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CASE ARTICLE

Unconventional Presentation of Multiple Myeloma: A Series of Three Cases

Kalita Lohit kumar[1], Kalita Chayanika[2], Gogoi Pabitra Kumar[3], Sarma Umesh Chandra[4]

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ABSTRACT

Multiple myeloma is a clonal plasma cell malignancy, characterized by the proliferation of neoplastic plasma cells. Usually abnormality of most plasma cell originates as bone marrow tumor, but they occasionally present in extra medullary sites. Here, we report a series of three cases of multiple myeloma presenting with extra medullary dissemination in pulmonary parenchyma, acute renal failure at young age and non-specific back pain with a view to demonstrate the variability in the presentation of multiple myeloma which can easily be missed and give us insight for considering the possibility of multiple myeloma with such uncommon findings.

***Keywords**: Multiple myeloma, plasma cell, bone marrow, haemoglobin*

Address for correspondence and reprint:

[1]Assistant Professor of Oncology (**Corresponding Author**)
Gauhati Medical College and Hospital (GMCH)
Email: lkkalita2013@gmail.com
Mobile: 9435061804
[2]Assistant Professor of Dermatology, [3]Prof. (Rtd) of Clinical Hematology, GMCH, [4]Vice-Chancellor, Srimanta Sankadeva University of Health sciences, Guwahati, Assam

INTRODUCTION

In multiple myeloma the circulating monoclonal immunoglobulins and/or their subunits are leading cause of Proteinuria, renal tubular damage and amyloid deposits. Stimulation of osteoclasts results in hypocalcaemia and bone loss.[1,] About 1-5% cases may not demonstrate immunoglobulins or their subunits in serum or urine (non-secretory multiple myeloma).[3] The occurrence of extramedullary disease is uncommon in multiple myeloma. The sites of extramedullary dissemination reported in the literature are spleen, liver, kidney, thyroid, adrenal, ovary, lung, pleura, and pericardium.[4]

Case report-1: A 55-year-old male came with a vague complaint of progressive mild chest pain, cough, mild breathlessness, palpitation on exertion and intermittent low grade fever for last two months duration and severe itching for last two days. The patient was a non-smoker, non-alcoholic with no history of fever or preceding trauma. Physical examination revealed no significant abnormality except mild pallor. There was no sign of pulmonary hypertension, organomegaly, cardiac or renal failure. The liver function was within normal limit. Laboratory investigation revealed haemoglobin –8 g/dl, ESR-90 mm (AEFH), peripheral smear showed marked rouleaux formation, random blood sugar – 80 mg/dl, LDH-940 U/L, serum creatinine – 0.9 mg/dl, pleural fluid for ADA 12.6 U/L, Serum protein electrophoresis showed no M –band, â2-microglobulin-3.40 mg/L (normal – 0.81 – 2.19 mg/L), bronchial lavage fluid did not show malignant cells, no acid fast bacillus and fungal elements seen on bronchial aspirate, prostate specific antigen - 0.92 ng/ml. Chest radiographs suggested left sided pleural effusion with mediastinum shifting towards right side causing

obliteration of the cardiac shadow (**Figure 1**) X-ray of skull showed multiple punched out radiolucent lytic areas. Percutaneous fine needle aspiration cytology and biopsy from pleura was done which showed cellular infiltrate comprising mature and immature plasma cells, including binucleate and multinucleate forms along with pulmonary parenchymal cells (**Figure 2**). Bone marrow aspiration examination showed 70% plasma cell constituting both mature and immature type (**Figure 3**).There was no Bence Jones protein in urine. **Diagnosis of plasmacytoma was suggested and further work up of patient was advised to rule out pulmonary dissemination of multiple myeloma.** Based on these findings, a final diagnosis of multiple myeloma of plasmablastic type was made.

