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Case Series

Pancytopenia as the initial presenting feature in multiple myeloma: a case series

Somnath S. Roy*, Aritra Saha, Ajit K. Pegu, Navil F. Islam, Jinku Ozah, Sofiur Rahman

Department of Medicine, Assam Medical College and Hospital, Dibrugarh, Assam, India

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***Correspondence:**
Dr. Somnath S. Roy,
E-mail: docroy14@gmail.com

ABSTRACT

Multiple myeloma is a plasma cell neoplasm characterized by abnormal proliferation of clonal cells in the bone marrow. Anaemia is generally the most common feature from hematologic aspect and bone pain being the other important symptom, but pancytopenia as the presenting feature is unusual. Here, we shared our experience of 3 cases with non-specific symptoms with pancytopenia which on through evaluation revealed our diagnosis. A hospital based observational descriptive case series was conducted wherein all the cases of multiple myeloma presenting with pancytopenia were included. Complete blood picture, peripheral smear, bone marrow aspirate and serum protein electrophoresis were reviewed and analysed. Pancytopenia as the initial presenting feature of multiple myeloma is an unique manifestation and diagnosing such cases require high degree of suspicion to avoid delay in the initiation of treatment.

Keywords: Pancytopenia, Multiple myeloma, Initial presentation

INTRODUCTION

Multiple myeloma is a plasma cell neoplasm characterized by abnormal proliferation of clonal cells in the bone marrow causing an increase in monoclonal immunoglobulins resulting in anaemia, hypercalcemia, renal dysfunction and pain due to osteolytic lesions and ultimately leading to specific end organ damage.[1] Multiple myeloma accounts for almost 10% of all hematologic malignancies and is the second most common hematologic malignancies in developed nations, with a median age of diagnosis in USA of 70 years and approximately 72 years in Europe.[4,19] The median age of diagnosis in India varies between 65 to 70 years.[5]

Multiple myeloma is classified as, monoclonal gammopathy of clinical significance (MGUS), solitary plasmacytoma, smouldering (asymptomatic) disease, or active (symptomatic) disease and the initial presenting feature in patients with myeloma can vary, ranging from asymptomatic disease and fatigue to life threatening renal failure.[1]

In general bone pain is the most common presenting complaint, from hematological aspect, clinical and laboratory features of anemia is the usual one, but pancytopenia as the presenting feature is unusual.[2,6]

Here, we shared our experience of three cases of multiple myeloma who presented with nonspecific symptoms with an underlying pancytopenia and a thorough evaluation revealed the diagnosis of multiple myeloma.

CASE SERIES

Case 1

A 53-year-old woman, resident of the northern part of the state of Assam, presented to the medicine outpatient department of Assam Medical College and Hospital with the chief complaints of easy fatiguability, palpitation and

decreased appetite from 1month. She had a history of an episode of gum bleed which was self-limiting. Following that event her appetite gradually deceased and eventually her general wellbeing declined and henceforth she presented to our institute. The patient did not give any history of trauma, bleeding diathesis, recreational drug abuse or any similar history in the past, or in her family. The patient had no known comorbidities.

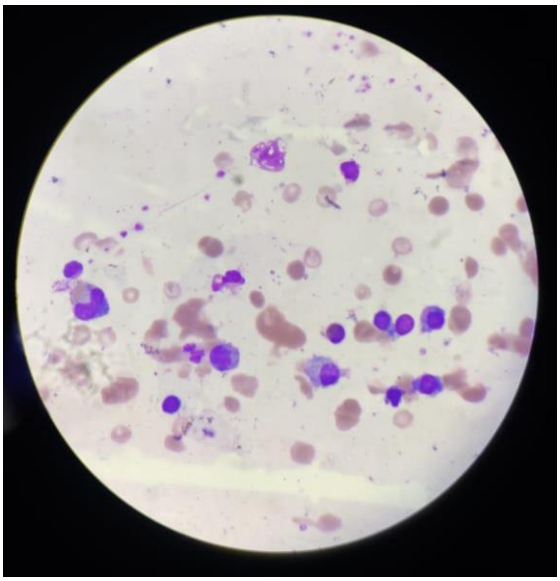

Figure 1: Bone marrow examination showing plasma cells of case 1.

