Case Report:

Primary Plasma Cell Leukaemia with Lambda Light Chain secretion and Chromosomal abnormalities presenting as hyperleukocytosis - A case report.

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Abstract:

Primary plasma cell leukaemia (pPCL) is a rare and lethal form of plasma cell dyscrasia that can occur either de novo (primary) or as a leukemic transformation of refractory or relapsed multiple myeloma. We report a case of pPCL with lambda light chain disease and multiple chromosomal abnormalities in a 75-year-old female who presented with generalized weakness. Her peripheral blood smear showed hyperleukocytosis with 78% circulating plasma cells. Serum protein electrophoresis (SPE) does not reveal the M band and serum immunofixation (SI) light chain analysis in serum showed an elevated lambda light chain. Skeletal radiography and PET-CT (positron emission tomography—computerized tomography) did not reveal any lytic lesions. Immunophenotypic studies reveal a CD38-positive population with negativity for T cells, B cells, myeloid markers, and a negative CD45. Fluorescent in situ hybridization (FISH) analysis results disclosed the deletion of 13q14.3 and t(11; 14). This case highlighted the usefulness of the peripheral smear findings and high fluorescent lymphocyte activity, which directed the pathologist to initiate workup for pPCL, and comprehensive laboratory biochemical and radiological evaluation further helps to confirm and differentiate pPCL from multiple myeloma.

Keywords: Primary plasma cell leukemia; peripheral smear findings; flow cytometry; light chain disease; Chromosomal abnormality; Positron emission tomography/CT

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Introduction:

Primary plasma cell leukaemia (pPCL) is a malignant plasma cell disorder and is defined as the circulating plasma cells more than 20% of the differential white count or the presence of $2x10^9$/ul peripheral blood clonal plasma cells in the absence of preexisting multiple myeloma(MM). The incidence of pPCL is 60–70%, whereas approximately 40% of cases are secondary. PCL is similar to that of MM in the form of the expansion of malignant plasma cells within the bone marrow**.** However, unlike other MM forms, it is distinct in terms of age of presentation, clinical severity, immunoelectrophoresis pattern, light chain values, immunophenotype expression, genetic findings and treatment outcome.[1]

The circulating plasma cells in the peripheral blood are difficult to assess on an automated haematology cell analyzer, as they masquerade as monocytes or an increased high fluorescent lymphocyte count (HFL) and are difficult to differentiate from viral infection-related reactive lymphocytes, acute leukemia, or chronic leukaemia [2]. However, morphological

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Table:1 Laboratory findings

S.N.	Lab Parameters	Test Results		Biological reference Interval
		Day of Admission	Day of Discharge	
1	**Haemogram**			
	Hemoglobin	**6.5gm%**	9.0gm%	12-15 gm%
	WBC	**1.54 lakhs/ mm^3**	8760/mm^3	4000-11000 /mm^3
	Platelet count	1.77	1.0	1.5-4.5 lakhs/cumm
	Peripheral Smear abnormal cells	**78%**	**00%**	
2	**LFT**			
	Total Bilirubin	0.8	1.1	0.2 - 1.3 mg/dl
	Direct	0.2	0.2	0- 0.3 mg/dl
	Indirect	0.6	0.9	0- 1 mg/dl
	SGOT	59	26	14-60 U/L
	SGPT	20	28	0-35 U/L
	Alkaline Phosphate	63	84	38-126 U/L
	Total protein	6.7	5.6	6.3 - 8.5 gms/dl
	Albumin	4.1	3.3	3.5 - 5.0 gms/dl
	Globulin	2.6	2.4	2.3 - 3.5 gms/dl
3	Creatinine	0.6	0.7	0.7 - 1.2 mg/dl
4	Serum Calcium	**8.1**	8.7	8.4-10.2mg/ dl
5	**Electrolytes**			
	Sodium	139	137	137- 145 mmol/L
	Potassium	4.0	3.8	3.7 - 5.1 mmol/L
	Chloride	101	136	98 - 107 mmol/L

findings of plasmacytoid lymphocytes in peripheral blood smears provide an early clue to predict plasma cell neoplasm. According to recent studies, having 5% or more circulating abnormal PCs in peripheral blood has similar unfavourable prognostic effects and low survival rates as those patients with >20% PCs. As a result, patients with circulating PCs of 5% in the peripheral blood white cell differential count may be considered for early PCL diagnosis and treatment[3]. Further flow cytometry, SPE, SI, PET-CT and FISH molecular testing help in the final diagnosis, staging, and prognosis of the disease.

