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Case Series

Pathology Section

Atypical Morphological Presentation of Neoplastic Plasma Cells: A Series of Five Cases

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ABSTRACT

The diagnosis of Multiple Myeloma (MM) is made by demonstration clonal plasma cells in Bone Marrow (BM) aspiration/biopsy, in addition to assessing serum biochemical parameters, conducting radiological examinations, and considering the clinical presentation. In most cases, predominantly mature plasma cells are observed, along with scattered immature forms in the BM. Several morphological variants of plasma cells have been reported, including Auer rod-like inclusions, small lymphocyte-like cells, hairy cell-like cells, anaplastic variants, promonocyte-like cells, crystal-storing histiocytes, Burkitt-like cells, and blastoid cells. In this series of five cases, most showed a typical clinical presentation and laboratory findings suggestive of plasma cell dyscrasia. However, the morphology of each case exhibited unusual morphological variants, posing diagnostic challenges. These variants included Auer rod-like inclusions, small lymphocytes/lymph-plasmacytoid cells, hairy-like cells, multilobulated nuclei, and anaplastic variants mimicking dysplastic megakaryocytes, leading to various differential diagnoses. The age range of these cases was 57-76 years. Most of the cases presented with generalised dull aching body pain. Imaging studies revealed lytic lesions involving various parts of the bone, including the skull, ribs, vertebrae, and femur. Biochemical assays suggested the possibility of plasma cell dyscrasia. Two of the cases had primary Plasma Cell Leukaemia (PCL), which is a rare and highly aggressive plasma cell neoplasm. The anaplastic variant is associated with a poor prognosis, aiding in predicting treatment responses. However, due to the unusual morphological presentation, the diagnosis of MM or PCL was made after conducting ancillary studies such as Serum Protein Electrophoresis (SPEP), serum free light chain assay, Immunofixation Electrophoresis (IFE), and immunophenotyping through Immunohistochemistry (IHC) or flow cytometry.

Keywords: Bone marrow, Flow cytometry, Immunohistochemistry, Plasma cell

INTRODUCTION

Multiple Myeloma (MM) is characterised by the monoclonal proliferation of plasma cells. Signs and symptoms of these patients are related to renal damage caused by an excess of light chain or the infiltration of immunoglobulin-producing plasma cells into the organs. Common presentations of MM include fatigue, bone pain, hypercalcaemia, elevated serum protein or creatinine, and anaemia. The diagnosis of MM is made according to the International Myeloma Working Group (IMWG-2014): ≥10 percent clonal plasma cells in the BM or biopsy-proven bony or soft tissue plasmacytoma plus one or more of the following myeloma-defining events. One of the myeloma-defining events is organ or tissue impairment that can be attributed to the plasma cell proliferative disorder (e.g., increased calcium, kidney impairment, anaemia, lytic bone lesions). Another myeloma-defining event is a biomarker associated with near-inevitable progression to end-organ damage (i.e., ≥60 percent clonal plasma cells in the BM; involved/uninvolved free light chain ratio of 100 or more {the involved free light chain level must also be at least 100 mg/L or more}; or MRI with more than one focal lesion) [1].

Diagnosing conventional mature or immature plasma cells in morphology may not be difficult. However, several morphological variants of plasma cells have been reported, including Auer rod-like inclusion [2], small lymphocyte-like cells [3], hairy cell-like cells [4], anaplastic variants [5], promonocytes-like cell [6], crystal-storing histiocytes [7], Burkitt-like cells [8], and blastoid cells [9]. These morphological variations pose considerable diagnostic challenges for the pathologist. Present study observed the following five morphological variants of MM, which include Auer rod-like inclusions, small lymphocytes/lympho-plasmacytoid-like cells, hairy cell-like cells, plasma cells with multilobulated nuclei, and cells resembling dysplastic megakaryocytes. Ancillary investigations like serum electrophoresis, serum-free light chain assay, SPEP, IFE, and immunophenotyping by IHC or flow cytometry complement the diagnosis.