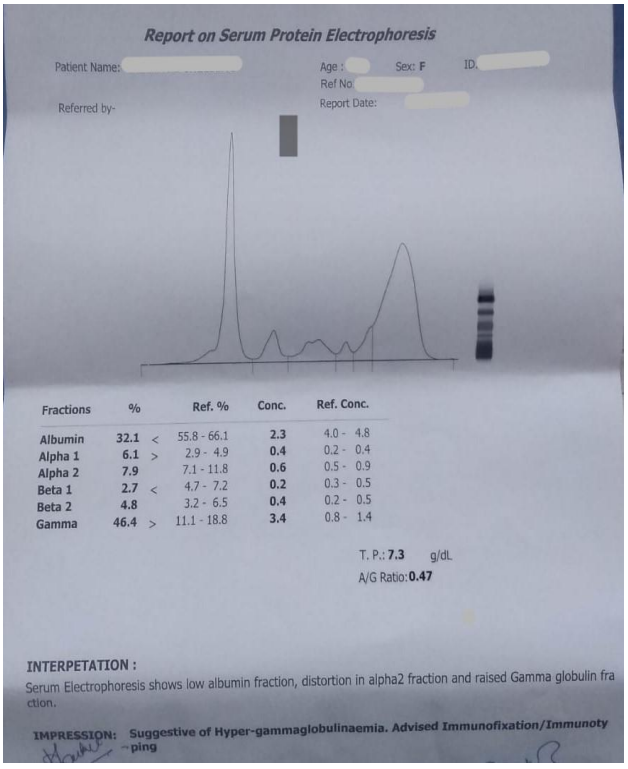

Figure 2: Serum protein electrophoresis showing hyper gammaglobulinemia of case 1.

On general physical examination, the patient had pallor and bipedal oedema. Rest of the examination was unremarkable.

Routine investigations were suggestive of pancytopenia, Hb: 5.1 g/dl, TLC: 3500 mm^3, platelet count: 42000 mm^3 and reticulocyte count: 0.4%. Rest of the parameters are mentioned in Table 1.

The patient later developed 2 episodes of melena and 4 episodes of gum bleed. She was transfused with total 4 units of PRBC and 6 bags of platelet transfusion, owing to the incessant bleeding manifestations. The patient's symptoms and blood counts, both improved following the transfusions and subsequently she was planned for bone marrow examination. Her bone marrow examination revealed hypocellular marrow with increase in lymphocytes (54%) with 61% monoclonal plasma cells along with decreased erythroid, myeloid and megakaryocytic series (Figure 1). Serum protein electrophoresis revealed hyper-gammaglobulinaemia (Figure 2).

The patient is currently under follow up.

Case 2

A 68-year-old female, also a resident of upper Assam, presented to medicine outpatient department of our institute with the chief complaints of easy fatiguability, palpitation, backache and epistaxis. Patient was referred to our institute from a local hospital because of multiple episodes of epistaxis. There was no history of trauma, fever, recreational drug abuse or purpuric rashes over the body. The patient had no known comorbidities, any significant past medical history and no similar history in the family.

On general physical examination, the patient had marked pallor with no other significant findings. Otorhinological examination revealed no obvious abnormality.

Routine blood parameters again showed a picture of pancytopenia, Hb: 8.3 g/dl, TLC: 3300 mm^3, platelet count: 75000 mm^3 and reticulocyte count: 1.6%. The other parameters are mentioned in Table 1.