Case Report:

A 74-year-old female patient presented to the department of medicine's OPD with a history of generalized weakness and dry mouth for four weeks. On a clinical examination, the patient was afebrile and pale. Her pulse rate was 74 beats per minute. The blood pressure was 140/80 mm Hg and the rate of breathing was 22 breaths per minute. The systemic examination was unremarkable. Initial laboratory investigations revealed (Table 1) anaemia (6.5 g/dL), normal RBC indices, marked leukocytosis (1.54 lakhs/cu mm), and a normal platelet count (1.77 lakhs/cu mm).

Peripheral blood examination revealed normocytic, normochromic RBCs, hyperleukocytosis, and a 78% predominance of atypical lymphoid, mononuclear, and plasmacytoid cells. The cytoplasm is nongranular with a fuzzy cytoplasmic border. Few cells are binucleate, and even fewer have intracytoplasmic inclusions (Figure 1). There was no RBC rouleaux formation.

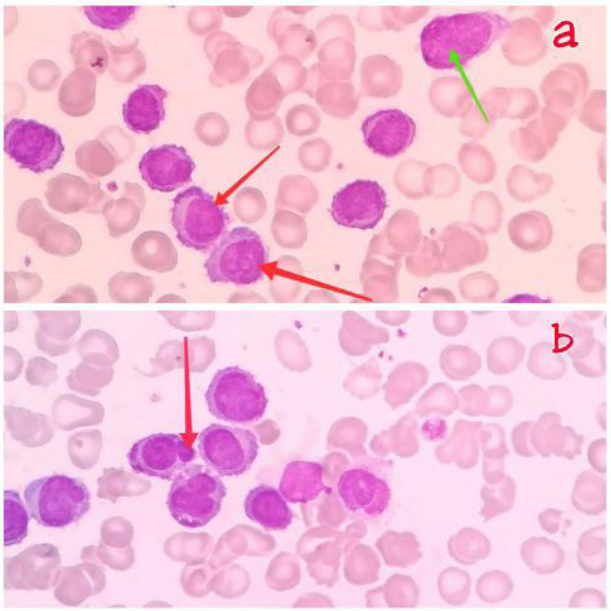

Figure:1 Peripheral photomicrograph show plasmacytoid cells (red arrow), mononuclear cells(green arrow), binucleate cells.

Hemogram leukocyte differential plot demonstrating a uniform population in lymphocytic and monocytic

Table 2: Immunofixation with light chain assay

Test Report Status	Results	Biological Reference Interval
Myeloma M Band	Not detected	Not detected
Electrophoretic Zone		
IGG band	Not detected	Not detected
IGM band	Not detected	Not detected
IGA band	Not detected	Not detected
Kappa band	Not detected	Not detected
Lambda band	**DETECTED**	Not detected
Immunofixation-Quantitative		
Total IgA	40mg/dl	70-400 mg/dl
Total IgG	614	700-1600mg/dl
Total IgM	25 mg/dl	40-230 mg/dl
Serum Light Chains (kappa & lambda)		
Kappa Light Chain	13.1mg/L	.30 - 19.40 mg/L
Lambda Light Chain	588mg/L	5.71 - 26.30 mg/L
Kappa Lambda Ratio	0.02mg/L	0.26 - 1.65 mg/L
B2-Microglobulin	4175 ng /ml	609.0 - 2366.0 ng/mL

regions with the majority of cells with increased fluorescence located in lymphocyte-monocytic, blastic, or atypical lymphocytic regions, indicating high fluorescence activity. The results of the blood coagulation study, including PT, APTT, and fibrinogen, were normal. Serological tests for HBV, HCV, HIV, and syphilis were negative. Complete urine examinations were normal. Biochemical investigations revealed normal liver function tests, normal renal function tests, mild hypocalcemia, and normal electrolytes (table 1)**.** The lab physician requested that a workup be initiated to rule out plasma cell neoplasm based on the haematological findings.

Radiological imaging PET-CT and X-rays of the skull, dorsal spine, lumbar spine, and both femurs did not reveal any lytic lesions or soft tissue masses. Serum protein electrophoresis did not show the myeloma band (M-band). Serum immunoglobulins quantified by the immune-turbidimetric method revealed normal serum IgG, IgA, and IgM. IgE and serum IgD levels were not assessed. Free light chains showed increased lambda and a decreased kappa–lambda ratio of 0.02. The level of 2-microglobulin was elevated (Table 2).

