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Case Series

Pathology Section

Aberrant Cytomorphological Features of Primary Plasma Cell Leukaemia: A Case Series

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ABSTRACT

Primary Plasma Cell Leukaemia (pPCL) is a rare but distinctive sub-type of Plasma Cell Myeloma (PCM) comprising approximately 2-4% of cases of PCM and characterised by short remissions and survivals. Apart from these clinical distinctions, this entity also demonstrates unique cytomorphological features. The authors here attempted to highlight this unusual spectrum of leukaemic plasma cells, posing diagnostic challenges in the blood and bone marrow examinations. The cases presented in this series (48 years old male, 72 years old male,68 years old male and 63 years old female) patients, showed presence of atypical cells in the peripheral smear with few cells portraying the characteristic "hairy cell" morphology, the fourth case in addition, showed small sized plasma cells resembling lymphocytes. Bone marrow biopsy in three cases showed haematopoetic cells replaced by sheets of atypical plasma cells. In addition, the fourth case showed atypical cells having convoluted and notched nuclei giving a differential diagnosis of lymphoplasmacytic lymphoma and small B-cell lymphoma with plasmacytic differentiation. As plasma cell neoplasm was not suspected clinically in all four cases, flow cytometry was sought for confirmation which showed atypical cells expressing CD38 (+), CD138 (+), CD56 (–) with Cykappa (+) in first case, Cylambda (+) in the second case and Cykappa (+) in the fourth case with aberrant expression of cyclin D1 thus confirming a diagnosis of PCL in first two cases and PCM-lymphocytic type with PCL in the fourth case. Immunophenotyping was not performed in the third case due to financial constraints. This case series showcases this mélange of cytomorphological variations of plasma cells ranging from cells masquerading as hairy cells to small sized plasma cells resembling lymphocytes, each posing a unique diagnostic dilemma. This has been rarely discussed in prior published case series. Aberrant morphological features rarely seen in PCL, could lead the pathologist astray from the diagnosis, therefore appropriate use of ancillary tests are essential to arrive at a correct diagnosis.

Keywords: Aberrant morphological features, Cyclin D1 expression, Hairy cell like, Plasma cell myeloma

INTRODUCTION

The PCL is one of the rare variants found in 2-4% cases of PCM [1]. The original Kyle's criteria established in 1974 is based on the presence of more than 20% circulating clonal plasma cells and an absolute count greater than 2×10^9/L plasma cells in the peripheral blood. However, the consensus definition by the International Myeloma working group in year 2021, is the presence of more than or equal to 5% circulating plasma cells in patients otherwise diagnosed with symptomatic myeloma [2]. The quintessential plasma cells in PCL are morphologically mature or of intermediate maturity and do not pose any diagnostic difficulty. On the contrary the atypical/aberrant morphological cases of PCL masquerading as hairy cell leukaemia, B cell lymphoma, acute myeloid leukaemia though rare can be challenging to interpret and thus in such cases the utility of ancillary tests cannot be overstated [3].

Identifying and describing more such cases would be helpful in understanding the nuances of this rare variant and to emphasise the importance of incorporating ancillary tests when appropriate [4-6]. Owing to this rarity, search of published literature revealed a dominance of case reports with only a handful of case series [3,4,7-9]. As PCL is known to be an ultra high risk disease, prompt identification of these cases with early treatment is paramount [2]. Herein, the authors present this case series of primary PCL with their varied cytomorphological presentation and diagnostic conundrums.

CASE SERIES

The authors reviewed all the cases of pPCL diagnosed in the department of Pathology over a period of 6 years from May 2015 to May 2021. Four such cases were identified. The criteria for the diagnosis were the presence of circulating clonal plasma cells of more than 20% and or absolute count of plasma cells exceeding 2×10^9/L [5]. In each of these cases, clinicopathological details were recorded. Haematological parameters included haemoglobin level, White Blood Cells (WBC) count, Platelet count and Erythrocyte Sedimentation Rate (ESR). Serum biochemical analysis included S. Creatinine, urea, calcium, lactate dehydrogenase. Serum Protein Electrophoresis (SPE), S. immunoassay, peripheral smear examination, Bone marrow aspiration and biopsy. Immunohistochemistry analysis and Immunophenotyping by flow cytometry were obtained whenever sought for.