The patient was transfused with 3 units of PRBC and was subsequently planned for bone marrow examination. Her bone marrow examination revealed normocellular picture with 64% monoclonal plasma cells along with normocellular erythropoietic and adequate megakaryocytic series (Figure 3). Serum protein electrophoresis showed consistent with multiple myeloma (monoclonal peak) (Figure 4). Her skeletal survey revealed no bony lytic lesions. After establishing the diagnosis of MM, patient was referred to higher centre for further management, as our institute doesn't have a dedicated Department of Haematology, where she was started on VrD regimen. The patient is currently under follow up.

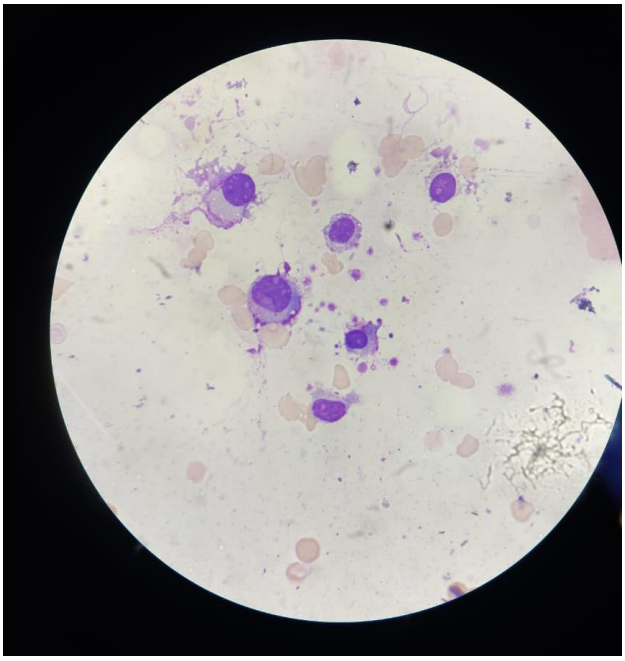

Figure 3: Bone marrow examination showing plasma cells of case 2.

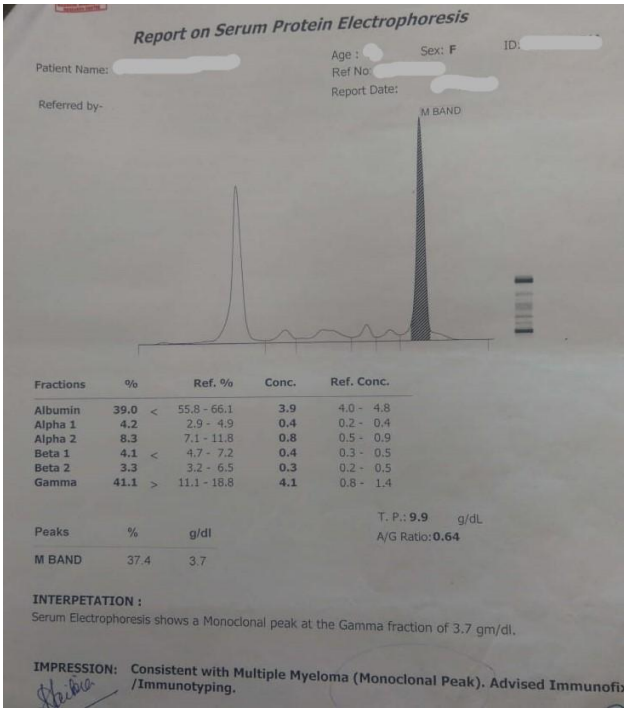

Figure 4: Serum protein electrophoresis showing hyper gammaglobulinemia of case 2.

Case 3

Our third patient, a 56-year-old male, resident of upper Assam, presented to the medicine outpatient of our institute with complaints of easy fatiguability from 1 month.

