Case Report

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Pleural Involvement and True Hyponatraemia in Multiple Myeloma: A Report of Two Rare Cases

Internal Medicine Section

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ABSTRACT

Multiple Myeloma (MM) is a plasma cell proliferative malignancy that produces monoclonal immunoglobulin. Pleural effusion in MM, caused by the direct infiltration of the pleural space by plasmacytes, leading to true myelomatous pleural effusion, is rare. Patients with MM often exhibit pseudohyponatraemia due to high serum paraprotein levels; a far less common occurrence is true hyponatraemia resulting from the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH). This report presents two such cases. In Case 1, a 45-year-old woman with no known co-morbidities presented with complaints of shortness of breath and pain in both hips. Investigations revealed anaemia, renal impairment, a reversed albumin-to-globulin ratio and the presence of an M band on serum electrophoresis. Imaging showed lytic lesions and minimal pleural effusion. A bone marrow biopsy confirmed plasmacytosis and diagnostic pleural tapping was performed, revealing malignant myelomatous pleural effusion. The pleural effusion progressed to a massive effusion, necessitating therapeutic tapping. Despite treatment with dexamethasone, cyclophosphamide and bortezomib, the patient eventually succumbed. In Case 2, a 56-year-old man, previously treated for MM, presented with complaints of back pain, giddiness and vomiting. Investigations revealed anaemia, hyponatraemia and elevated globulin levels. A Positron Emission Tomography-Computed Tomography (PET-CT) scan indicated the possibility of relapse. The patient exhibited low serum osmolality alongside high urine spot sodium and urine osmolality, while renal, adrenal and thyroid functions were normal, pointing towards SIADH. He responded well to fluid restriction, salt supplementation, tolvaptan and chemotherapy, resulting in the resolution of hyponatraemia. These cases are reported to shed light on the various presentations of MM that may be overlooked during patient evaluation.

Keywords: Myelomatous pleural effusion, Plasma cell myeloma, Syndrome of inappropriate antidiuretic hormone secretion

CASE REPORT

Case 1

A 45-year-old woman with no known co-morbidities presented with complaints of shortness of breath, dull aching pain in both hips that was non radiating, persistent and of moderate intensity, as well as generalised fatigue for one month. Upon examination, she exhibited pallor, stable vitals and was euvolemic.

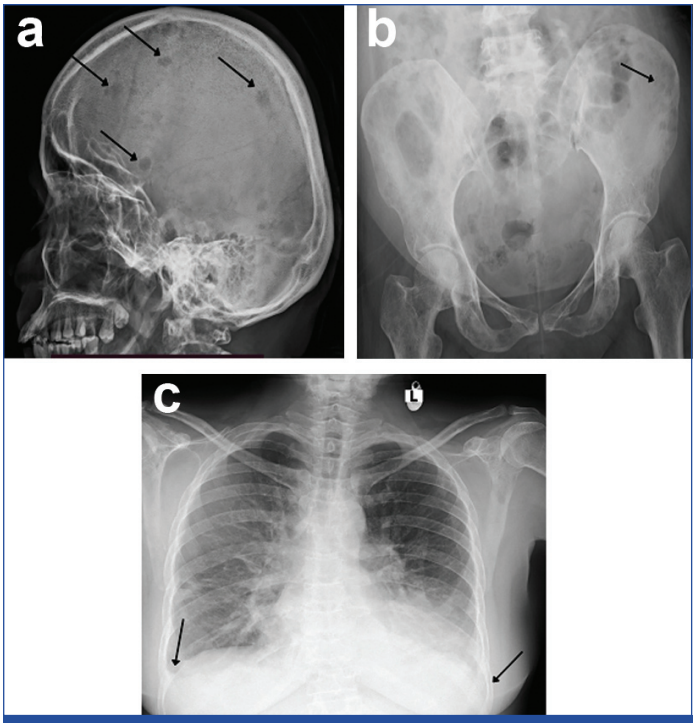
Systemic examination revealed decreased air entry intensity in the bilateral infrascapular regions, while other systemic examinations were normal. Investigations showed a high creatinine level of 2 mg/dL, a low albumin level of 2.7 g/dL and a low haemoglobin level of 6.3 g/dL, with normal White Blood Cells (WBC) and platelet counts. There was also a reversed Albumin:Globulin (A:G) ratio of 0.8. Elevated levels of beta-2 microglobulin (16.9 mg/L) and Lactate Dehydrogenase (LDH) (274 U/L) were noted [Table/Fig-1]. An echocardiogram indicated an Ejection Fraction (EF) of 64% with no Regional Wall Motion Abnormalities (RWMA). X-rays of the skull and pelvis showed punched-out lytic lesions [Table/Fig-2a,b]. An initial chest X-ray revealed minimal pleural effusion [Table/Fig-2c].