CASE SERIES

This series summarises five atypical plasma cell morphologies in five different patients with MM who presented to the Department of Haematology at Christian Medical College, Vellore, Tamil Nadu, India from January 1, 2016, to December 31, 2021. Diagnostic reporting was performed by the departments of transfusion medicine and immunohaematology, general pathology, radiodiagnosis, and molecular haematology. Most of the cases presented with generalised dull aching body pain. Imaging studies showed lytic lesions involving various parts of the bone, ranging from the skull, ribs, vertebrae, and femur. Biochemical assays suggested the possibility of plasma cell dyscrasia. However, due to the unusual morphological presentation, the diagnosis of MM or PCL was made after conducting IHC and flow cytometry. In all these cases, the diagnosis of MM was based on the IMWG-2014 diagnostic criteria [1].

Case 1

A 63-year-old male, known to be hypertensive and on antihypertensive medication for 10 years, as well as having type 2 diabetes mellitus and taking oral hypoglycaemic agents for two years, experienced intermittent, sharp, severe back pain for two months [Table/Fig-1a]. Imaging studies revealed multiple lytic lesions over the thoracic vertebrae. Other relevant investigations showed anaemia (9 g/dL, normal range 13-17 g/dL), increased β2 microglobulin (6.7 mg/L, normal range 0.8 to 2.2 mg/L), elevated calcium (11.2 mg/dL, normal

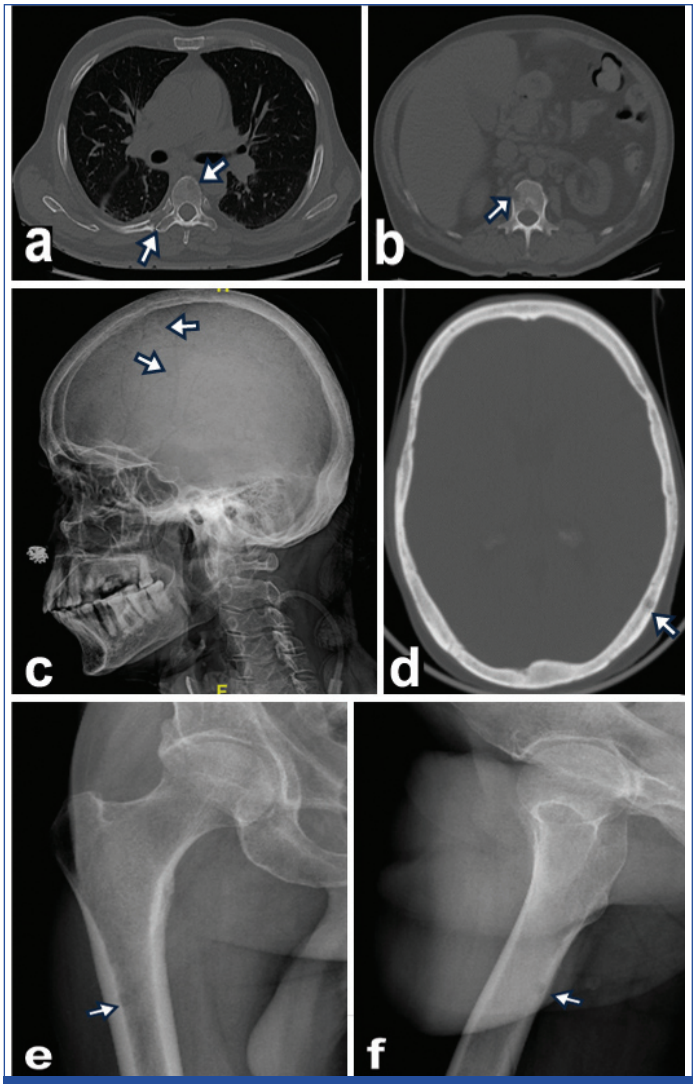
range 8.3 to 10.4 mg/dL), positive Bence Jones Protein (BJP), an increased κ/λ ratio (140, normal κ/λ ratio 0.26 to 1.65), an M band in SPEP (SPEP-1.9 G%) and IFE with IgG kappa [Table/Fig-2]. Bone marrow aspirate revealed atypical plasma cells (57%) with Auer rod-like inclusions [Table/Fig-3a]. On IHC, these cells showed positive expression for CD38 [Table/Fig-4g]. The diagnosis of MM was made based on the above findings. The patient was lost to follow-up.