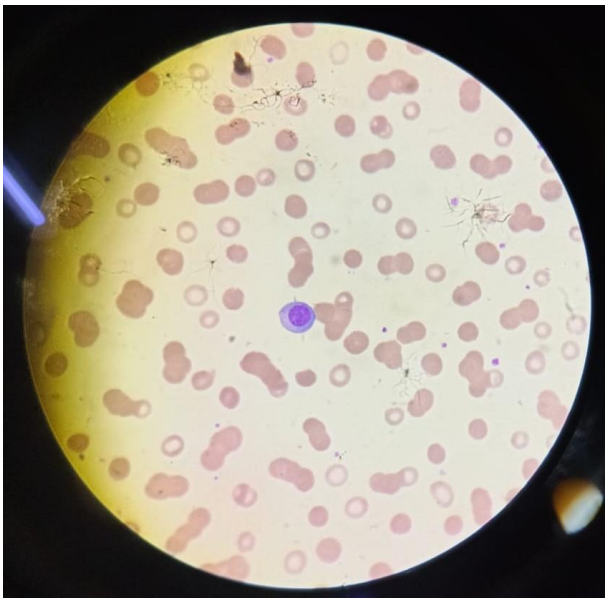

Figure 5: Bone marrow examination showing plasma cells of case 3.

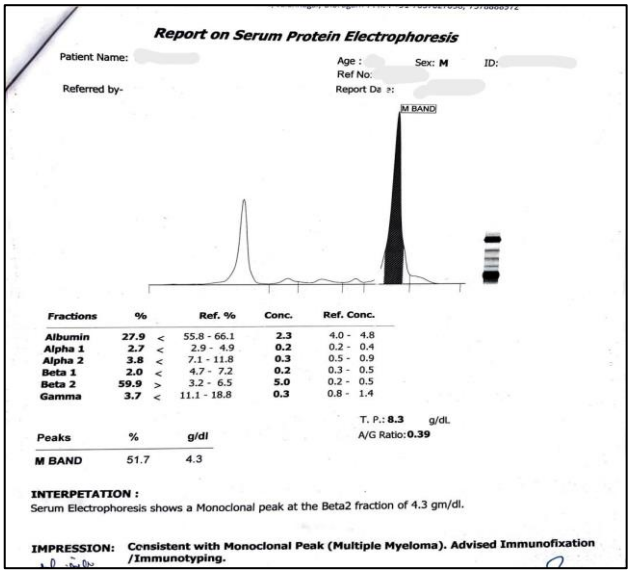

Figure 6: Serum protein electrophoresis showing hypergammaglobulinemia of case 3.

Physical examination revealed only pallor with no other positive findings as well as his systemic examination revealed no other abnormalities. The routine blood parameters showed a reduced count in all the cell lines, with Hb: 8.9 g/dl, TLC: 3200 mm^3, platelet count: 47000 mm^3 and reticulocyte count: 0.1%. Rest of the investigations are mentioned in Table 1.

The patient was transfused with 4 units of PRBC and 7 bags of platelets following which he was subjected to bone marrow examination. His bone marrow examination revealed monoclonal plasma cells accounting for 67% of the total nucleated cells along with hypocellular marrow with normal myeloid to erythroid ratio and suppressed

myeloid, erythroid and megakaryocyte series (Figure 5). Serum protein electrophoresis showed consistent with monoclonal peak (multiple myeloma) (Figure 6). His skeletal survey revealed no bony abnormalities. After establishing the diagnosis of MM, the patient was referred to higher centre, where he was started on VrD regimen.

He is currently under follow up.

Table 1: Clinical and laboratory profile of patients.