Serum protein electrophoresis indicated the presence of an M band, suggesting a monoclonal gammopathy [Table/Fig-3]. The patient was started on a regimen of dexamethasone, cyclophosphamide and bortezomib. During the treatment, she experienced severe breathlessness due to a progressive massive pleural effusion that developed from the initial minimal pleural effusion [Table/Fig-4], resulting in a drop in SpO_2 to 85%.

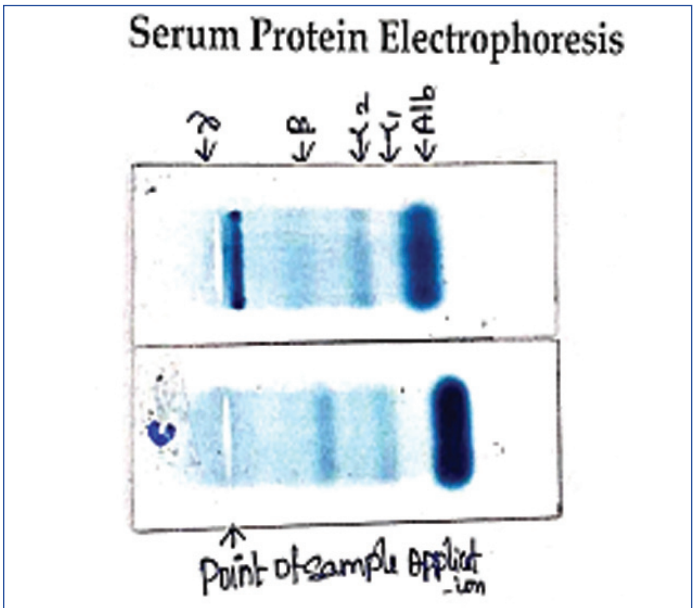
A bone marrow biopsy confirmed plasmacytosis [Table/Fig-5] and therapeutic pleural tapping was performed and cytological analysis of the pleural fluid revealed a malignant pleural effusion from a poorly differentiated malignancy. The analysis showed a cellular smear with clusters of reactive mesothelial cells and loosely aggregated, discretely arranged atypical plasma cells with pleomorphic, hypochromic nuclei. Binucleate, multinucleate and bizarre-looking

Investigations	Observed values	Laboratory reference values
Haemoglobin (Hb) (g/dL)	6.3	12-15
Creatinine (mg/dL)	2	0.6-1.2
Albumin (g/dL)	2.7	3.5-5.2
WBC (cu.mm)	6060	4000-11000
Neutrophil (%)	71.1	40-80
Platelets (cu.mm)	1,82,000	1,50,000-4,10,000
A:G Ratio	0.8	1.4-1.7
Beta-2 Microglobulin (mg/dL)	16.9	1.09-2.53
LDH (U/L)	274	125-220
Urea (mg/dL)	38	17-43
BUN (mg/dL)	18	6-20
Sodium (mmol/L)	132	136-145
Potassium (mmol/L)	3.5	3.5-5.1
Chloride (mmol/L)	98	98-107
Bicarbonate (mmol/L)	28	21-31
Calcium (mg/dL)	15	8.8-10.6
Fasting glucose (mg/dL)	89	70-100
Postprandial glucose (mg/dL)	114	70-140
Uric acid (mg/dL)	12.3	2.6-6
Total bilirubin (mg/dL)	0.4	0.5-1
Direct bilirubin (mg/dL)	0.07	0.3
Indirect bilirubin (mg/dL)	0.34	0.8
ESR (mm/hr)	60	0-12
TSH (µlU/L)	1.83	0.4-4
Free T3 (pg/dL)	2.58	2.5-3.9
Free T4 (ng/dL)	1.98	0.58-1.64