Case 2

A 76-year-old male, known to have type 2 diabetes mellitus for 12 years and taking oral hypoglycaemic agents, as well as having bilateral osteoarthritis of the knee joint and using analgesics, presented with a three-month history of 10 kg weight loss, a firm, non tender swelling of size 1×1 cm on the left side of the neck, and dull aching body pain. Relevant investigations revealed [Table/Fig-2] anaemia (10.5 g/dL, normal range 13-17 g/dL), mildly elevated creatinine (1.49 mg/dL, normal range 0.7 to 1.4 mg/dL), and increased β2M (10.59 mg/L, normal range 0.8 to 2.2 mg/L). Bence Jones Protein was negative. SPEP and IFE were normal. Imaging studies revealed multiple lytic lesions over the ribs and lumbar vertebrae [Table/Fig-1b]. The Peripheral Smear (PS) showed small lymphocytes/lymphoplasmacytoid-like plasma cells (92%). Bone marrow aspirate was inadequate [Table/Fig-3c,d]. Bone marrow trephine biopsy showed solidly cellular marrow with medium-sized atypical lymphoid cells with an irregular nuclear membrane, coarse chromatin, inconspicuous nucleoli, and scant cytoplasm. On flowcytometry, atypical cells showed strong positive staining for CD138, MUM1 with kappa light chain restriction, and negative for CD3 and CD20 [Table/Fig-4a-f]. Flow cytometry showed positive expression for CD138 and CD38 with kappa light chain restriction. In view of the peripheral blood showing ≥5 plasma cells, the diagnosis of PCL was made. The patient died during the first hospital admission due to refractory shock and cardiac arrest.