The patient was not willing to have a bone marrow aspiration. The flow cytometry immunophenotypic and a molecular examination was done on her peripheral blood. Immunophenotypic studies reveal positivity for CD38, CD43, and HLA-DR. Cytoplasmic lambda was positive and markers are negative for cytoplasmic kappa. markers for B cells (CD19, CD20, CD79b), T cells (CD2, CD3, CD5, CD7, CD8), and myeloid markers (CD13, CD33) came back negative. Immunophenotypic findings were consistent with a peripheral smear that was provisionally diagnosed as plasma cell leukemia. Fluorescence in situ hybridization (FISH) was performed on the heparinized peripheral blood to detect the IgH/CCND1 fusion signal in 20% of cells, which is positive for t(11; 14). A del 13q14.3 signal was detected in 82% of cells. Patients are treated as pPCL. She responded clinically well with improved haematological parameters to the RVd regimen of lenalidomide (R), bortezomib (V), and dexamethasone (d) for four cycles at 21-day intervals. The patient is now being monitored on a regular basis.

Discussion:

Primary plasma cell leukaemia is a rare haematological cancer. An estimated incidence of PCL is 1 case per million individuals per year. The median age at presentation in primary PCL is between 50 and 59 years. This is younger than for multiple myeloma patients, where the median age at diagnosis is between 66 and 70 years. It is slightly more common in men than women (60% to 40%). Lymphadenopathy, organomegaly, and renal failure are more common, and lytic bone lesions and bone pain are less common in pPCL. The laboratory parameters associated with pPCL are significant anemia, thrombocytopenia, renal insufficiency, hypercalcemia, increased tumour burden (reflected by elevated lactate dehydrogenase), β2-microglobulin and marked bone marrow (BM) plasma cell infiltration. The causes of primary PCL are currently unclear.[1,4]

In many cases, the first line of pPCL diagnosis is based on a careful examination of a peripheral smear and flags generated by an automated haematology cell analyzer. In peripheral blood films with PCL, plasma cells can have a variety of morphological forms, including mature or classic plasma cells, immature plasma cells, and plasmablasts. In our case majority of plasma cells resembled mature lymphocytes with fuzzy cytoplasmic borders and there was no RBCs rouleaux formation in background. The automated hematology cell analyzer (eg. Sysmex XN-1000) able to perform high fluorescent lymphocytes (HFL) count. More the nucleic acid more fluorescent dyes will attach leading to high fluorescence activity (HFL), which reflect in atypical lymphocytes zone on scattergram. [5] Thus careful peripheral blood smear examination needed to rule out other conditions causing high HFL.

A bone marrow aspirate and biopsy are required to assess morphology, proliferation rate, immunophenotyping and cytogenetic analysis using fluorescence in situ hybridization (FISH). The bone marrow is usually extensively and diffusely infiltrated with neoplastic plasma cells. Surface immunophenotype markers for plasma cells in PCL are similar to those found in plasma cells from multiple myeloma bone marrow. Plasma cells in pPCL express CD20, CD38, and CD138, along with CD56. However, the majority of PCL patients (80%) have plasma cells that lack the aberrant CD56 expression that is considered a hallmark of PCL and could distinguish it from MM [6]. In our case, immunophenotyping and cytogenetic analysis were performed in peripheral blood, which showed negative expression for CD56 and the deletion of 13q14.3 and t(11;14), respectively. The existence of the M band in PCL is not detected by serum protein electrophoresis. A higher proportion of light chain-only, Ig E, and IgD myelomas present as PCL in serum immunofixation studies when compared to IgG or IgA myelomas[1]. To detect both lytic bone lesions and extramedullary plasmacytomas, whole-body imaging with magnetic resonance imaging (MRI), computerised tomography (CT), or 18F-fluorodeoxyglucose positron emission tomography (PET)/CT should be performed[7]

A specific treatment for pPCL is not well defined. Combination chemotherapy with immunomodulatory agents such as bortezomib, proteasome inhibitors, lenidomide, and steroids such as dexamethasone, followed by high-dose melphalan improves prognosis in pPCL. Allogeneic stem cell transplantation is less favored in pPCL due to high treatment-related mortality, especially in elderly patients. Considering the low incidence of primary PCL, data on its prognosis are relatively limited. The overall survival of patients with primary PCL is known to be poor when treated with conventional chemotherapy and the majority are known to die within one year of diagnosis [8].

Conclusion:

In conclusion, pPCL is a rare aggressive plasma cell disorder that rarely presents as leukocytosis. Due to the rarity of this disease, no general consensus regarding diagnostic approaches and standard chemotherapy regimens has been defined so far. This case report is intended to highlight the laboratory physician for careful review of histogram results and peripheral blood smear morphology as well as a comprehensive evaluation of laboratory **tests** performed including bone marrow cytology, histology, flow cytometry, SI, serum light chain testing and beta 2 microglobulin to diagnose and differentiate from MM.

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