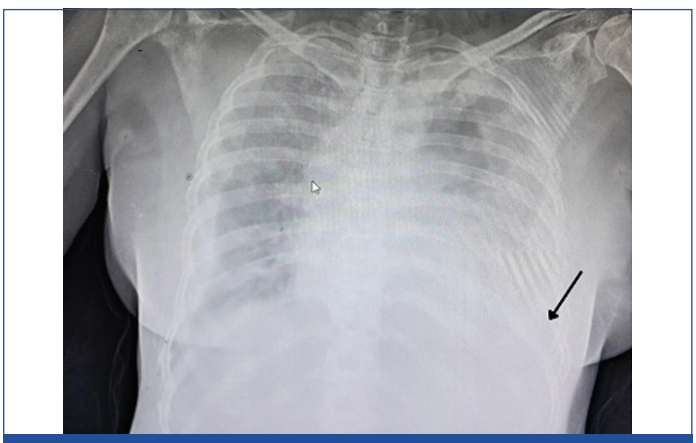
[Table/Fig-1]: Laboratory investigations.
WBC: White blood cells; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; TSH: Thyroid stimulating hormone; BUN: Blood urea nitrogen



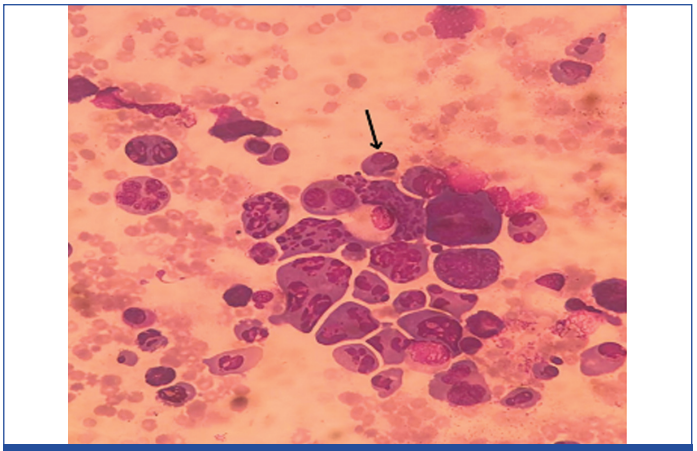
[Table/Fig-2]: Radiological findings in Case 1 demonstrate Multiple Myeloma (MM) -related skeletal and thoracic involvement. Lateral skull X-ray; a) Shows multiple punched-out lytic lesions (black arrows). Pelvis X-ray; b) Reveals lytic lesions in the pelvis (black arrow). Chest X-ray in posteroanterior view; c) Indicates minimal bilateral pleural effusion (black arrows).



[Table/Fig-3]: Serum protein electrophoresis in Case 1 showing a discrete prominent M band in the gamma region, suggestive of monoclonal gammopathy, when compared with control.