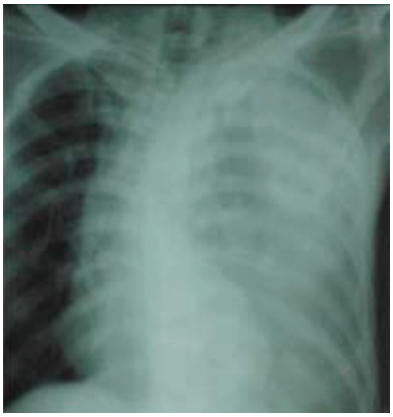

Figure 1 Chest radiographs suggested left sided pleural effusion with mediastinal midline shift

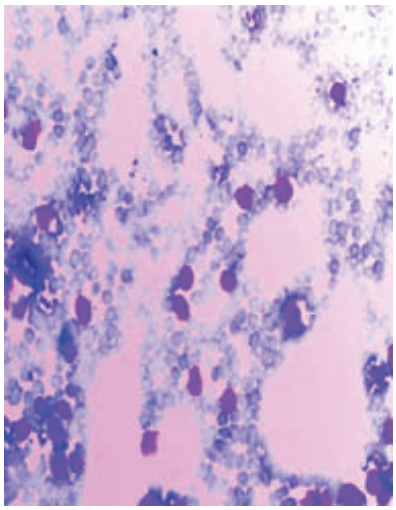

Figure 2 Histology of pleural aspirate shows plasma cells in necrotic proteineous and haemorrhagic background (40X)

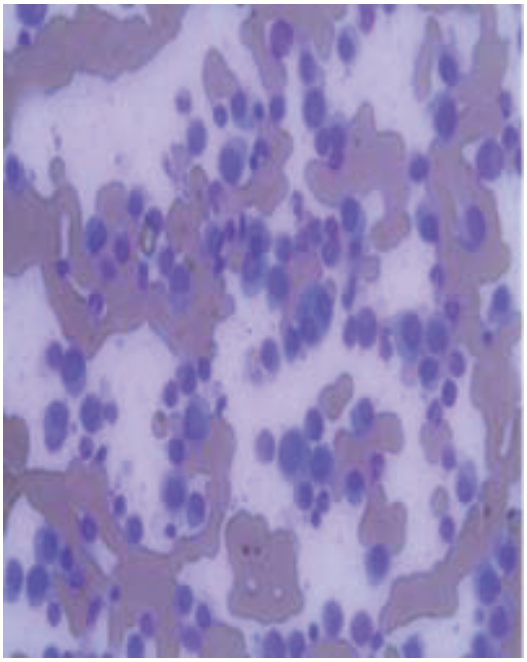

Figure 3 Bone marrow aspiration examination showed 70% plasma cell constituting both mature and immature type (H and E : 20X)

Case report-2: A 38-year-old male experienced abdominal cramps associated with nausea, vomiting, and decreased appetite. Physical examination revealed only mild discomfort on deep palpation of abdomen. Investigation revealed haemoglobin (4.4 g/dl) , ESR – 90 AEFH, . Serum urea - 131 mg/dl (19.26 – 42.8 mg/dl) , serum creatinine 8.4 mg/dl (0.66 – 1.25 mg/dl) with normal serum calcium and total protein. X-ray skull, pelvis, spine and long bones was normal. Urine analysis showed mild proteinuria, hematuria and granular casts. Serum protein electrophoresis did not show M spike (Figure-1). Serum protein immunotyping showed polyclonal gammopathy (**Figure 4**). There was no Bence Jones protein in urine. Bone marrow cytology revealed 70% plasma cells (**Figure 5**). Bone marrow trephine biopsy showed hypercellular marrow particles with atypical plasma cell infiltration consistent with plasma cell. Serum free light chain assay revealed kappa 33 mg/dl (3.3 0 – 19.40 mg/L) and lamda 29 mg/L (5.70 – 26.30 mg/L). Urine protein electrophoresis revealed total protein 0.67 g/24 hours and total volume 1000 ml/24 hours. Cytogenetic profile revealed normal Karyotype 46, XY. Based on these findings patient was diagnosed as multiple myeloma with acute renal failure. He was treated with Bortezomib-Dexamethasone and also underwent dialysis.

