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ONLINE CASE REPORT

Primary Plasma Cell Leukaemia

Case report and review of the literature

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سرطان خلية بلازما الدم الأولية

تقرير حالة ومراجعة الأدبيات

ساريكا سينج، أشوتش راث، سوريكا ياداف

ABSTRACT: Plasma cell leukaemia (PCL) is one of the most aggressive and rarest forms of plasma cell dyscrasia. However, the diagnostic criteria for this condition have not yet been revised and there is no specific treatment to significantly improve the course of the disease. We report a 69-year-old male who presented to the Lok Nayak Hospital, New Delhi, India, in 2017 with dyspnoea and chest pain. A peripheral blood smear showed an absolute plasma cell count of 2.16×10^9/L. A bone marrow examination showed 61% atypical plasma cells exhibiting kappa light chain restriction. Biochemical investigations were consistent with a diagnosis of primary PCL with renal involvement. Bortezomib-based chemotherapy was initiated, which resulted in an improvement in the patient's haematological and biochemical parameters. This case report includes a comprehensive review of the clinical and diagnostic features, pathobiology and treatment of PCL.

Keywords: Plasma Cell Leukemia; Multiple Myeloma; Plasma Cells; Case Report; India.

الملخص: سرطان خلية بلازما الدم الأولية هي واحدة من الأشكال الأكثر عدوانية وأندر أعتلالات خلية البلازما. ومع ذلك ، لم يتم بعد تنقيح المعايير التشخيصية لهذه الحالة ولا يوجد علاج محدد لتحسين مسار المرض بشكل كبير. هذا تقرير عن حالة ذكر يبلغ من العمر 69 عامًا قدم إلى مستشفى لوك نایاك في نيودلهي بالهند عام 2017 بسبب ضيق في التنفس وألم في الصدر. وأظهر الفحص المجهري للدم وجود عدد من خلايا البلازما يبلغ 2.16×10^9 L/ لتر. كما أظهر فحص لنخاع العظم أن 61% من خلايا البلازما غير النمطية التي تظهر قيودًا على سلسلة الكابا الخفيفة للأجسام المضادة. كانت التحريات البيوكيميائية متسقة مع تشخيص سرطان خلية بلازما الدم الأولية مع تأثر الكلى بالمرض. وبدأ العلاج الكيميائي بواسطة عقار البورتيزوميب ، مما أدى إلى تحسن في مؤشرات صورة الدم ونتائج الفحوصات الكيميائية للمريض. يتضمن تقرير الحالة هذا مراجعة شاملة للخصائص السريرية والتشخيصية ، والمرضية وطرق علاج سرطان خلية بلازما الدم الأولية.

الكلمات المفتاحية: سرطان خلية بلازما الدم؛ المايلوما المتعددة؛ خلايا البلازما؛ تقرير حالة؛ الهند.

Plasma cell leukaemia (PCL) is a rare and aggressive form of plasma cell dyscrasia.[1] Primary PCL occurs *de novo*, whereas secondary PCL is the leukaemic transformation of relapsed or refractory multiple myeloma (MM). The incidence of PCL is 2–4%, of which 60–70% of cases are primary and 30–40% are secondary, although the incidence of the latter type is rising.[2,3] The median age of patients with primary PCL is younger than those with secondary PCL (52–65 years old versus 65–70 years old).[2] In a case series by Rajeswari *et al.*, four out of 16 patients with PCL were under the age of 40 years, with the youngest being 25 years old.[4] Although primary and secondary PCL are considered different clinical entities, both have a poor prognosis. The median survival rate ranges from 6.8–12.6 months without novel therapy, although this increases to over three years after autologous stem cell transplantation.[1,5]

Case Report

A 69-year-old male presented to a local hospital in New Delhi, India, in 2017 with a two-month history of rectal bleeding and dyspnoea during routine activities. Heart disease was suspected and the patient was managed accordingly, with minimal investigations. Despite transient improvement, he subsequently presented to the Lok Nayak Hospital, New Delhi, in 2017 with dyspnoea and chest pain. During a general physical examination, there was evidence of pallor without lymphadenopathy. A systemic examination was unremarkable with no evidence of hepatosplenomegaly.