Case 1

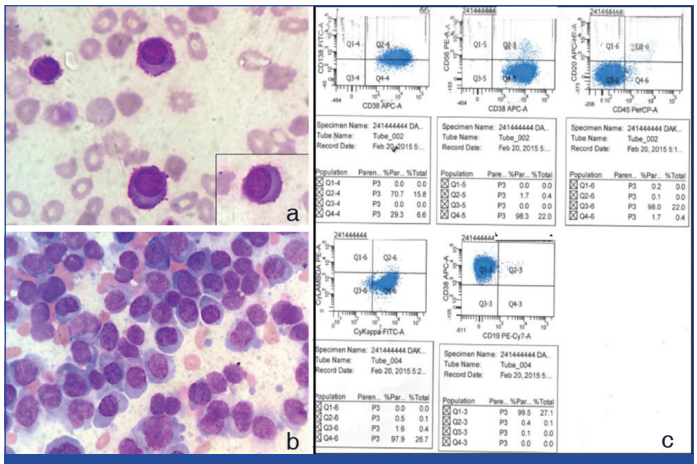
A 48-year-old male patient, presented with a history of easy fatigability, and significant weight loss of >10% over the past six months with recent onset of fever, vomiting, abdominal pain, and yellowish discoloration of the skin. There was no significant past medical history. He was afebrile at presentation and had mild hepatosplenomegaly. The patient appeared acutely ill on admission. His initial investigation revealed anaemia {haemoglobin (Hb) 6.8 g/dL}, thrombocytopenia (Platelet count of 75,000/cumm), and leukocytosis (19,370/cumm). Preliminary biochemical evaluation was suggestive of azotemia with serum creatinine of 7.9 mg/dL, blood urea of 195 mg/dL, uric acid of 7.6 mg/dL, and elevated calcium levels of 13.5 mg/dL. Serum electrolytes were normal and liver function tests were normal except for mild elevation in alkaline phosphatase. Routine urine test showed proteinuria (3+). Urine Bence Jones protein was negative.

Ultrasound revealed hepatosplenomegaly with moderate ascitis. However, further investigatons with peripheral smear showed a dimorphic anaemia with thrombocytopenia and leukocytosis with the presence of atypical cells accounted for 28% of the differential count (neutrophils 36%, lymphocytes 29%, eosinophils 04%, monocytes 03% and atypical cells 28%), and absolute count

on peripheral smear was 5423 cells/mm^3 of Total Leucocyte Count (TLC). The abnormal cells had a characteristic "hairy cell" morphology with central to eccentrically placed nucleus, prominent nucleoli and abundant bluish cytoplasm exhibiting circumferential cytoplasmic projections. The abnormal cells were large, about twice the size of a small lymphocyte. Few cells exhibited cleaved and bilobed nuclei. Occasional typical plasma cells were also noted. The Erythrocyte Sedimentation Rate (ESR) was high-141 mm/hours. SPE and immunofixation were negative. Free light chain assays were not performed due to financial constraints.

Bony pains were absent, and a skeletal survey was also normal. His renal function further deteriorated on consequent days with creatinine of 8.8 mg/dL, thus requiring haemodialysis. In view of abnormal cells in the peripheral smear bone marrow aspiration was sought which showed a hypercellular marrow with good cellular trails and replacement of the normal marrow elements by sheets of plasma cells (83%), immature plasma cells, and plasmablasts with diminished myeloid, erythroid, and megakaryocytic series. The bone marrow aspiration yield was insufficient for flowcytometry hence peripheral blood was sent for immunophenotyping by flow cytometry. Immunophenotyping showed 27% of atypical cells expressing CD38 (+), CD138 (+), Cykappa (+), and CD56 (–) and serum immunoassay showed an increase in IgE (170 IU/mL). The patient was diagnosed to have pPCL based on the findings of peripheral smear, bone marrow, flow cytometric analysis, and immunoassays. He was treated with melphalan/prednisolone regime along with supportive care. However, the patient did not comply with the treatment and succumbed to the illness within four years.

The peripheral smear finding, bone marrow and flow cytometry findings are depicted in [Table/Fig-1].