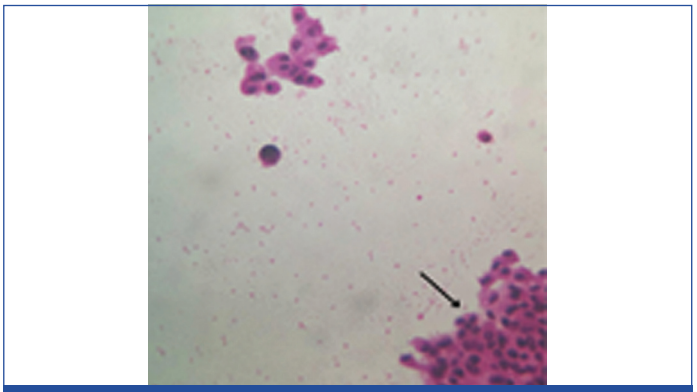


[Table/Fig-4]: Chest X-ray in posteroanterior view showing progression to massive left-sided pleural effusion (black arrow).



[Table/Fig-5]: Bone marrow biopsy showing plasmacytosis (black arrow).

atypical cells were also observed [Table/Fig-6]. The patient was classified under the International Staging System as Stage 3 and Durie-Salmon Staging as Stage 3, indicating a poor prognosis [1].



[Table/Fig-6]: Pleural cytology showing atypical plasma cells (black arrows).

During her hospital stay, she did not respond well to the regimen of dexamethasone, cyclophosphamide and bortezomib and ultimately succumbed to her illness.

Case 2

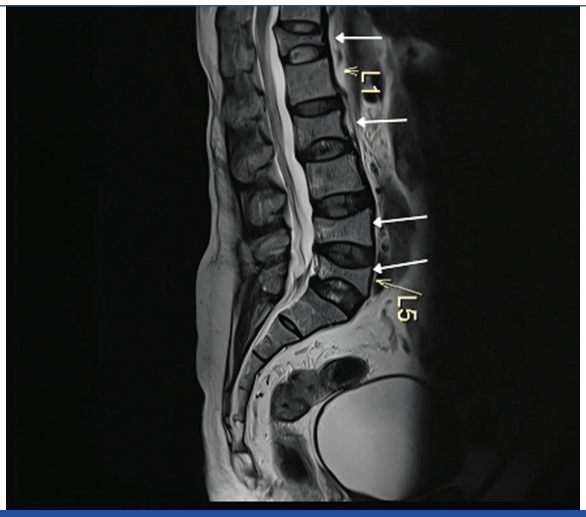
A 56-year-old man was diagnosed with Multiple Myeloma (MM) three years ago and completed 13 cycles of chemotherapy. He presented with complaints of back pain for the past two months, giddiness for the last 10 days and nausea and vomiting for seven days. Upon examination, the patient exhibited pallor, but his vital signs were stable. Systemic examination was unremarkable, with a Glasgow Coma Scale score of 15/15 and no focal neurological deficits.

All routine and relevant investigations were conducted, revealing a creatinine level of 1 mg/dL, a decreased haemoglobin level of 6.5 g/dL, serum sodium at 121 mmol/L, potassium at 3.5 mmol/L, a low albumin level of 2.7 g/dL, globulin of 9.3 g/dL and a reversed A:G ratio of 0.3. LDH was elevated at 585 U/L. Other results included free T3 of 2.78 pg/mL, free T4 of 1.58 ng/dL, Thyroid-Stimulating Hormone (TSH) of 1.83 µIU/mL, serum uric acid of 5 mg/dL, serum cortisol of 9.6 µg/dL, serum osmolality of 265 mosm/kg, urine osmolality of 504 mosm/kg and urine spot sodium of 74 mmol/L [Table/Fig-7]. An echocardiogram showed an EF of 64% with no RWMA.

Magnetic Resonance Imaging (MRI) of the spine revealed wedge compression fractures of the T12, L2, L4 and L5 vertebral bodies [Table/Fig-8]. Serum protein electrophoresis indicated the presence of an M band, suggesting a monoclonal gammopathy [Table/Fig-9]. Bone marrow aspiration yielded a diluted sample. A PET CT scan confirmed the wedge compression fractures, sclerosis in the D12, L2 and L5 vertebrae and increased metabolic activity, suggesting a potential relapse.