A complete blood count revealed anaemia with a haemoglobin (Hb) level of 72 g/L, mild leukocytosis with a total leukocyte count (TLC) of 12×10^9/L and thrombocytopaenia with a platelet count of 97×10^9/L. The erythrocyte sedimentation rate was 70 mm/hour. A peripheral

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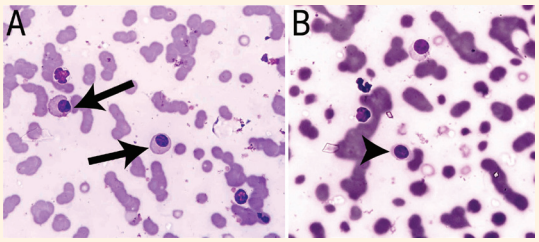

Figure 1: Peripheral blood smears at x200 magnification showing (**A**) rouleaux formation, plasma cells (arrows) and (**B**) atypical lymphocytes (arrowhead).

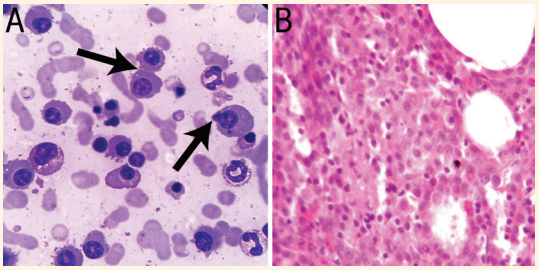

Figure 2: A: Bone marrow aspirate smear at x1,000 magnification showing atypical plasma cells (arrows). **B:** Haematoxylin and eosin stain at x400 magnification showing plasma cells.

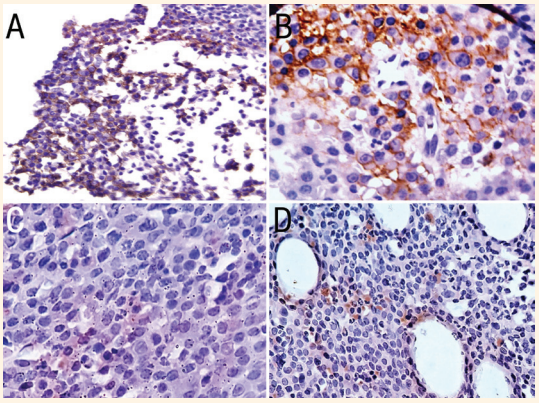

Figure 3: Immunohistochemistry panel at x400 magnification showing (**A**) positivity for cluster of differentiation (CD)38, (**B**) kappa light chain restriction, (**C**) reduced lambda light chain expression and (**D**) focal positivity for CD20.

blood smear exhibited normocytic/normochromic to microcytic/hypochromic red blood cells with extensive rouleaux formation. A differential leukocyte count revealed 18% plasma cells with an absolute platelet cell count of 2.16 × 10^9/L and 15% atypical lymphocytes [Figure 1]. Mature plasma cells as well as plasma cells with bipolar cytoplasm were present. The atypical lymphocytes had central and eccentrically placed nuclei and a moderate amount of cytoplasm with fuzzy cytoplasmic borders.

A bone marrow examination was performed to establish the extent of PCL involvement. A bone marrow aspirate smear and haematoxylin and eosin stain showed 61% atypical plasma cells [Figure 2]. The morphological spectrum of these cells included thesaurocytes, plasma cells with bipolar cytoplasm and one to two prominent *nucleoli* in the nucleus and binucleated plasma cells. The bone marrow was hypercellular for age and showed the near-total replacement of the marrow spaces by the plasma cells, with focal areas of haematopoietic cells. Upon immunohistochemical analysis, the plasma cells were immunoreactive for cluster of differentiation (CD)38, showed kappa light chain restriction and reduced lambda light chain expression and demonstrated focal positivity for CD20 [Figure 3]. The cells were immunonegative for CD19 and p53.