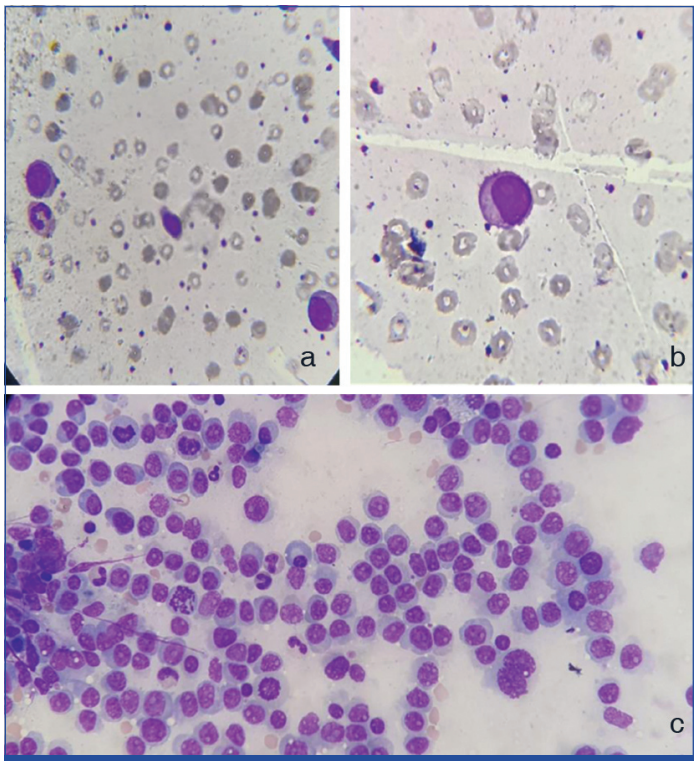


[Table/Fig-1]: Case 1 Peripheral smear, bone marrow and flow cytometry findings. Case 1; a) Peripheral smear shows 28% atypical cells with the characteristic "hairy cell" morphology and occasional typical plasma cells. (a-1000X); b) Bone marrow aspiration shows 83% immature plasma cells and Plasmablasts, (b- 400X). c) Immunophenotyping by flowcytometry showing 27% of atypical cells expressing CD38, CD138, Cykappa (+), and CD56 (–) (c).

Case 2

A 72-year-old male patient presented to the Medicine outpatient department with a clinical history of generalised weakness for one month with recent onset of fever since one week. He reported no significant past medical history. On investigations he was anaemic (Hb: 5.2 g/dL) with leukocytosis 16,700 cells/cumm, and thrombocytopenia (platelet count: 72,000/cumm). On peripheral smear examination, there was rouleax formation of red blood cells with a dimorphic picture, and 8 nucleated Red Blood Cells (RBCs)/100 White Blood Cell (WBC) were noted. Differential count showed neutrophils of 42% with shift to the left upto myelocytes, lymphocytes 28%, eosinophils 4%, and monocytes 6%, with 20% plasma cells and few abnormal cells having centrally placed nucleus with grey-blue cytoplasm. A dimorphic anaemia with a leukoerythroblastic blood picture and plasmacytosis (20% plasma cells) (absolute plasma cell count of 3140 cells/cumm) was reported [Table/Fig-2a,b]. Following this Bone marrow examination was performed which revealed hypercellular marrow with replacement of the normal marrow elements by sheets of plasma cells (79%) with markedly diminished haematopoietic precursors [Table/Fig-2c]. Further investigations with SPE showed a thick M band. Ultrasonograph showed mild hepatosplenomegaly. The ESR was high at 154 mm/1 hour. Serum Lactate Dehydrogenase (LDH) was elevated at 813 IU/l and biochemical parameters including calcium levels were within normal limits. Bone scan was normal. Immunophenotyping by flow cytometry was performed which showed atypical cells expressing CD38, Cylambda, CD20, and negative for CD56. Immunoassays showed an increase in IgA (630 mg/dL). He was treated with melphalan/prednisolone regime along with supportive care. Patient survived for four years with treatment.

The peripheral smear finding, bone marrow findings are depicted in [Table/Fig-2].