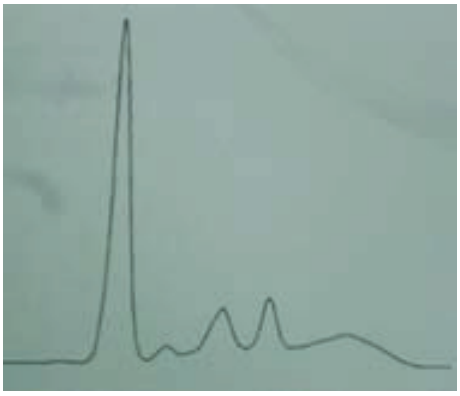

Figure 4 Serum Protein Electrophoresis shows no M band in gamma region

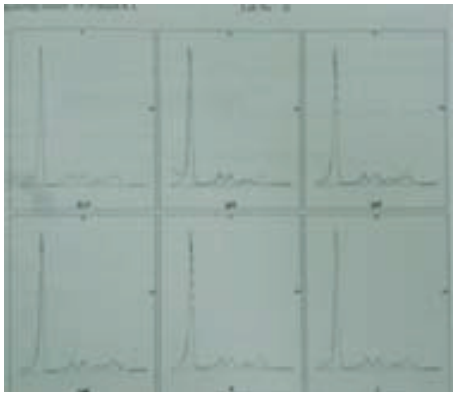

Figure 5 Serum Protein Immunotyping shows polyclonal gammopathy

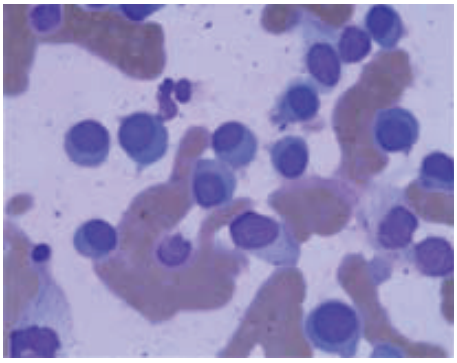

Figure 6 Histopathology of bone marrow aspiration shows large amount of plasma cell (40X)

Case Report-3: A 53-year-old female experienced pain in the back bone and right knee joint for three years duration without any such past history. Examination revealed tenderness on the right side of the thoracolumbar spine along with paravertebral muscle spasm , normal hip joint and neurological deficit. Laboratory evaluation revealed mild low haemoglobin and normal biochemical parameters. Radio imaging revealed collapse and compression fracture of T9 vertebrae (**Figure 7**). Bone scan showed abnormal increase uptake in thoracolumbar vertebrae, multiple bilateral ribs and right iliac bone. Serum protein electrophoresis was normal (**Figure 8**). There was no Bence Jones protein in urine. Bone marrow aspiration revealed a hypercellular marrow with near total replacement by mature and immature plasma cells (80%) (**Figure 9**). Diagnosis of non-secretory multiple myeloma was made. Patient received radiation to relieve her back pain followed by chemotherapy.

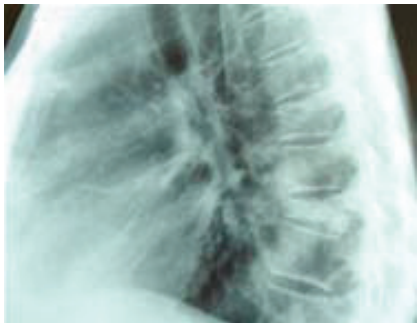

Figure 7 X-ray of dorsolumber spine shows collapse vertebrae at D9

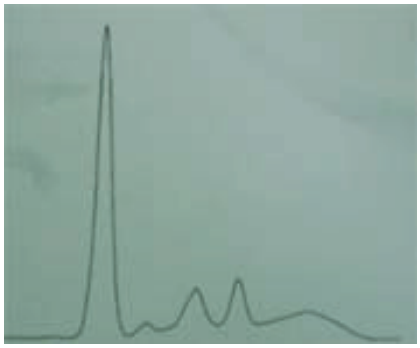

Figure 8 Normal Serum protein electrophoresis

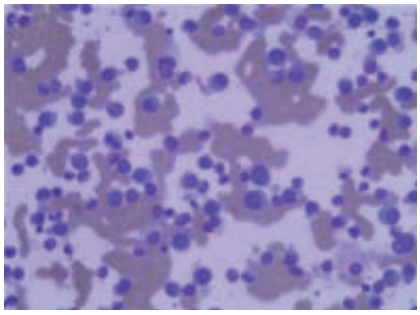

Figure 9 Histology of bone marrow aspiration shows large amount of mature and immature plasma cells (H and E : 10X)

