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Case report

Primary plasma cell leukaemia in a 39-year-old man

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SUMMARY

Plasma cell leukaemia (PCL) is an aggressive haematological malignancy which is classified into primary (pPCL) and secondary PCL. A 39-year-old Indian man presented to the Department of Hematology with a 2-week history of fever and lethargy. Clinically, he was pale and febrile. Haemogram revealed bicytopenia with leucocytosis. The peripheral blood film portrayed rouleax formation with 45% of circulating plasma cells. Serum protein electrophoresis and immunofixation revealed IgG lambda paraproteinaemia of 48 g/L. Bone marrow aspirate, flow cytometry and trephine were consistent with IgG lambda pPCL. He was treated with six cycles of bortezomib, thalidomide and dexamethasone combination chemotherapy followed by high-dose melphalan conditioning and autologous stem cell transplant. Currently, he is in complete remission for the past 18 months and is on oral lenalidomide maintenance therapy. Prognosis is often dismal in pPCL with the median overall survival below 1 year if treatment is delayed.

BACKGROUND

Plasma cell leukaemia (PCL) is a rare haematological malignancy which is classified into primary (pPCL) and secondary PCL (sPCL). The rising incidence of sPCL is attributed to improved survival in multiple myeloma especially in those who are heavily pretreated, and these patients live long enough for clonal evolution to take place. Kyle's criteria define pPCL as 20% or more plasma cells and at least 2×10^9/L plasma cells in the peripheral blood but the International Myeloma Working Group (IMWG) suggests that either one is sufficient for a diagnosis of PCL.[1] pPCL demonstrates an aggressive course and progresses rapidly without therapy. The prognosis is often poor with mortality within the first month as high as 15%.[2] Elevated lactate dehydrogenase, anaemia, increased serum beta-2 microglobulin, hypercalcaemia, hypoalbuminaemia and renal impairment are commonly seen in pPCL.[2] Osteolytic lesions are less commonly seen in pPCL as compared with multiple myeloma.[3] Untreated multiple myeloma may lead to sPCL within 20–22 months.[4] This case report aims to highlight the need for awareness among clinicians of this disorder and the importance to examine for other associated clinical features to avoid missing such a vital diagnosis.

CASE PRESENTATION

A 39-year-old Indian man who was previously healthy presented to the Department of Hematology with a 2-week history of persistent fever, lethargy and back pain. He did not have lower limb weakness, bleeding tendencies or night sweats. He has no significant family history. He is single, a non-smoker and does not consume alcohol. He works as a bank clerk. He has no known allergy history.

Physical examination revealed a medium-built man who was pale and febrile at 38.5°C. His blood pressure was 142/84 mm Hg with a heart rate of 96 beats per minute. There were no palpable lymph nodes or organomegaly. His systemic examinations were unremarkable.

INVESTIGATIONS

The haemogram portrayed normochromic normocytic anaemia of 6.8 g/dL, leucocytosis of 15.2×10^9/L and thrombocytopenia of 31×10^9/L. His creatinine clearance (Cockcroft–Gault equation) was 56 mL/min. The other laboratory parameters are as tabulated in table 1.

The peripheral blood film (figure 1A) at diagnosis showed rouleax formation with 45% of circulating plasma cells. The peripheral blood smear immunophenotyping by flow cytometric analysis revealed 49% cluster of neoplastic plasma cells expressing CD20, CD38, CD138 and cLambda. The bone marrow aspiration (figure 1B) portrayed 90% of neoplastic plasma cells. The plasma cells were described as multinucleated, containing basophilic cytoplasm and indiscernible nucleoli. Bone marrow for flow cytometry showed 44% cluster of cells expressing positivity for CD20, CD38, CD138 and cLambda. The cells lacked CD56 and cKappa positivity. Fluorescent in-situ hybridisation cytogenetics revealed t(4:14) and TP53 deletion. The bone marrow trephine biopsy showed infiltration by sheets of plasma cells staining positive for CD20, CD38, CD138 and demonstrating severe lambda light-chain restriction. Congo red stain of the bone marrow trephine biopsy was negative for amyloid deposition. Serum protein electrophoresis (figure 2A,B) and immunofixation (figure 3) revealed IgG lambda paraproteinaemia of 48 g/L in the gamma region with severe immunoparesis. The serum-free light-chain ratio (lambda–kappa ratio was elevated at 1800; lambda of 450 mg/dL, kappa of 0.25 mg/dL). The 24 hours urine protein electrophoresis and immunofixation studies showed monoclonal free lambda light chain of 185 mg. Skeletal survey did not demonstrate any lucencies or lytic bone lesions. Positron emission tomography-computed tomography (PET-CT) imaging showed hypermetabolic activity in the thoracic and lumbar spine with visible pelvic lesions.