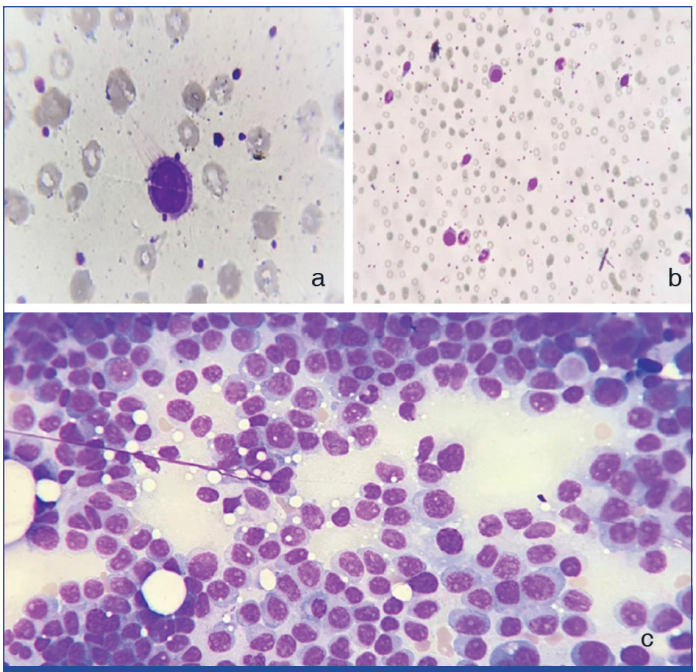


[Table/Fig-2]: Case 2 Photomicrograph of peripheral smear showing atypical Plasma cells and plasmablasts; a) (200X) with occasional Hairy cell like morphology; b) 400X. Bone marrow aspiration shows 70% immature plasma cells and Plasmablasts. (c, 400X).

Case 3

A 68-year-old male patient, a known case of systemic hypertension since eight years had presented to the medicine outpatient department with the complaints of low back ache since a week with h/o fever since three days. Systemic examination was normal. Routine investigations revealed azotemia with increased levels of creatinine (3.3 mg/dL), urea 92 mg/dL and uric acid 7.4 gm/dL. The calcium levels were also elevated. Rest of the biochemical tests were within normal limits. Complete blood count showed anaemia with the Hb level of 8.4 gm/dL. Platelet and total leukocyte counts were within normal limits. Ultrasonography (USG) revealed Grade 1 prostatomegaly. In view of acute kidney injury, a nephrologist opinion was taken and was treated conservatively with i.v. fluids and i.v. antibiotics. Patient improved symptomatically and was adviced to follow-up. Meanwhile as the patient was anaemic, peripheral smear examination was done which showed dimorphic anaemia with the presence of 20% atypical Plasma cells and plasmablasts [Table/Fig-3a,b]. Blood was sent for SPE which showed the presence of M band. ESR was elevated. Further bone marrow aspiration and

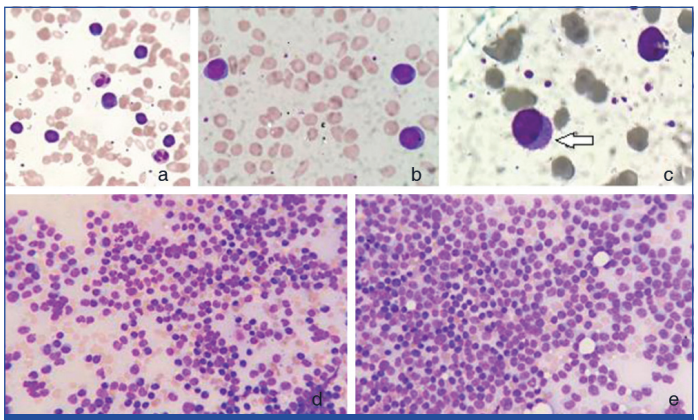
biopsy was performed which showed hypercellular marrow with sheets of plasma cells, immature plasma cells and plasmablasts (90%) replacing the haematopoetic elements [Table/Fig-3c]. Bone scan was normal. Immunophenotyping was not sent in this case as peripheral smear, bone marrow cytomorphological features and SPE clearly pointed to the diagnosis of PCL. The patient is on regular follow-up on maintenance therapy and is currently in complete remission.



[Table/Fig-3]: Case 3: Peripheral smear and bone marrow findings; Case 3: a) 400X. Photomicrograph of peripheral smear showing atypical Plasma cells and plasmablasts; b) (200X) with occasional Hairy cell like morphology; c) 400X. Bone marrow aspiration shows 90% immature plasma cells and Plasmablasts.