Case 3

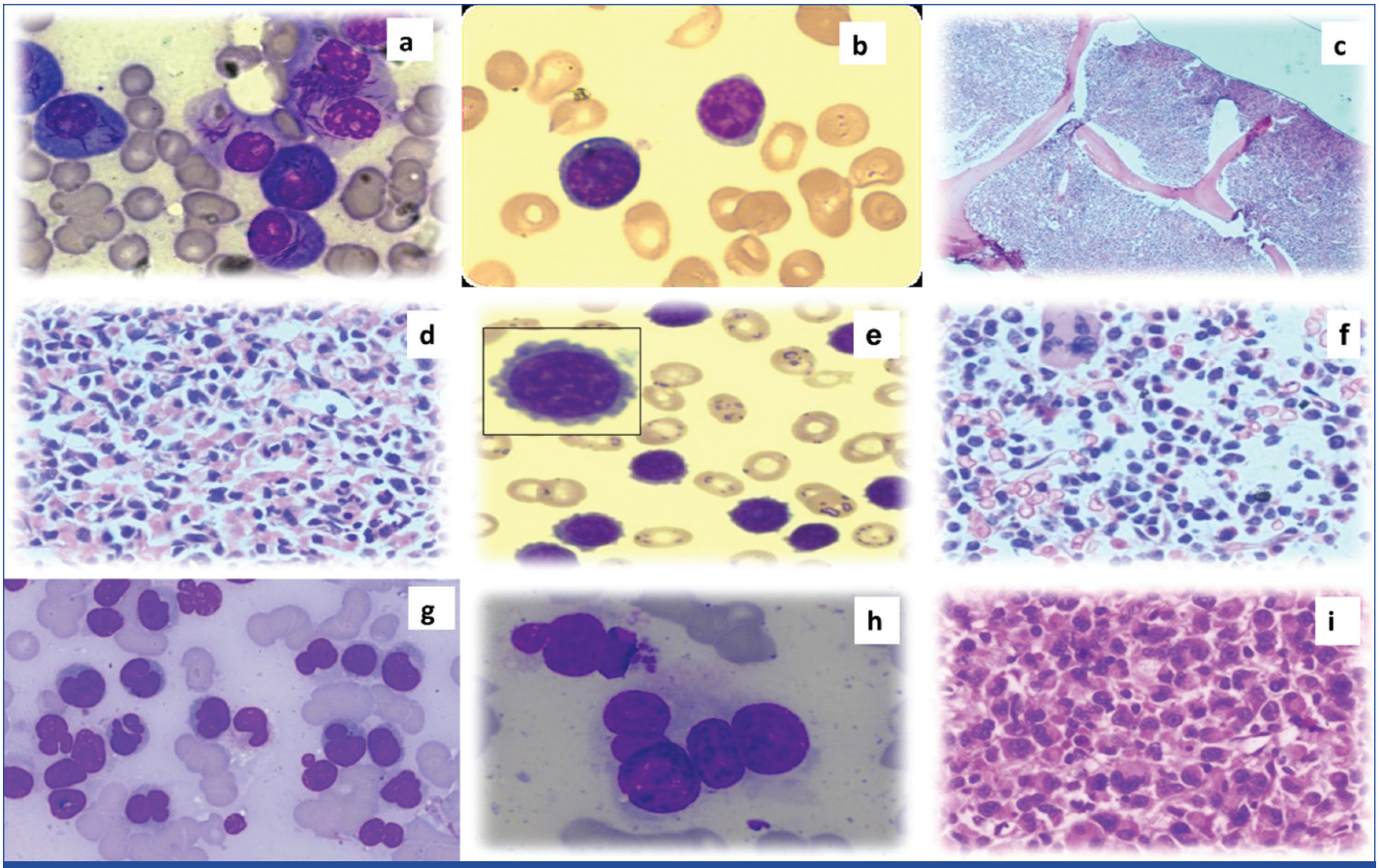
A 60-year-old male with no co-morbid conditions presented with weight loss and dull aching generalised body pain for two months. Imaging studies revealed multiple lytic lesions over the skull [Table/Fig-1c] and lumbar vertebrae. Investigations revealed [Table/Fig-2] anaemia (8 g/dL, normal range 13-17g/dL) and increased β2m (8.13 mg/L, normal range 0.8 to 2.2 mg/L). Serum Protein Electrophoresis (SPEP), Immunofixation Electrophoresis (IFE), creatinine, and calcium were normal. Bence Jones Protein was



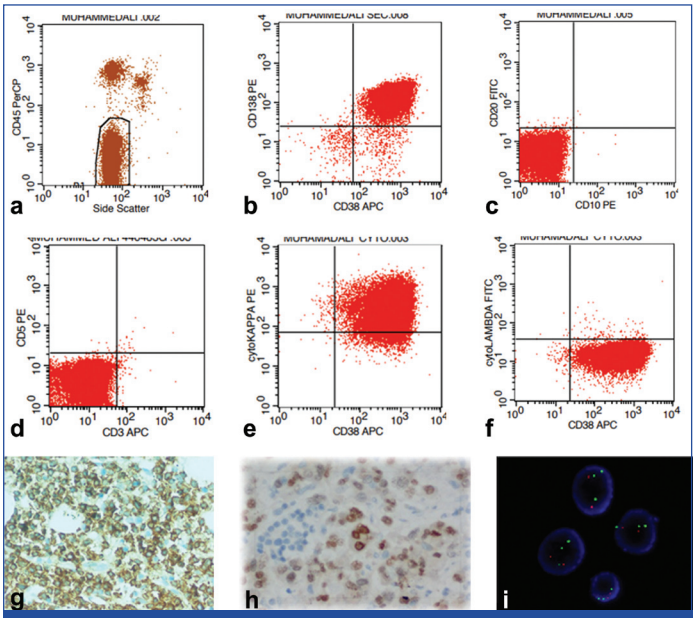
[Table/Fig-1]: (a and b) axial CT sections of thorax in bone window show lytic lesions (arrow) with no extra osseous soft tissue component involving neck and angle of right sixth rib and right transverse process and body of D6 vertebra (a) and in anterior aspect of the L2 vertebral body (b). (c) Skull. radiograph (lateral view) shows multiple lytic lesions (arrow) with thin non sclerotic margin and no matrix mineralisation; (d) CT brain axial section in bone widow shows lytic lesions (arrow) in the diploic space of left parietal bone with no soft tissue component; (e and f) Radiographs of right femur (AP and oblique views) show another intramedullary eccentric lytic lesion (arrow) with thin non sclerotic rim, narrow zone of transition and cortical involvement; no specific matrix, no periosteal reaction, no fracture and no added soft tissue thickening.

