resulted in remission; at presence of MPE, CVD (Cyclophosphamide+Velcade+Dexamethasone) resulted in good response, no re-accumulate for 3 months; At reoccurrence of MPE, Melphalan+dexamethasone started, and progression was halted.	Progression remained halted by the time of case reported (8 months after presence of MPE). No long term outcomes reported
74	Male	3 years after diagnosis	Right chest wall and paravertebral space; subcutaneous mass in abdominal wall; multiple gastric polyps	Bilateral	Igg kappa	Observation for 2 years; 12 courses of monthly melphalan + prednisolone resulted in partially remission; at the progression, daily thalidomide+dexamethasone resulted in good response for 3 months	Expired 8 months after the presence of mpe
63	Female	3 years after diagnosis	Pleural thickening	Left	Iga kappa	Four cycles of vad (vincristine+ adriamycin+ dexamethasone) resulted in partial response, followed by maintenance thalidomide; at presence of mpe, vad regimen followed by salvage bortezomib+ dexametazone	Expired 11 months after the presence of mpe
55	Not available	7 years after diagnosis	Left thoracic wall	Left	Igg lambda	Plasmapheresis and several courses of chemotherapy, radiotherapy	Not available
51	Female	4 years after diagnosis	Subcutaneous, abdominal cavity	Right	Igg kappa	Repeated courses of melphalan+prednisolone resulted in remission for 4 years; one course of vcap (vincristine+cyclophosphamide+adriamycin +prednisolone) at the presence of subcutaneous lesion; at progression, alpha-interferon+ mod (mitoxantrone, vincristine, dexamethasone) followed by intrapleural adriamycin, methotrexate + leucovorin, and intraperitoneal of α-interferon	Expired 3 weeks after the appearance of pleural effusions
81	Female	At diagnosis	Subcutaneous, right chest wall	Right	Lambda light chain restriction	CyBorD (cyclophosphamide + bortezomib + dexamethasone) for 12 days	Expired within 1 month after initial presence of MPE due to aspiration event

Discussion

Clinical characteristics

Multiple Myeloma (MM) is typically confined to the bone marrow and skeleton. EMP is an uncommon initial manifestation of MM, while MPE is an even rarer form of extramedullary disease. A decade ago, the incidence of EMP was reported to range from 7%-18% in newly diagnosed MM and 6%-20% later in the disease course [20]. Although our screening and diagnostic means have become more widely available, the incidence has not increased. The most recently observed incidence was reported as 3%-5% at time of initial MM diagnosis [21-25]. In a recent observational retrospective study [26], incidence of MPE at relapse of MM was found to be more common than at initial clinical presentation. In our literature review, concurrent soft tissue EMP and MPE at the initial diagnosis of MM were found in only 7 out of 19 cases while the remaining 12 cases developed concurrent presentation of those disease manifestations at relapse.

The majority of EMPs (68%-85%) observed at diagnosis were soft-tissue masses adjacent to bone lesions [3]. In the 19 cases we reviewed, chest wall masses (7 out of 19) were the most common, and paravertebral involvement (4 out of 19) is the second common sites of EMPs. This also suggests that local growth from focal bone lesions remains the most likely mechanism of EMPs. In our case, a large EMP surrounding the distal thoracic aorta had involved the nearby vertebral body, and the epidural lesions appeared to be extraosseous in origin. Extraosseous myeloma is a rare cause of spinal cord compression; most spinal cord compression in MM is related to pathological fracture of the involved vertebral body or extension of a vertebral body myeloma lesion [27]. In prior analysis of EMPs with invasion of the spinal canal, most patients (19 out of 36) were observed to have thoracic spinal cord involvement, similar to our case [28].