Investigations	Case 1	Case 2	Case 3
Age	53	68	56
Sex	Female	Female	Male
Presenting complaint	Easy fatiguability, palpitation, decreased appetite, gum bleed	Easy fatiguability, palpitation, backache, epistaxis	Easy fatiguability
Duration (month)	1	1.5	1
Haemoglobin (gm/dl)	5.1	8.3	4.9
Total leucocyte count (mm^3)	3500	3300	3200
Platelet count (mm^3)	42000	75000	47000
Reticulocyte count (corrected %)	0.04	1.6	0.1
PBS	Leucopenia with no immature cells	Shows normal count with normal morphology	Decrease in total count with few activated lymphocytes
ESR	115	90	130
Corrected calcium (mg/dl)	9.4	8.3	10.3
Creatinine	0.78	1.15	1.03
Serum iron	110	32	97
Ferritin	996	239	610
TIBC	189	249	115
Vitamin B12	811	778	805
Albumin	2.77	3.67	2.59
Globulin	5.60	6.17	6.15
B2 microglobulin (%)	4.8	3.3	5.9
Stool for occult blood	Positive	Negative	Negative
Serum protein electrophoresis	Suggestive of hyper-gammaglobulinemia	Consistent with monoclonal peak	Consistent with monoclonal peak
Bone marrow biopsy	Hypocellular marrow with 54% lymphocytes and 61% plasma cells	Consistent with multiple myeloma with 64% plasma cells	Plasma cell dyscrasia with 67% plasma cells
ISS STAGE	Stage II	Stage I	Stage III
Outcome	Under follow up	Under follow up	Under follow up
Treatment planned	VrD regimen	VrD regimen	VrD regimen

In our case series, we reported 3 patients who presented with pancytopenia and was eventually diagnosed with multiple myeloma.

Out of the three patients, 2 were female and 1 was male and the average age was 59 years. The most common chief complaint was backache and fatigue, followed by bleeding manifestations, with an average duration of disease of just over 1 month.

At presentation, the average Hb, TLC, PC, plasma cells were 6.1 mg/dl, 3333 cell/cumm, and 54667 cells/mm^3, respectively. The ESR was high, with an average ESR of 111.6±20.20 mmAEFH. The renal function and serum calcium were normal, with an altered albumin:globulin ratio in all patients. The average amount of beta^2 microglobulin was 22.66 mg/dl.

All of them were being treated with VrD regimen and is under follow up.

DISCUSSION

Multiple myeloma is a plasma cell dyscrasia characterized by clonal proliferation of the plasma cells leading to suppression of normal haematopoiesis, renal failure, destruction of bones and recurrent infections and for

establishing the diagnosis of multiple myeloma, The International Myeloma Working Group Criteria (IMWG) is used which include signs of end organ damage such as hypercalcemia, anemia, bony lesions or renal insufficiency.[1]

Table 2: Causes of pancytopenia.

S. No.	Parameters	Causes
1.	Nutritional deficiency	-Vitamin b12 -folate -excessive alcohol intake
2.	Due to bone marrow failure	-Aplastic anaemia -myelodysplastic syndrome -paroxysmal nocturnal haemoglobinuria -fanconi anaemia
3.	Malignant infiltration of bone marrow	-Acute myeloid leukaemia, acute lymphoblastic leukaemia, hairy cell leukaemia, lymphoma, multiple myeloma, plasma cell leukaemia, malignant histiocytosis, metastatic cancer
4.	Infectious causes	-Disseminated koch, malaria, leishmaniasis, viral hepatitis, enteric fever, septicemia
5.	Storage diseases	Gaucher disease, neimann-pick disease
6.	Hypersplenism	-Liver cirrhosis, portal hypertension, tropical splenomegaly, thalassemia, congestive splenomegaly, myelofibrosis
7.	Drugs	-Cytotoxic drugs, non-steroidal anti-inflammatory drugs, anti-thyroid drugs, anticonvulsants [lithium, valproate, levetiracetam], antimicrobials sulfonamides, ganciclovir, quinidine, zidovudine, dapsone], anti-gout [colchicine, allopurinol]

Bone pain is the most common initial presenting feature in patients with myeloma, followed by fatigue, many patients are asymptomatic at presentation.[7] Among the laboratory parameters, anemia is the most frequent finding in patients with myeloma, however, patients may also presented with pancytopenia rarely, often associated with advanced disease.[3] As pancytopenia is an unusual finding in patients with myeloma, the diagnosis therefore may get delayed in such patients. The exact etiopathogenesis of pancytopenia in myeloma is not well understood, and multiple possibilities have been suggested, out of which, replacement of the hematopoietic stem cells by the plasma cells is the most common one.[8] In this case series we highlighted the diagnostic challenges associated with multiple myeloma presenting with cytopenia and the presentation may range from being asymptomatic to an aggressive picture which may mimic acute leukemia.