Case	Age/ Sex	Chief complaints	Morphology	Lab findings	Radiology	SPEP and urine BJP	κ/λ ratio and IFE	Atypical cells immunophenotyping
1	63/M	Intermittent sharp severe back pain for two months	BM aspirate-atypical plasma cells (57%) with multiple Auer rod like inclusions	CA-11.2 mg/dL CR-1.2 mg/dL Hb-9 g/dL β2 M- 6.7 mg/L	Multiple lytic lesions	SPEP: M band in gamma region (1.9 G%) BJP: positive	κ/λ ratio: 140 IFE: IgG kappa	IHC: positive for CD 38, 138 with kappa restriction.
2	76/M	Weight loss,firm, swelling (1×1 cm) in the left-side of the neck for three months	PS (92%) Small lymhpocytes/lympho-plasmocytoid like plasma cells.	CA-9.69 mg/dL CR-1.49 mg/dL Hb-10.5 g/dL β2M-10.59 mg/L	Multiple lytic lesions	SPEP Normal BJP: Negative	κ/λ ratio: 20 IFE- Normal	IHC:positive for CD138, MUM1 with kappa restriction. IPT by flow cytometry-positive for CD 138 and CD 38.
3	60/M	Weight loss and dull aching generalised body pain for two months	PS (84%)-lymphoid like cells with irregular membrane projection (Hairy cell like)	CA-8.2 mg/dL CR-1.09 mg/dL Hb-8 g/dL β2m 8.13 mg/L	Multiple lytic lesions	SPEP Normal BJP: Negative	κ/λ ratio: 09 IFE- Normal	IHC: positive for CD38, CD138, MUM1 with kappa restriction. IPT by flow cytometry-positive for CD 138 and CD 38.
4	68/F	Generalised dull aching body pain for 20 days and decreased urine output for 10 days	BM aspirate-plasma cells (60%) with predominantly mature and display multilobulated nuclei	CA-11.9 mg/dL CR-20.84 mg/dL Hb-5.7 g/dL β2 M-4.32 mg/L	Multiple lytic lesions	SPEP: M band in gamma region (6.68 G%) BJP: positive	κ/λ ratio:540 IFE: IgG kappa and IgA kappa	IHC: positive for CD 38, CD138 with kappa restriction.
5	57/M	Easy fatigability for one month	BM aspirate-atypical cells (49%) with markedly pleomorphic bulbous nuclei resembling dysplastic megakaryocytes	CA-9.1 mg/dL CR-0.91/dL Hb-7.2g/dL β2M-7.83 mg/L	Single lytic lesion	SPEP:M band in gamma region (2.91G%) BJP: positive	κ/λ ratio: 0.03 IFE: IgG lambda	IHC: positive for CD 138 and MUM 1 and negative for CD61.