Biochemical investigations showed high levels of serum creatinine (3.3 mg/dL; normal range: 0.6–1.2 mg/dL), blood urea (147 mg/dL; normal range: 8–23 mg/dL) and serum uric acid (13.0 mg/dL; normal range: 4–8.5 mg/dL). However, serum calcium levels were slightly low (8.5 mg/dL; normal range: 9.2–11 mg/dL). Radiological investigations, including a chest X-ray, abdominal ultrasound and skeletal survey, did not show any lesions. Serum protein electrophoresis indicated a total protein level of 15.20 g/dL (normal range: 6.40–8.10 g/dL), albumin level of 3.83 g/dL (normal range: 3.50–5.64 g/dL), α1-globulin level of 0.62 g/dL (normal range: 0.17–0.41 g/dL), α2-globulin level of 1.19 g/dL (normal range: 0.31–0.85 g/dL), β-globulin level of 0.59 g/dL (normal range: 0.49–1.32 g/dL), γ-globulin level of 8.97 g/dL (normal range: 0.62–1.53 g/dL) and albumin/globulin ratio of 0.34 (normal ratio: 0.90–2.00). Furthermore, the γ-globulin region showed a monoclonal spike. The raised globulins were found to be immunoglobulin (Ig)D on serum immunofixation electrophoresis. Bence Jones proteins were absent in the urine. A serum free light chain assay revealed kappa light chain restriction with elevated kappa free light chains at 204.00 mg/L (normal range: 3.30–19.40 mg/L) and a kappa/lambda ratio of 27.72 (normal ratio: 0.26–1.65). Serum β2-microglobulins were markedly raised at 15,576 ng/mL (normal range: 609–2,366 ng/mL).

Following confirmation of the diagnosis of primary PCL, the patient decided to undergo treatment at an oncology centre, at which point bortezomib-based chemotherapy was initiated. However, a follow-up haematological profile was performed at the Lok Nayak Hospital. After the first cycle of chemotherapy, the patient's TLC was 8.72 × 10^9/L, Hb level was 106 g/L, platelet count was 157 × 10^9/L, serum creatinine level was 1.4 mg/dL and blood urea level was 27 mg/dL. On day 11 of the first cycle, a peripheral blood smear did not show any plasma cells. At the time of writing, the patient was stable; however, a follow-up bone marrow examination had not yet been performed to assess his remission status.

Discussion

Myeloma cells are dependent for their survival on interactions with the bone marrow microenvironment.[6] Myeloma cells require CD56—a neuronal cell adhesion molecule—to anchor to the bone marrow *stroma*. As CD56 expression decreases, myeloma cells gain access to the peripheral blood due to loss of contact with the bone marrow *stroma*. Patients with PCL therefore usually show decreased expression of CD56.[7] Other molecules, such as CD27, CD117 and human leukocyte antigen-DR isotype, are usually negative, whereas CD19, CD20 and CD23 are often positive. In addition, cases of secondary PCL often show CD28 positivity.[5] Interleukin-6 is considered an important cytokine for PCL proliferation.[8]

In most primary PCL cases, genetic aberrancies are already present at the time of diagnosis; in contrast, the gradual accumulation of various genetic mutations make MM more aggressive, resulting in secondary PCL.[1] Hypodiploidy or diploidy are present in 80% of PCL cases and are considered poor prognostic factors compared to hyperdiploidy, a common feature of MM.[9] Both forms of PCL commonly show IgH translocations, notably in chromosome 14q32. Furthermore, amplifications of chromosome 1q21, *MYC* abnormalities and *Ras* mutations are more frequently seen in PCL than MM.[10] In addition, 11q13 (cyclin D1) translocations are almost exclusive to primary PCL.[1] However, Tp53 inactivation has been observed in both forms of PCL.[2] It has been suggested that a phosphatase and tensin homolog deletion is responsible for the transition of MM to PCL.[5]

Due to extensive infiltration of the bone marrow by atypical plasma cells, the most common symptoms of PCL are related to severe anaemia and thrombocytopaenia, notably dyspnoea and haemorrhagic diathesis.[1] Patients may also present with other clinical features, such as organomegaly, lymphadenopathy, pleural effusion and central nervous system involvement leading to neurological deficits and extramedullary plasmacytomas. In the current case, the patient initially presented with bleeding from the rectum and dyspnoea. Renal involvement can also occur, presenting as acute kidney failure, with studies indicating this is more commonly associated with PCL than MM (53–62% versus 22–43%).[11,12] A renal biopsy may show interstitial plasma cell infiltration, tubular casts and light chain restriction with direct immunofluorescence.[13] The current case also showed renal involvement with raised blood urea and serum creatinine levels which normalised after chemotherapy.