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Table 1 Tabulation of laboratory parameters

Laboratory parameters	Values (unit and normal range)
Haemoglobin	6.8 (13.5–16.5 g/L)
Total white cell count	15.2 (4–10 × 10^9/L)
Platelet	31 (150–400 × 10^9/L)
C-reactive protein	0.5 (<5 mg/L)
Creatinine	155 (40–100 µmol/L)
Alanine aminotransferase	24 (0–40 U/L)
Serum calcium	2.8 (2.2–2.6 mmol/L)
Serum albumin	26 (35–51 g/L)
Serum globulin	51 (20–35 g/L)
Hepatitis B surface antigen	Not detected
Anti-Hepatitis C	Not detected
Anti-HIV-1,2	Not detected
Lactate dehydrogenase	615 (90–180 U/L)
Beta-2 microglobulin	7 (<2 mg/L)
Antinuclear antibody	Not detected

DIFFERENTIAL DIAGNOSIS

A diagnosis of IgG lambda pPCL, Revised-International Staging System (stage 3) was made. The Durie–Salmon Staging System for this patient was stage II (haemoglobin concentration <8.5 g/dL, serum calcium <3 mmol/L, renal impairment present, IgG component protein <70 g/L, urine lambda light chain <4 g/24 hours and skeletal survey demonstrated no bony lesions).

The diagnosis of pPCL was based on bone marrow morphology, flow cytometry, cytogenetic studies, serum and urine protein electrophoresis. The differential diagnoses need to be considered are amyloidosis, multiple myeloma, B-cell chronic lymphocytic leukaemia, hairy cell leukaemia, marginal zone lymphoma and reactive polyclonal plasmacytosis. Amyloidosis is often diagnosed on a positive Congo-red stain biopsy sample taken from the subcutaneous abdominal fat or involved organ system. In this case, the Congo-red stain of the bone marrow trephine biopsy was negative for amyloid deposition. Multiple myeloma without transformation to sPCL would not fulfil the diagnostic criteria of 20% or more clonal plasma cells on the peripheral blood film. Reactive polyclonal plasmacytosis is usually associated with infection or autoimmune disorders. Absence of kappa or lambda light-chain restriction excludes reactive polyclonal plasmacytosis. In this case, they were no clinical features of underlying infection or autoimmune disorders. Other forms of leukaemia and lymphoma are distinguished from pPCL by bone marrow morphology, flow cytometry, trephine immunohistochemistry and lymph node biopsy.

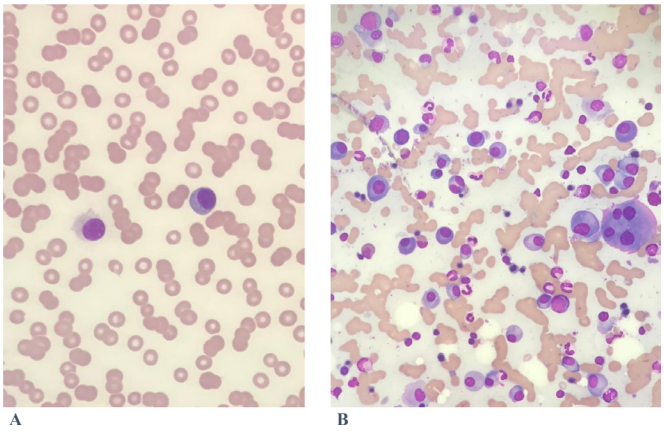

Figure 1 (A) Peripheral blood film shows rouleax formation and circulating plasma cells. (B) Bone marrow aspirate shows 90% of neoplastic plasma cells. The plasma cells are described as multinucleated with basophilic cytoplasm and indiscernible nucleoli. No moth cells, morula cells, Russell bodies or Dutcher bodies are seen.