Case 4

A 63-year-old female patient presented to the Neurology outpatient department with complaints of neck pain and lower limb weakness since one week. Blood investigations showed hypercalcaemia with low levels of vitamin D3, and normal serum parathyroid hormones. Rest of the biochemical parameters were within normal limits. Her chest X-ray and Ultrasonography were normal. Magnetic Resonance Imaging (MRI) LS spine showed diffuse posterior bulge of L4-L5 disc. SPE were normal. Routine haematological investigations revealed anaemia (8.2 gm/dL) with normal platelet count and total leucocyte counts.ESR was elevated. Peripheral smear showed 52% small sized plasma cells resembling lymphocytes, immature plasma cells, plasmablasts, and abnormal cells with hair like projections bone marrow aspiration and biopsy were performed which shows 80% atypical cells with round to irregular convoluted and notched nuclei, open chromatin, few with nucleoli, scant to moderate amount of basophilic cytoplasm. Many had fine cytoplasmic vacuolations. Some had plasmacytoid appearance with admixed small lymphocytes and binucleate cells. The peripheral smear and bone marrow morphology is depicted in [Table/Fig-4]. Patient was diagnosed to have PCL one and a half years ago and has discontinued the treatment after two months due to financial constraints.



[Table/Fig-4]: Case 4: Peripheral smear and bone marrow findings; Case 4: Photomicrograph of small sized plasma cells resembling lymphocytes; a (200X), immature plasma cells, Plasmablasts, abnormal cells with hair like projections; b(400X); c (1000X) Plasmablasts depicted with arrow; d,e (400X) Bone marrow aspiration showing 80% atypical cells with round to irregular convoluted and notched nuclei, open chromatin, few with nucleoli, scant to moderate amount of basophilic cytoplasm. Many had fine cytoplasmic vacuolations. Some had plasmacytoid appearance with admixed small lymphocytes and binucleate cells.

A differential diagnosis of PCL, Lymphoplasmacytic lymphoma and small B cell lymphoma with plasmacytic differentiation were offered and flow cytometry was suggested. As bone marrow aspiration yield was insufficient for flowcytometry, Immunohistochemistry was performed on the bone marrow biopsy. The atypical cells expressed CD138, Kappa (light restriction), CD56 and cyclin D1 rendering a diagnosis of PCM- lymphocytic type with PCL.

pPCL accounted for 3.8% (4/105) cases of PCM with the mean age of 64 years. A 75% (3/4 cases) of the patients were males. Patients had varied symptoms- easy fatiguability, generalised weekness, fever, weight loss, nausea, vomiting, low back ache and abdominal distension. A 50% (2/4) of the cases showed hepatosplenomegaly. All the cases (100%, 4/4 cases) presented with anaemia and elevated ESR, 50% cases (2/4 cases) had leukocytosis and thrombocytopenia.

The demographic data, clinical features, provisional diagnosis, radiological and laboratory findings including the CRAB features (Creatinine, Renal derangements, Anaemia, Bone lytic lesions) along with SPE, S.Immunoassay whenever available are presented in [Table/Fig-5]. [Table/Fig-6] shows the spectrum of cytomorphological features of circulating plasma cells in peripheral smears, bone marrow aspiration and biopsy findings, immunophenotyping by flowcytometry and IHC findings.

Demographic and clinical parameters	Case 1	Case 2	Case 3	Case 4
Age (years)	48 years	72 years	68 years	63 years
Sex	Male	Male	Male	Female
Clinical features	Easy fatiguability, weight loss, fever, vomiting, abdominal pain, yellowish discolouration of skin	Generalised weakness and fever	Low back ache and fever	Neck pain and lower limb weakness
Provisional diagnosis	Acute kidney injury under evaluation	Acute febrile illness	Systemic hypertension with acute kidney injury and hypercalcaemia under evaluation	Hypercalcaemia under evaluation
Ultrasonography (USG)	Mild hepatosplenomegaly	Mild hepatosplenomegaly	No	No
Leukocytosis	+	+	-	-
Thrombocytopenia	+	+	-	-
CRAB criteria				
S.Calcium (Normal: 8.5-10.5 mg/dL)	11.2 mg/dL, Elevated	Normal	11.8 mg/dL, Elevated	12.2 mg/dL, Elevated
Renal derangement (Azotemia)	Present	Present	Present	Normal