[Table/Fig-2]: Summary of patient details.
BM: Bone marrow; PS: peripheral smear; CA: Calcium; CR: Creatinine; Hb: Haemoglobin; β2M: β2 microglobulin; SPEP: Serum protein electrophoresis; IFE: immunofixation electrophoresis; BJP: Bence jones protein;, κ/λ: Ratio:kappa/lambda ratio; IHC: Immunohistochemistry



[Table/Fig-3]: Morphology of five cases: a) Case 1: Bone Marrow (BM) examination with atypical plasma cells showing with multiple Auer rod like inclusions; b) Case 2- Peripheral Smear (PS) showed small lymphocytes/lympho-plasmocytoid like plasma cells; c) Case 2- BM trephine: Solidly cellular marrow (H&E, 40X); d) Case 2- Medium sized atypical lymphoid cells with irregular nuclear membrane, coarse chromatin, inconspicuous nucleoli and scant cytoplasm (H&E,400x); e) Case 3: 3A-PS: Hairy cell like plasma cells (WG, 1000X); f) Case 03- BM trephine: Diffuse and interstitial infiltrates of atypical cells (H&E, 200X). f) Atypical small to medium sized plasmacytoid cells with high N/C ratio, coarse chromatin and scant cytoplasm (H&E, 400X); g) Case 4: Bone marrow aspirate with atypical cells with display multilobulated nuclei; h) Case 5: Bone marrow aspirate (MGG, 1000X), large atypical cell with markedly pleomorphic nuclei and moderate amounts of pale eosinophilic cytoplasm resembling dysplastic megakaryocytes; i) Case 5-Trephine biopsy H&E stain (X400), Immature/atypical cells with eccentrically placed hyperchromatic, lobated and pleomorphic nuclei with clumped chromatin and moderate amounts of pale eosinophilic cytoplasm resembling dysplastic megakaryocytes.



[Table/Fig-4]: (a-f) Case 2 Immunophenotyping by flowcytometry- Neoplastic plasma cells express strong CD138 and CD38 and are negative for CD3, CD5, CD10 and CD20. These cells express strong cytoplasmic kappa light chain and negative for cytoplasmic lambda light chain; g-Case 1-Trephine biopsy Immunohistochemistry (IHC) (X400)– Neoplastic plasma cells show strong cytoplasmic membrane positivity for CD38; h) Case 3-Trephine biopsy Immunohistochemistry (IHC) (X400)- Neoplastic plasma cells show strong nuclear positivity for MUM1; i- Case 5- Fluorescence In Situ Hybridisation (FISH) for del (17p) is positive. 1R2G and 2R3G both indicating that TP53 is deleted. Probe used: VYSIS LSI TP53/CEP 17. Spectrum Orange- TP53 (17p13.1). Spectrum Green- CEP 17 (17p11.1- q11.1).

negative. The Peripheral Smear (PS) showed lymphoid-like cells (84%) with irregular membrane projection (Hairy cell-like) [Table/Fig-3e,f]. Bone marrow trephine biopsy showed diffuse and interstitial infiltrates of atypical cells. These cells are small to medium-sized plasmacytoid cells with a high N/C ratio, coarse chromatin, and scant cytoplasm [Table/Fig-4h]. On Immunohistochemistry (IHC), atypical cells showed positive expression for MUM1. Flow cytometry showed positive expression for CD138, CD38 with kappa restriction. In view of the peripheral blood showing ≥5 plasma cells, the diagnosis of PCL was made, and the patient was lost to follow-up.

