Primary Plasma Cell Leukaemia
Case report and review of the literature

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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.

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 thrombocytopenia with a platelet count of 97 × 10^9/L. The erythrocyte sedimentation rate was 70 mm/hour. A peripheral

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血膜显示正细胞正色素红细胞和微小细胞低色素性红细胞，伴有广泛的球状血膜。白细胞分类显示18%的浆细胞，绝对血小板计数为2.16 × 10^9/L，15%异常淋巴细胞。浆细胞和浆细胞具有双极型的浆细胞和极性浆细胞（图1）。异常淋巴细胞的中心和偏心核和中等量的细胞质，细胞质边界模糊。

骨髓检查用于确定PCL的侵袭程度。骨髓涂片和苏木素-伊红染色显示61%异常浆细胞（图2）。这些细胞的形态学谱包括瑟索球，浆细胞具有双极型的细胞质，以及一个到两个显著的核仁和双核浆细胞。骨髓是超常细胞，显示浆细胞和髓系细胞的近全置换。

免疫组化分析显示浆细胞对CD38免疫反应性，κ轻链限制，λ轻链表达减少，并显示对CD20的局部阳性。细胞对CD19和p53免疫阴性。

血清学检查显示高血清肌酐（3.3 mg/dL；正常范围：0.6–1.2 mg/dL），血尿素（147 mg/dL；正常范围：8–23 mg/dL）和血尿酸（130 mg/dL；正常范围：4–8.5 mg/dL）。然而，血清钙水平略有下降（8.5 mg/dL；正常范围：9.2–11 mg/dL）。影像学检查，包括胸部X光片，腹部超声波和骨骼扫描，没有显示任何病变。血清蛋白电泳显示总蛋白水平为15.20 g/dL（正常范围：6.40–8.10 g/dL），白蛋白水平为3.83 g/dL（正常范围：3.50–5.64 g/dL），α1-球蛋白水平为0.62 g/dL（正常范围：0.17–0.41 g/dL），α2-球蛋白水平为1.19 g/dL（正常范围：0.31–0.85 g/dL），β-球蛋白水平为0.59 g/dL（正常范围：0.49–1.32 g/dL），γ-球蛋白水平为8.97 g/dL（正常范围：0.62–1.53 g/dL）和白蛋白/球蛋白比率为0.34（正常比值：0.90–2.00）。此外，γ-球蛋白区域显示单克隆峰。升高的球蛋白被认为是由免疫球蛋白（Ig）D在血清免疫电泳。Bence Jones蛋白在尿液中未被检测。血清游离轻链测定显示κ轻链限制和κ自由轻链水平为204.00 mg/L（正常范围：3.30–19.40 mg/L）和κ/λ比值为27.72（正常比例：0.26–1.65）。血清β2-微球蛋白明显升高至15,576 ng/mL（正常范围：609–2,366 ng/mL）。

在确认诊断为PCL后，患者决定在肿瘤中心接受治疗，其中包括bortezomib为基础的化疗。然而，第一周期化疗后的血象检查结果显示：白细胞计数为8.72 × 10^9/L，血红蛋白水平为106 g/L，血小板计数为157 × 10^9/L，血清肌酐水平为1.4 mg/dL，血尿素水平为27 mg/dL。在第一周期第11天的一份血膜检查显示未见浆细胞。到写作时为止，患者状况稳定，但尚未进行骨髓检查以评估其缓解状态。

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.
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%). A renal biopsy may show interstitial plasma cell infiltration, tubular casts and light chain restriction with direct immunofluorescence. 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. 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. 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. 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 >2×10⁹/L. Hypodiploidy or diploidy are present in 80% of PCL cases and are considered poor prognostic factors compared to hyperdiploidy, a common feature of MM. 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. In addition, 11q13 (cyclin D1) translocations are almost exclusive to primary PCL. However, Tp53 inactivation has been observed in both forms of PCL. It has been suggested that a phosphatase and tensin homolog deletion is responsible for the transition of MM to PCL.

Due to extensive infiltration of the bone marrow by atypical plasma cells, the most common symptoms of PCL are related to severe anaemia and thrombocytopenia, notably dyspnoea and haemorrhagic diathesis.

### Table 1: Remission criteria per category for plasma cell leukaemia cases

<table>
<thead>
<tr>
<th>Category</th>
<th>Plasma cells</th>
<th>M-protein levels</th>
<th>Extramedullary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peripheral blood</td>
<td>Bone marrow</td>
<td>Serum</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Absent</td>
<td>&lt;5%</td>
<td>Negative</td>
</tr>
<tr>
<td>Stringent complete remission</td>
<td>Absent</td>
<td>Undetectable by flow cytometry</td>
<td>Negative</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>Absent</td>
<td>&lt;5%</td>
<td>≥90% reduction</td>
</tr>
<tr>
<td>Partial response</td>
<td>1–5%</td>
<td>5–25%</td>
<td>≥50% reduction</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>&gt;5% absolute increase</td>
<td>&gt;25% increase or absolute increase of ≥10%</td>
<td>&gt;25% increase</td>
</tr>
<tr>
<td>Stable disease</td>
<td>None of the above criteria are met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Reappearance</td>
<td>&gt;10% increase</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>
in peripheral blood can also be seen in other plasma cell dyscrasias and certain non-malignant conditions such as severe sepsis and infectious mononucleosis. 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. 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. 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. Allogenic stem cell transplantation can be considered in patients under 50 years of age; however, the risk of transplantation-related mortality is increased. Nevertheless, high-dose chemotherapy followed by autologous stem cell transplantation improves survival, although mainly for patients with primary PCL.

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. 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. Jelinek et al. also recommended the assessment of minimal residual disease-negative remission by multicolour flow cytometry or allele-specific oligonucleotide polymerase chain reaction.

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.

ACKNOWLEDGEMENTS


References

15. Heerema-McKenney A, Waldron J, Hughes S, Zhan F, Sawyer J, Bladé J, et al. Revised diagnostic criteria for primary and secondary PCL, resulting in some cases in complete remission. 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. Allogenic stem cell transplantation can be considered in patients under 50 years of age; however, the risk of transplantation-related mortality is increased. Nevertheless, high-dose chemotherapy followed by autologous stem cell transplantation improves survival, although mainly for patients with primary PCL.

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