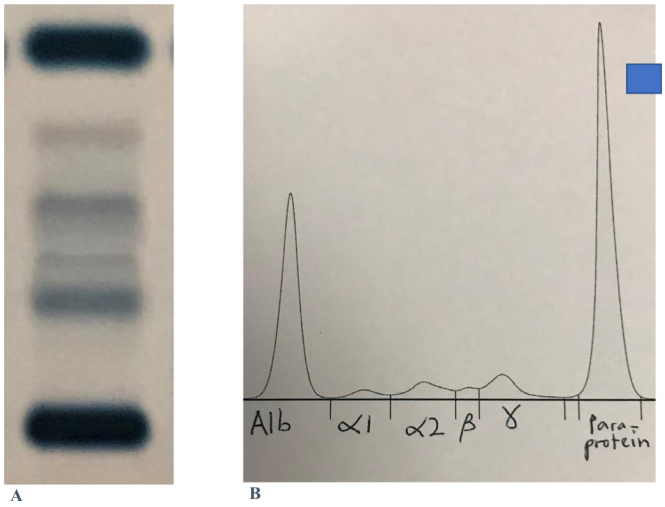

Figure 2 (A) Separation on agarose gel with amido black 10B staining for plain gel electrophoresis. (B) Schematic representation of protein electrophoresis shows the fractions in percentage: albumin (Alb), 32.3%; alpha-1 (α1), 2.3%; alpha-2 (α2), 5.0%; beta (β), 1.8%; gamma (γ), 7.0%; paraprotein, 51.6%.

TREATMENT

He was treated with six cycles of subcutaneous bortezomib 1.3 mg/m^2 given on days 1, 8, 15 and 22, daily oral thalidomide 100 mg continuously and oral dexamethasone 20 mg twice a day on days 1–4 and days 15–18 of each cycle. He was also given a renal-adjusted dose of intravenous zoledronate (bone-modifying agent) 3.5 mg every 4 weeks for 18 months. His repeated peripheral blood film and immunophenotyping did not reveal any

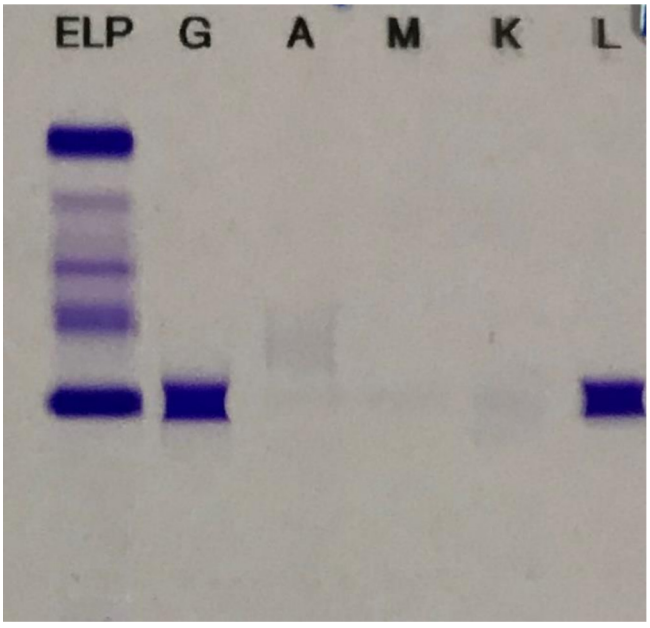

Figure 3 Acid violet staining for immunofixation electrophoresis shows monoclonal IgG lambda paraproteinaemia.

plasma cells. The repeated bone marrow morphology, immunophenotyping and trephine biopsy did not demonstrate any disease. The serum protein electrophoresis and serum-free light chain showed a very good partial response to treatment with his renal function being normalised. Following this, he underwent high-dose melphalan conditioning and autologous stem cell transplant (ASCT). He was compliant to therapy and did not develop any significant adverse effects from the treatment.

OUTCOME AND FOLLOW-UP

He has been in complete remission for the past 18 months and is on daily oral lenalidomide 10 mg maintenance therapy. He has returned to his work as a bank clerk. He is currently on a 3-monthly follow-up at the haematology clinic.