Case 4

A 68-year-old female, known to be hypertensive and on antihypertensive medication for five years, and with chronic kidney disease undergoing haemodialysis for one year, presented with generalised dull aching body pain for 20 days and decreased urine output for 10 days. Imaging studies showed multiple lytic lesions over the skull [Table/Fig-1d]. The patient had anaemia (5.7 g/dL, normal range 11-15 g/dL for females), markedly elevated creatinine (20.84 mg/dL, normal range 0.5 to 1.1 mg/dL for females), increased β2 M (4.32 mg/L, normal range 0.8 to 2.2 mg/L), increased calcium (11.9 mg/dL, normal range 8.3 to 10.4 mg/dL), positive biclonal Bence Jones Protein, an increased κ/λ ratio (540, normal κ/λ ratio 0.26 to 1.65), an M band (6.68 G%) in Serum Protein Electrophoresis (SPEP) and Immunofixation Electrophoresis (IFE) with IgG kappa and IgA kappa [Table/Fig-2]. Bone marrow aspirate showed plasma cells (60%) that were predominantly mature and displayed multilobulated nuclei [Table/Fig-3g]. On Immunohistochemistry (IHC), atypical cells showed positive expression for CD138 and MUM1, and were negative for CD3 and CD20. Fluorescence In Situ Hybridisation (FISH) was negative for tp53 mutation. The diagnosis of MM was made based on all findings. The patient was treated with cyclophosphamide and bortezomib and survived for one year, then was lost to follow-up.

Case 5

A 57-year-old man, a known to have diabetes and hypertension for four years and on regular oral medication, presented with easy fatigability for one month. Imaging studies showed a solitary lytic lesion in the proximal diaphysis of the right femur [Table/Fig-1e,d]. Investigations revealed anaemia (7.2 g/dL, normal range 13-17 g/dL), increased β2M (7.83 mg/L, normal range 0.8 to 2.2 mg/L), and an M band (2.91G%) in serum Protein Electrophoresis (SPEP) and Immunofixation Electrophoresis (IFE) showed IgG lambda. The κ/λ ratio was deranged (0.03, normal κ/λ ratio 0.26 to 1.65). Urine Bence Jones Protein was positive [Table/Fig-2]. Bone marrow aspirate showed large atypical cells (49%) with markedly pleomorphic bulbous nuclei resembling dysplastic megakaryocytes [Table/Fig-3h]. Bone marrow trephine biopsy also showed atypical cells with eccentrically placed hyperchromatic, lobated and pleomorphic nuclei with clumped chromatin and moderate amounts of pale eosinophilic cytoplasm [Table/Fig-3i]. On Immunohistochemistry (IHC), atypical cells were positive for CD138 and MUM1 and negative for CD61. Fluorescence In situ Hybridisation (FISH) was positive for tp53 mutation [Table/Fig-4i]. The diagnosis of MM was made based on all findings. The patient died during hospital admission due to septic shock. All the above five cases have been summarised in [Table/Fig-2].

DISCUSSION

The diagnosis of MM may not be difficult; however, it poses diagnostic challenges when the morphological appearance is uncommon. In this series of five cases, most of them showed a typical clinical presentation and laboratory findings suggestive of plasma cell dyscrasia. However, the morphology of each case showed unusual morphological variants, causing diagnostic challenges.

The age group of these cases ranged from 57 to 76. Most of the cases presented with dull aching generalised body pain. Case 2 presented with weight loss and neck swelling. X-rays revealed lytic lesions involving the skull, ribs, and vertebrae (cases 1-4), and case 5 showed a lytic lesion in the right femur. All cases showed anaemia and increased β2m. M bands in SPEP and Bence Jones Protein in the urine were positive in cases 1, 4, and 5, and negative in cases 2 and 3. Cases 2 and 4 also had elevated creatinine, and cases 1, 3, and 5 showed normal levels. Cases 1 and 4 had hypercalcaemia, and cases 2, 3, and 5 showed normal calcium levels. All cases had kappa light chain restriction, except case 5, which showed lambda light chain restriction. In all cases, atypical cells showed positive expression for CD138 by IHC. Immunophenotyping by flow cytometry was available for case 2 and case 3, which showed positive expression for CD138 and CD38 monoclonal antibodies. Molecular studies were available for cases 4 and 5. Case 04 tested negative for 17p (tp53) deletion by FISH, whereas case 05 showed deletion (17p).

The first case of this series shows Auer rod-like inclusions within the mature and immature plasma cells. This may cause morphological confusion in resource-limited settings when differentiating from acute myeloid leukaemia. Auer rod-like inclusions are made up of lysosomal enzyme deposition [2]. This is particularly seen in MM with kappa light chain restriction. As similar to literature, this case also showed kappa light type paraprotein.