Prior studies have suggested that direct plasma cell infiltration of the pleura is the mechanism of MPE development, and patients with adjacent chest wall or pulmonary lesions more commonly develop MPE. Of the cases of MPE we reviewed, the majority (78.9%, 15/19) followed this pattern: chest wall (7/19), mediastinal (3/19), pleural thickening (2/19), para-tracheal (1/19), and pericardial (1/19). Like pleural effusions from other etiologies, our review suggested MPEs have a right-sided preponderance in the setting of concurrent soft tissues EMPs. The number in our selected cases are 11 on the right side, 5 bilateral, and 4 on the left side. This is consistent with one prior observational study [26], but differed from another study reporting left side more commonly involved than right [7]. The reason for this tendency remains unclear.

Although MPE has been reported to be associated with IgG kappa [26] or IgA subtype [7], we have not seen very concentrated distribution in subtypes, with 6 IgG kappa and 6 IgA (1 lambda, 5 kappa) in the 19 cases.

Diagnosis and differentials

EMPs can be found at diagnosis or at relapse of MM with screening by imaging modalities like PET-CT and MRI. Serum Protein Electrophoresis (SPEP) with immunofixation and quantitation of immunoglobulins and serum light chains can also be helpful. The key part of diagnosis is to confirm the presence of malignant plasma cells based on both cytology and immunohistochemistry in the biopsy of EMPs tissues. Thoracentesis followed by pleural fluid studies are essential to diagnose suspected MPE.

In a recent retrospective study of MM patients with pleural effusions, MPE was found in as high as 38.2% of patients [6]. The true rate can be even higher given not all patients undergo appropriate diagnostic evaluation with thoracentesis and biopsy. In our case, the pleural fluid flow cytometry found involvement by an abnormal

lymphoplasmacytic population consistent with surface lambda light chain-restriction. A rare differential diagnosis which was considered was Primary Effusion Lymphoma (PEL). All patients with PEL have HHV-8 infection and many have EBV infection. Therefore, in situ hybridization testing of pleural fluid for HHV-8 and EBV are needed to exclude the possibility of PEL. In areas with high prevalence of Tuberculosis (TB), possible etiology of pleural effusions also includes reactive pleural effusion to TB. It has been previously reported that localized extramedullary plasma cell proliferation can be a transient reactive process to pulmonary TB, which subsides when the underlying TB is treated [29].

In our case, the BM pathology and flow cytometry were both negative for plasma cell neoplasm. This can be due to patchy myeloma involvement as noted on PET-CT, which is seen in approximately 4% of MM patients [30]. In this case, there was diagnostic suspicion for underlying genetic syndrome such as PTEN hamartoma tumor syndrome due to hemangiomas in brain and spine, lipomas, and hematologic malignancy, but genetic testing was not performed prior to our patient's passing.

Treatment

Extramedullary Disease (EMD) was reported to be resistant to conventional treatments but responded well to regimens containing novel drugs such as bortezomib. In a recent review [1], an approach to EMD in newly diagnosed MM is suggested for elderly patients with age greater than 65 years with CyBorD as an initial induction therapy followed by lenalidomide-bortezomib-dexamethasone (RVd) regimen, and then high-dose chemotherapy and autologous stem cell transplant can be considered based on the response. As observed in the 19 cases with concurrent EMPs and MPE over the past three decades, treatment has always been a challenge with no consistent results or trends. However, considering MPE is a rare form of EMPs, the observed benefit still favors the trial of CyBorD as an initial therapy. In our case, patient showed excellent radiographical response to only one cycle of CyBorD prior to her unexpected passing.

Prognosis

MPE confers very poor prognosis with a median time of death of 4 months from onset of the pleural effusions [7]. In a case series of 19 patients with MPE, seven expired within 3 months after initial diagnosis of MPEs, and 2 more expired within 12 months of MPE diagnosis. Among cases with reported cause of death (9 out of 19), most were attributed to direct progression of MM (7/9). In our case, the patient passed due to complications from an aspiration event, which is not a typical sign of MM progression. In a prior observational study of 23 MM patients with MPE, respiratory failure and cardiac tamponade were the two most common causes of death [31].

Conclusion

This data along with our case suggest that patients with MPE may be more likely to deteriorate from pulmonary and/or cardiogenic events rather than the more commonly known complications of MM such as infection or renal failure.

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