The worldwide incidence of MM is currently 160,000 and mortality is 106,000.[9] The primary distribution of multiple myeloma is found to be remarkably higher in the middle aged and elderly persons.[10] Mortality in myeloma patients increases with age, with a drastic decline in survival rates after the age of 60 and the disease is uncommon below the age of 40 years and accounts for only 2% of all cases.[11]

Bone pain and fatigue has been reported as the most common presenting symptoms in multiple myeloma patients.[6] The patients in our case series mainly presented with non-specific symptoms like easy fatigability, decreased appetite, bone pain and gum bleed.

Pancytopenia is a hematological condition characterized by a decrease in all the hematologic cell lines and is not a disease by itself, instead it served as a window to see the underlying pathology that may have caused it.[12] The clinical features may vary from being asymptomatic with mild pancytopenia with life threatening conditions which may occur with severe pancytopenia.[12] Bone marrow examination is essential, especially if the peripheral, infective and autoimmune causes of pancytopenia are absent and the corrected reticulocyte index is less than 2.5%, suggestive of hypo-proliferative pattern. The causes of pancytopenia are discussed in table given below.[17]

In patients with multiple myeloma, pancytopenia may occur due to: heavy infiltration by plasma cells in bone marrow resulting in bone marrow failure; drugs causing bone marrow suppression like cytotoxic agents and antimicrobials; infections; erythropoietin deficiency due to renal failure; myelodysplastic syndromes, aplastic anaemia, vitamin B12 deficiency, autoimmune disorders.[17]

After a thorough review of literature, there were only two similar studies done in the same field, to the best of our knowledge, although there were handful of case reports.[8,15,16]

In the study of Sridevi et al a total of 10 cases which presented with pancytopenia, the mean age being 66.3 years with higher male preponderance. Out of all the symptoms, fatigue and weakness were the most common

and pallor was the most common sign. None of them presented with bleeding manifestations. Additive features were fever, bone pain, loss of appetite and weight loss.[10] In comparison to our study groups the major complaint was fatiguability and bleeding manifestations.

In a case series, conducted by Al-Anazi et al two cases were reported, the first case had bi-cytopenia in addition with leucocytosis and symptomatology was compatible with that of acute leukemia. In this patient the myeloma presented at a relatively young age, the patient eventually showed relapse after the first autologous hematopoietic stem cell transplantation and needed salvage therapy followed by a second autologous hematopoietic stem cell transplantation and maintenance therapy. While the second case presented with asymptomatic neutropenia diagnosed to have multiple myeloma during investigations for stem cell donation.[17]

As a comparative analysis amongst our study group, fatiguability and bleeding manifestations were found to be the profound clinical features., suggesting that myeloma patients, with underlying pancytopenia may have higher incidence of bleeding manifestations, however, further large-scale studies are required to confirm this.

CONCLUSION

Pancytopenia as the initial presentation of multiple myeloma is a unique manifestation. An elderly patient with non-specific complaints and pancytopenia as the foremost presentation can mislead us to some other differential diagnosis resulting in a delay in diagnosis and increases the treatment latency. Hence a differential diagnosis of multiple myeloma should be kept in mind while dealing with elderly patients presenting with pancytopenia, especially if associated with bone pain, as it can be easily diagnosed by bone marrow examination and quantitative serum protein electrophoresis.

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