Investigations	Observed values	Laboratory reference values
Haemoglobin (Hb) (g/dL)	6.5	12-15
Creatinine (mg/dL)	1	0.6-1.2
WBC (cu.mm)	8,800	4000-11000
Neutrophil (%)	66	40-80
Platelets (cu.mm)	1,75,000	1,50,000-4,10,000
Sodium (Na^+) (mmol/L)	121	136-145
Potassium (K^+) (mmol/L)	3.5	3.5-5.1
Chloride (mmol/L)	99	98-107
Bicarbonate (mmol/L)	15	21-31
Total bilirubin (mg/dL)	0.60	0.5-1
Direct bilirubin (mg/dL)	0.03	0.3
Indirect bilirubin (mg/dL)	0.57	0.8
Albumin (g/dL)	2.7	3.5-5.2
A:G Ratio	0.3	1.4-1.7
BUN (mg/dL)	24	6-20
Urea (mg/dL)	51	17-43
LDH (U/L)	585	125-220
Free T3 (pg/dL)	2.78	2.5-3.9
Free T4 (ng/dL)	1.58	0.58-1.64
TSH (µIU/mL)	1.83	0.4-4
Uric acid (mg/dL)	5	2.6-6
Serum cortisol (µg/dL)	9.6	3.7-19.4
Serum osmolality (mosm/kg)	265	275-285
Urine osmolality (mosm/kg)	504	50-1200
Urine spot sodium (mmol/L)	74	0-40
Fasting glucose (mg/dL)	92	70-100
Postprandial glucose (mg/dL)	134	70-140

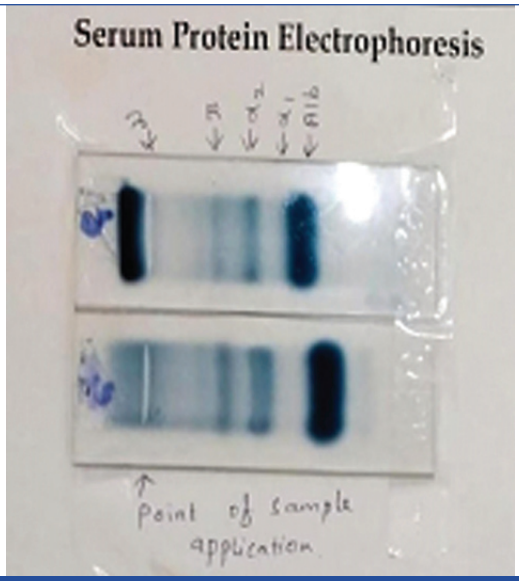
[Table/Fig-7]: Laboratory investigations.



[Table/Fig-8]: MRI sagittal section of the lumbar spine showing a wedge compression fracture of T12, L2, L4 and L5 vertebral bodies (white arrows).

Typically, in MM, pseudohyponatraemia occurs due to the displacement of water by high globulin content in the blood [2]. However, in this case, there was hypo-osmolality, increased urine spot sodium, increased urine osmolality, euvolemia and normal renal, adrenal and thyroid function, pointing toward true hyponatraemia due to SIADH, fulfilling Bartter-Schwartz criteria [3].

The patient was started on a regimen of dexamethasone, cyclophosphamide and vincristine; salt capsules were administered, along with tolvaptan and fluid restriction. Subsequently, the patient's serum sodium improved to 136 mmol/L and his symptoms of hyponatraemia, such as giddiness, nausea and vomiting, resolved. The patient received three cycles of chemotherapy, but later, due to personal issues, he committed suicide.



[Table/Fig-9]: Serum protein electrophoresis in Case 2 showing a discrete M band in the gamma region, suggestive of monoclonal gammopathy, when compared with the control.