Anaemia	Present	Present	Present	Present
Bone lesions	Present	Absent	Absent	Absent
M band	Absent	Present	Present	Absent
S. Immunoassay	IgE	IgE	Not done	Not done

[Table/Fig-5]: Clinico-haematological profile.
CRAB: Creatinine, renal dysfunction, anaemia, bone disease criteria

Cytomorphological features	Case 1	Case 2	Case 3	Case 4
PS	28% atypical cells with the characteristic "hairy cell" morphology and occasional typical plasma cells.	20% Atypical Plasma cells, plasmablasts, Occasional Hairy cell like morphology	20% Atypical Plasma cells and plasmablasts occasional hairy cell like morphology	52% Small sized plasma cells resembling lymphocytes, immature plasma cells, Plasmablasts, abnormal cells with hair like projections
BMA	83% immature plasma cells, Plasmablasts	78% plasma cells, immature plasma cells and plasmablasts	90%, Plasma cells, immature plasma cells and Plasmablasts	80% atypical cells with round to irregular convoluted and notched nuclei, open chromatin, few with nucleoli, scant to moderate amount of basophilic cytoplasm. Many had fine cytoplasmic vacuolations. Some had plasmacytoid appearance with admixed small lymphocytes and binucleate cells.
BM biopsy	Replacement of the normal marrow elements by sheets of plasma cells.			Marrow replaced by sheets of atypical monomorphic cells.
IPT/IHC	27% of atypical cells CD38, CD138, Cykappa (+), and CD56 (–)	22% atypical cells CD38, CD 138, Cylambda (+), CD56 (-)	Not done	Atypical cells expressed CD138, Kappa (light restriction), CD56 and cyclin D1

[Table/Fig-6]: Cytomorphological features of primary plasma cell leukaemia.
PS: Phosphatidylserine; BMA: Bone marrow aspirate; BM: Bone marrow; IPT; Isopentenyltransferase; IHC: Immunohistochemistry

DISCUSSION

The PCL is a rare and clinically aggressive variant of PCM [5,6]. In this case series, the authors highlight the cytomorphological variations of PCL which are not adequately discussed in literature. The leukaemic plasma cells are barely recognisable as plasma cells in these cases, imparting a diagnostic challenge to the pathologist. In the present case series, pPCL accounted for 3.8% (4/105) cases of PCM over the period of six years, with the mean age of 64 years. The incidence found in the present case series is lower than the incidence found in case series by Kar R et al., 5.6% (5 in 89 cases over 5 years) [7]. The age of the patients ranged from 48 to 72 years and there were three male and one female patient. Male: female ratio is 3:1. The youngest patient in this series was 48 years, although there are Indian reports of pPCL at even younger age of presentation at 21 years [7].

In the conventional cases of PCL, the morphology of plasma cells in the peripheral blood range from mature forms to immature blastic forms [8]. All these features are easily recognisable and diagnosis is usually straight forward. But unusual findings like "hairy cells" [9] in the peripheral smear seen in two of the cases discussed here, posed diagnostic difficulty to conclude it as PCL in PBS, in the absence of which would suffice to call as PCL in PBS. But Bone marrow in these cases was straight forward and showed replacement of the normal marrow elements by sheets of plasma cells. Immunophenotyping by flowcytometry also helped us as it showed 27% of atypical cells in 1st case and 20% in 2nd case expressing CD38 (+), CD138 (+), Cykappa (+) in 1st case and Cylambda in 2nd case with CD56 and B-cell lineage negativity in both the cases. These unusual cytomorphological features were also seen in a case series by Kar R et al., Rajeswari G et al., and another study by Kumar TN et al., where the plasma cells were masquerading as hairy cells [7,8,10]. However, these cells were negative for tartarate-resistant acid phosphatase stain, B lineage, and hairy cell markers and positive for plasma cell markers CD38 and CD138. The 3rd case showed 20% atypical plasma cells within the peripheral smear with replacement of the normal marrow elements by sheets of plasma cells also seen by Rastogi P et al., [11]. Flow cytometry was not sought in this case as it fulfilled the definition of PCL.