DISCUSSION

The median age of diagnosis for pPCL is 55 which is a decade younger in comparison with multiple myeloma (MM).[5] However, the patient in this case was young at 39 years of age. The most common subtype is IgG followed by light-chain-only PCL. Extramedullary involvement is common in pPCL with the IMWG suggesting a baseline 18-fluorodeoxyglucose positron emission tomography computed tomography to be performed in all newly diagnosed PCL.[5]

Flow cytometry is crucial in assessing plasma cell clonality. Polyclonal plasmacytosis can be attributed to infection which is commonly seen in pPCL as they have moderate to severe immunoparesis. Plasma cells in pPCL express CD20, CD38 and CD138 with CD56 positivity more frequently seen in MM.[6]

The genetic biology in pPCL differs in comparison with MM. Increased incidence of hypodiploidy, 17p deletion, TP53 and DIS3 mutations, t(11;14), t(4;14) and t(14;16) is seen in pPCL.[7]

The diagnosis of pPCL is often based on bone marrow morphology, flow cytometry, cytogenetic studies, serum and urine protein electrophoresis. The differential diagnoses need to be considered are amyloidosis, multiple myeloma, B-cell chronic lymphocytic leukaemia, hairy cell leukaemia, marginal zone lymphoma and reactive polyclonal plasmacytosis.[8] Amyloidosis is often diagnosed by a positive Congo-red stain biopsy sample taken from the subcutaneous abdominal fat or involved organ system. Multiple myeloma without transformation to sPCL would not fulfil the diagnostic criteria of 20% or more clonal plasma cells on the peripheral blood film. Reactive polyclonal plasmacytosis is usually associated with infection or autoimmune disorders. Absence of kappa or lambda light-chain restriction excludes reactive polyclonal plasmacytosis.[8] Other forms of leukaemia and lymphoma are distinguished from pPCL by bone marrow morphology, flow cytometry, trephine immunohistochemistry and lymph node biopsy.

Therapy incorporating proteasome inhibitors (PI) such as bortezomib; immunomodulators such as thalidomide or lenalidomide and steroids such as dexamethasone followed by high-dose melphalan conditioning and ASCT have improved the prognosis in pPCL.[9] The presence of t(11;14) predicts a favourable response using venetoclax that is a BCL-2 inhibitor in pPCL.[10]

Allogenic stem cell transplantation is less favoured in pPCL due to high treatment-related mortality. Bortezomib and lenalidomide seem to be an ideal combination to maintain PCL patients in remission.[11] Second-generation PIs such as carfilzomib and ixazomib, and anti-CD38 antibodies such as daratumumab and isatuximab are being investigated in pPCL. Anti-CD45 antibodies, combined BRAF/MEK inhibitors and chimeric antigen receptor-T therapy, are options of interest in pPCL.[11]

Patient's perspective

I was having persistent continuous fever for the past 2 weeks with significant fatigue and lethargy. I initially visited a local general practitioner at a nearby clinic where I live. The doctor at the clinic noticed I was pale, and he took a basic full blood count test. He then advised me to seek immediate treatment at the hospital. At the hospital, I was eventually admitted to the haematology ward. The attending doctor did a variety of tests including a bone marrow assessment. I was extremely shocked when I was told to have plasma cell leukaemia. I thought I was going to die in the next few months from this blood cancer. I began reading through the internet to find out more regarding this disease. I always thought that this disease occurred in the elderly. I was trying to figure out what I did in the past which could have contributed to this cancer. I neither smoked nor consumed any alcohol in my entire life. I was dedicated to my work as a clerk at a local bank. I did not have any positive family history. The doctors then counselled my family and I that I should undergo a series of at least six cycles of bortezomib-based therapy. During the course of treatment, I did not suffer from any significant side effects. I also underwent autologous stem cell transplantation at the transplant unit in the same hospital. I was discharged on day 12 of the transplant. The medical staff were kind and ensured I wasn't in much pain. They attended to me whenever I needed help. Currently, I am on a regular follow-up at the haematology clinic. I am glad to be back at work. I have become more cautious and ensure I practise a healthy life style. I shall not take life for granted.

Learning points

- Plasma cell leukaemia (PCL) is the most aggressive form of all plasma cell neoplasms.
- Prognosis is often dismal in primary PCL (pPCL) with the median overall survival below 1 year if treatment is delayed.
- Early diagnosis and effective therapy are vital to improve survival in pPCL.

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