DISCUSSION

Multiple myeloma is a clonal proliferation of plasma cells that occurs in older adults, median age at diagnosis is about 70 years.[5,6] Presenting symptoms include fatigue, generalized weakness, weight loss, bone pain, and there is often evidence of some organ damage.[7]The diagnosis of multiple myeloma depends on a concurrence of features, and several different diagnostic criteria as suggested by the International Myeloma working group.[8] They also have an increased risk of vertebral compression fractures.[9]One of our patients experienced nonspecific pain in his chest, back and knee joint with no improvement with symptomatic treatment. Typically, pain of pathological origin should be suspected in patients whose age is over 50, a previous history of cancer, no relief with rest, resistant to treatment and constitutional symptoms such as unexpected weight loss, fever, and fatigue.[10]Differential diagnosis includes metastatic tumors, lymphomas, primary bone lesions and other lesions of hematopoietic origin such as langerhan's cell histiocytosis.[11]Radiographic evaluation should always be persuaded in patients with pain. Our first case was diagnosed as multiple myeloma with plasmablastic malignant effusion. Malignant pleural effusion is usually a rare and late complication in the course of the disease.[9]Hence other aetiologies of reactive pleural effusions like pneumonia, tuberculosis, congestive heart failure, collagen vascular disease, viral illness, carcinomatosis, AIDS and pulmonary thromboembolism should be excluded before a diagnosis of malignant myelomatous effusion is made.[12]On cytological examination, the picture can have a predominant lymphocytic infiltration with scattered plasma cells showing atypical nuclear features. Other common conditions of the non-myelomatous effusions that present with pleural effusion includes Non-Hodgkin Lymphoma, acute and chronic lymphoid leukaemia, especially those with concomitant mediastinal involvement.[13] The three processes like Pleural fluid electrophoresis, flow cytometry and immunocytochemistry aid in confirming the monoclonality of the plasma cells.[12]Usually 15% to 30% of patients of multiple myeloma present with acute renal failure at the time of diagnosis and approximately 20% of the patient develops progressive renal failure during the course of the disease.[14]Renal function returns to normal after treatment in about 50% of patients.[15]In our case 2 young males suffering from acute renal failure with no evidence of anemia or hypercalcaemia despite numerous destructive bone lesion, made it a rare presentation of multiple myeloma. Multiple myeloma should always be considered in differential diagnosis of unexplained ARF in middle aged and elderly persons.[16] Rarely in advanced multiple myeloma, metastatic deposits outside the bone marrow (extramedullary) are seen.

Multiple myeloma patients also have an increased risk of vertebral compression fractures.[9] In case number -3, the patient experienced nonspecific pain in his chest, back and knee joint with no improvement with symptomatic treatment. Typically, pain of pathological origin should be suspected in patients whose age is over 50, a previous history of cancer exists, no relief with rest, resistant to treatment and constitutional symptoms such as unexpected weight loss, fever, and fatigue.[17]Differential diagnosis includes metastatic tumours, lymphomas, primary bone lesions and other lesions of hematopoietic origin such as Langerhan's cell histiocytosis.[18] Radiographic evaluation should always be persuaded in patients with pain. In nonsecretory multiple myeloma (NSMM), the plasma cells presumably fail to secrete an immunoglobulin. The first case of this variant was described in 1958, and the reported incidence has ranged from 1% to 5% of all cases of MM.[19]We present a case of delayed diagnosis of NSMM because of its illusive nature. Nonsecretory multiple myeloma is a variant of the classic form of MM and has a similar clinical presentation except for the absence of monoclonal gammopathy. Two types of NSMM have been described. In the first type, the plasma cells produce immunoglobulin but are not able to secrete it out of the cell. This form of NSMM the "producer" type (also called true nonsecretory or nonexcretory myeloma). In the "nonproducer" type, the plasma cells are unable to produce immunoglobulin. Although it is difficult to determine the exact frequency of the two types, more cases of the producer type have been reported.[20-22] At initial presentation, patients with NSMM usually have more advanced disease than those with classic myeloma. Although survival ranges from 6 months to 12 years, it may certainly be affected by a delay in diagnosis. Most published reports suggest that there is no significant difference in survival between NSMM and MM.[22-25]

CONCLUSION

The signs and symptoms of multiple myeloma are nonspecific. Patients can present in a variety of clinical settings, which may delay the diagnosis and result in additional disease related complications. We want to bring the clinicians attention to some uncommon presentations

of multiple myeloma which are missed because of few unconventional findings. In addition to a tissue biopsy, bone marrow aspiration, serum protein electrophoresis, ESR and Bence–Jones proteins in urine must be carried out to confirm the diagnosis

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Dr. Madhab Ch. Rajbangshi MS PhD is presently working as assistant professor of Surgery in Gauhati Medical College and Hospital, Guwahati, Assam and a founder member of IJHRMLP. He has completed his Ph.D. on the topic of "A Clinico-epidemiological Evaluation of gallstone Disease in Assam" under Gauhati University in the year 2015.