The 4th case showed 52% small sized plasma cells resembling lymphocytes, immature plasma cells, Plasmablasts, abnormal cells with hair like projections and suggested the possibility of PCL but the bone marrow showed 80% atypical cells with round to irregular convoluted and notched nuclei, open chromatin, few with nucleoli, scant to moderate amount of basophilic cytoplasm. Many had fine cytoplasmic vacuolations. Some had plasmacytoid appearance with admixed small lymphocytes and binucleate cells.

This case posed a diagnostic difficulty owing to the presence of small sized plasma cells giving a lymphoid appearance with bone marrow showing atypical cells displaying convolutions and notched nuclei which are unusual findings in a conventional PCL [1]. Flow cytometry was sought in this case to rule out lymphoplasmacytic lymphoma and small B cell lymphoma with plasmacytic differentiation but was not performed due to insufficient material. Hence, Immunohistochemistry was performed on the biopsy which showed atypical cells expressing CD138, Kappa (light restriction), CD56 and cyclin D1 rendering a diagnosis of PCM-lymphocytic type with PCL. It is a rare variant accounting for 3% of myelomas with high frequency of Cyclin D1 expression as seen in the presently discussed case. Small lymphocyte type of myeloma is a potential mimicker of mature B cell lymphoma [12-14]. Thus, cognizance about the unusual cytomorphological findings in PCL will help the pathologists to avoid misdiagnosis as they have a striking similarity between mature B cell lymphoma and lymphoplasmacytic lymphoma. The small lymphocyte– like PCM is distinguished from mature B cell lymphoma by the absence of CD 45 expression and the presence of CD 38 and CD 138 [12,13].

A study done by McKenney AH et al., showed 12 cases of Small Lymphocyte like plasma cells out of 351 PCM with morphologically similar appearing small cells as seen in the present case [12]. IHC showed lack of CD45 with CD138+, CD38+, MUM1+Lambda chain restriction. Most cases share hyperexpression of cyclin D1 or cyclin D3 genes. Sharma P et al., also reported a case of small lymphocytic type of PCM in a 68-year-old patient and concluded that plasma cells are notorious for their varied cytomorphology and awareness about this morphological masquerader is essential to avoid misdiagnosis [15]. These cases also showed high frequency of CD20 expression and Cyclin D translocation as seen in the present case [16]. [Table/Fig-7] depicts published case reports on PCL [8,10,12,17,18].

Parameters compared	Present case series 3 out of 4 cases of PCL (Case1, 2 and 4)	Present case series 1 out of 4 cases of PCl (Case 4)	Shibushawa M [17] (2020)	Toriyama E et al., [18] (2019)	Rajeswari G et al., [8] 2/ 16 cases of PCL (2014)	McKenney AH et al., [12] 12/351cases of PCN (2010)	Kumar TN et al., [10] [2014]
Cell morphology	atypical cells with the characteristic "hairy cell" morphology and occasional typical plasma cells	52% Small sized plasma cells resembling lymphocytes, immature plasma cells, Plasmablasts, abnormal cells with "hair like projections"	Flower shaped plasma cells mimicking adult T cell Leukaemia	Convoluted nucleus with basophilic cytoplasm	Atypical cells with "hairy cell" morphology	Small Lymphocyte like plasma cells	Small lymphoid cells with circumferential hairy projections and round nuclei with 1-2 prominent nucleoli and deeply basophilic cytoplasm
Immunohistochemistry (IHC)	CD38, CD138, Cykappa (+), and CD56 (–)	CD138, Kappa (light restriction), CD56 and cyclin D1	CD38+ CD138+ CD56+	CD38+ CD138+ CD20- CD56-	CD38, CD138, Cykappa (+), and CD56 (–)	CD45 with CD138+, CD38+, MUM1+Lambda chain restriction	CD38,CD138, Lambda and negative for CD19,CD25, CD23, CD103

[Table/Fig-7]: Case reports and case series of Primary Plasma Cell Leukaemia with cytomorphological abnormality- review of literature [8,10,12,17,18].

CONCLUSION(S)

Aberrant morphological features rarely seen in PCL, falsely conveys an element of doubt about the diagnosis which needs to be meticulously dealt with ancillary tests like IHC and flow cytometry to arrive at a correct diagnosis.

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- Manual Googling: Dec 05, 2022
- iThenticate Software: Dec 29, 2022 (9%)

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