DISCUSSION

The MM is a plasma cell proliferation malignancy that can result in extensive destruction of the skeleton, leading to osteopenia, pathologic fractures and/or osteolytic lesions due to plasma cell proliferation in the bone marrow [4]. MM constitutes 10% of haematologic malignancies. Pleural effusion occurs in 6% of cases of MM, with true malignant myelomatous pleural effusions accounting for less than 1% of these cases [5]. Pleural effusion in MM often arises from amyloidosis-induced restrictive cardiomyopathy, which results in cardiac failure, or from hyperviscosity and renal failure causing oliguria. Infections can lead to either parapneumonic effusion or true myelomatous effusion from plasmacyte infiltration of the pleura. Myelomatous pleural effusions may arise from invasion by neighbouring skeletal lesions, extension of chest wall plasmacytomas, direct pleural infiltration by myeloma (pleural plasmacytoma), or lymphatic blockage due to lymph node infiltration [6,7].

The most common diagnostic method for pleural effusion in MM is cytological analysis of the pleural fluid [8]. Due to the patient's poor general condition, a pleural biopsy was not performed in Case 1. Pleural biopsies can be risky and are not always diagnostic due to the patchy nature of the disease; thus, they are not routinely conducted [4,6]. In these cases, the distinctive clock-faced condensed chromatin pattern is absent. The nuclei of these cells are spherical to oval or pleomorphic, exhibiting a coarse and uneven chromatin structure with prominent nucleoli. Flow cytometry studies can also supplement the diagnosis; however, non specific light chain staining may occur due to poor-quality specimens [7].

Maat Z et al., reported pleural effusion as the first manifestation of MM in a 44-year-old patient with moderate pleural effusion [9]. Case 1 mimics this rare presentation, making early suspicion crucial. Myelomatous pleural effusion has a mortality rate of 90.9% and a median survival of 2.47 months [9].

Typically, increased serum paraprotein levels in myeloma result in pseudohyponatraemia rather than true hyponatraemia. These paraproteins cause displacement of water, leading to low serum sodium levels. When considering hyponatraemia, the presence of SIADH should be investigated when urine osmolality surpasses serum osmolality [2]. A serum osmolality of 280 mOsm/kg or above indicates pseudohyponatraemia, whereas true hyponatraemia is characterised by a serum osmolality of less than 280 mOsm/kg.

In patients with true hyponatraemia, a urine osmolality greater than 100 mOsm/kg (signifying poor water excretion) and a urine sodium concentration of 20 mmol/L or higher make the diagnosis of SIADH probable [2]. To establish this diagnosis, it is important to

exclude causes of salt wasting, the usage of diuretics and thyroid, adrenal and pituitary insufficiency. Generally, ADH levels are not routinely assessed; the diagnosis of SIADH is based on the Bartter-Schwartz criteria (1967) [10], which include hyponatraemia, true hypo-osmolality, increased urine sodium levels, euvolemia, normal renal, adrenal and thyroid function and correction of hyponatraemia through fluid restriction [3].

One important mechanism for the development of SIADH in myeloma is the increased production of Interleukin-6 (IL-6) by myeloma cells [2]. Arginine Vasopressin (AVP) is secreted from the posterior pituitary in response to IL-6 [11]. Elevated AVP stimulates adenylate cyclase in aquaporin-2, resulting in increased intracellular cyclic Adenosine Monophosphate (cAMP), which promotes water retention at the apical membrane of the renal collecting duct [2]. Similar cases have been reported, including cases of a 60-year-old and a 61-year-old patient who had SIADH associated with MM [2,12]. Case 2 mimics this rare presentation.

CONCLUSION(S)

Despite being rare, myelomatous pleural effusion at presentation usually indicates a poorer prognosis and requires prompt treatment. MM may manifest with diverse clinical features, potentially delaying the diagnosis and treatment of patients. Therefore, these cases are reported to draw clinicians' attention to these atypical presentations. Advancements in research and management protocols for this condition may improve the low survival rates among this patient population.

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