Certain parameters can help to differentiate PCL from MM, including leukocytosis, relatively high levels of serum lactate dehydrogenase and β2-microglobulins and lower frequencies of lytic bone lesions.[1] In addition, patients with PCL usually only secrete free light chains, unlike those with MM. Moreover, plasma cells in PCL cases often show varying morphologies, ranging from classic plasma cells, plasmablasts and hairy-cell-like morphology to marked anaplastic features.[4,14] In the current case, 15% of the lymphocytes were atypical in that their morphology differed from that of either classic or atypical plasma cells; instead, the cells resembled mature lymphocytes with fuzzy cytoplasmic borders. Previous case reports have documented similar lymphocyte-like morphologies in PCL cases.[15–17] Although flow cytometry can help establish the actual nature of such cells, this could not be performed in the current case as the patient had been referred to an external oncology centre.

The diagnostic criteria for PCL were initially laid down by Noel *et al*. in 1974 and include the presence of >20% of plasma cells ascertained to be clonal in nature in the peripheral blood or an absolute plasma cell count of $>2 \times 10^9$/L.[18,19] However, the presence of plasma cells

Table 1: Remission criteria per category for plasma cell leukaemia cases[5]

Category	Plasma cells		M-protein levels		Extramedullary disease
	Peripheral blood	Bone marrow	Serum	Urinary	
Complete remission	Absent	<5%	Negative	Negative	Absent
Stringent complete remission	Absent	Undetectable by flow cytometry	Negative	Negative	Absent
Very good partial response	Absent	<5%	≥90% reduction	<100 mg/24 hours	Absent
Partial response	1–5%	5–25%	≥50% reduction	<200 mg/24 hours	≥50% reduction
Progressive disease	>5% absolute increase	>25% increase or absolute increase of ≥10%	>25% increase	>25% increase	Definite increase
Stable disease	None of the above criteria are met				
Relapse	Reappearance	>10% increase	Reappearance	Reappearance	Any disease

in peripheral blood can also be seen in other plasma cell dyscrasias and certain non-malignant conditions such as severe sepsis and infectious mononucleosis.[20] It has therefore been suggested that the diagnostic criteria of PCL should be revised to >5% plasma cells or an absolute plasma count of >0.5 × 10^9/L so as to avoid underdiagnosis of the condition.[5] However, although the flow cytometric evaluation of PCL and revision of the criteria for diagnosis is currently under consideration, there is no consensus yet as further prospective multicentre analyses are required.

In terms of treatment, the proteasome inhibitor bortezomib has shown a relatively good response in both primary and secondary PCL, resulting in some cases in complete remission.[21] Bortezomib combined with dexamethasone and melphalan has also been documented to show a good response, whereas thalidomide and lenalidomide have only shown a transient partial response.[5] Allogenic stem cell transplantation can be considered in patients under 50 years of age; however, the risk of transplantation-related mortality is increased.[1,5] Nevertheless, high-dose chemotherapy followed by autologous stem cell transplantation improves survival, although mainly for patients with primary PCL.[2]

Seven categories of PCL remission have been proposed by the International Myeloma Working Group, based on the following four main parameters: (1) the plasma cell count in the peripheral blood; (2) the plasma cell count in the bone marrow; (3) serum and urinary M-protein levels; and (4) the assessment of extramedullary disease [Table 1].[5] In general, a patient is considered to be in complete remission if plasma cells are absent from the peripheral blood and there are <5% of plasma cells in the bone marrow. However, relapse is denoted by a >10% increase in bone marrow plasma cells with the reappearance of peripheral blood plasma cells and M-protein, along with evidence of extramedullary disease.[5] Jelinek *et al*. also recommended the assessment of minimal residual disease-negative remission by multicolour flow cytometry or allele-specific oligonucleotide polymerase chain reaction.[1]

Conclusion

Various significant yet subtle parameters can be used to differentiate primary PCL from MM. As the survival rate is low, such information is necessary to ensure that PCL cases can be diagnosed early and appropriate treatment regimens initiated.

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