Case 2 and 3 were diagnosed as PCL, which is a much rarer form of MM. The diagnosis of PCL is made when plasma cells are ≥5 percent of the manual white blood cell differential count on a conventional peripheral blood smear, along with diagnostic criteria for MM. PCL is subclassified based on clinical presentation as primary PCL and secondary PCL. Primary PCL is considered when it presents “de novo” in patients with no evidence of previous MM, whereas in secondary PCL, previously diagnosed MM transforms into the leukaemic form [10]. Immunophenotyping of both MM and PCL expresses the two common plasma cell markers CD38 and CD138 along with clonal kappa or lambda light chain.

The prognosis of PCL is worse than that of high-risk MM. PCL responds poorly to conventional chemotherapy. The median overall survival is only 6 to 11 months. Treatment in PCL is a combination therapy incorporating an immunomodulatory agent, a proteasome inhibitor, steroids, and/or chemotherapy, followed by autologous haematopoietic stem cell transplantation for eligible patients and then maintenance therapy [11]. There is limited data available for PCL relapse. The incidence of relapse at three years was 61% in autologous stem cell transplantation [12].

The second case belongs to primary PCL and presents with small lymphocyte-like morphology. This morphological variant is difficult to differentiate from B-cell lymphoma. IHC showed positive expression for CD 138 and negative for CD20 and CD3. Lambda restriction was present. Garand R et al., described MM of 25/48 (52%) cases with t(11;14) had lymphoplasmacytoid morphology, and most of these cases were found to have non secretory MM [13]. Similar to the literature, this case is a non secretory type. Due to the aggressive nature of PCL, as mentioned in the literature, this patient died due to refractory shock and cardiac arrest.

The third case was a primary PCL with hairy cell-like morphology. Tanioka F et al., described the origin of leukaemic cells from the immature stage compared to the more mature MM, with a good response to bortezomib-based therapy [4]. The fourth case was an MM with multilobated nuclei. The third and fourth cases were difficult to diagnose as MM morphologically due to the lack of any morphological nature of plasma cells. Hairy cell leukaemia was a differential for the third case, and the fourth case had monocytic or myeloid leukaemia and non haematological neoplasm as differentials. These atypical cells showed positive expression for CD 138 with kappa restriction, while CD13 and CD20 were negative, hence the diagnosis of MM was made.

Immunofixation Electrophoresis (IFE) in the fourth case revealed IgG kappa and IgA kappa monoclonal bands. Very rarely, some cases can show “double gammopathies” [14]. The occurrence of double gammopathies in the literature is 2–6% [15,16]. However, there is no prognostic significance among monoclonal gammopathy and double gammopathy [17]. The fourth case had a negative tp53 mutation and was alive after combination chemotherapy for 14 months and was lost to follow-up after that.

The fifth case was an anaplastic variant of MM masquerading as high-grade lymphoma [18], dysplastic megakaryocytes [19], and metastasis. Bone marrow revealed large atypical cells resembling dysplastic megakaryocytes, which were positive for MUM 1 and negative for CD61. Anaplastic MM has a higher prevalence of 17p (p53) deletion, hence causing aggressive disease leading to the failure of therapy [20]. Similar to the literature, this case had deletion 17p (p53) by FISH [Table/Fig-4i]. Since it is aggressive in nature, the patient was not responding to treatment and died.

CONCLUSION(S)

Even though myeloma is a diagnosis based on a constellation of diagnostic criteria, rare presentations with unusual plasma cell morphologies can be challenging for the pathologist. Recognising these atypical plasma cell variants is important for the correct diagnosis and to avoid misdiagnosis of other malignant conditions. Some of the morphological variants, such as the anaplastic variant, are associated with a poor prognosis, which helps in predicting treatment responses. Correlation of clinical presentation, laboratory tests, and available ancillary methods is necessary for diagnosing such cases.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 26, 2023
- Manual Googling: Dec 22, 2023
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