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A RARE CASE PRESENTATION OF PRIMARY PLASMA CELL LEUKEMIA WITH REVIEW OF LITERATURE, A CASE REPORT

Pathology

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ABSTRACT

Introduction: Primary Plasma Cell Leukemia (pPCL) is Plasma cell dyscrasia subtype which is rare and aggressive. It carries very poor prognosis. It has unique clinical and laboratory profile. Its first clinical presentation is leukemia. Peripheral blood examination shows circulating mature looking yet clonal, plasma cells. On molecular and cytogenetic examinations, many aberrations are seen which are unique and make it a distinct entity different from traditional Multiple Myeloma (MM).

Case presentation: 37 yr old Indian female presented with difficulty in breathing for last 3 months and was initially evaluated for cardiac function & COVID-19 screening. Peripheral blood examination revealed circulating plasma cells. Bone marrow apirate confirmed the initial diagnosis of pPCL. She received BIODRONATE + Inj. BORTEZOMIB + Inj. CYCLOPHOSPHAMIDE + Tab Dexa and was advised for PET scan and skeletal survey. But due to financial constraints, family decided to go for complete systemic workup in next phase of chemotherapy cycle. She was discharged with advise to be in close follow up and to complete her treatment cycles.

Discussion: pPCL needs to be diagnosed promptly to formulate optimal intensive therapy. This atypical presentation with shortness of breath of rare entity of pPCL in such young age emphasizes the need for quick and thorough initial workup.

Conclusion: Because of rarity of this disease, there is paucity of literature from India and especially the impact of the standard therapies in resource poor countries. Our case report highlights these challenges for conclusive management of this rare entity.

KEYWORDS

Primary Plasma Cell Leukemia, Plasma cell Myeloma, case Report

1. INTRODUCTION:

Plasma cell leukemia (PCL) is the most aggressive type of multiple myeloma (MM). It is characterized by circulation of clonal plasma cells within the Bone Marrow (BM) unlike other types of MM. It may cause end organ damage like lytic bone lesions, anemia, hypercalcemia and renal dysfunction.

Gluzinski and Reichenstein described first case of PCL in 1906. [1] Kyle and Noel defined it as the presence of >20% plasma cells in differential white blood cell count on peripheral blood examination, or an absolute peripheral plasma cell count of >2.0 x 10^9 cells/L.[2] If there is no prior history of MM, PCL is defined as primary plasma cell leukemia (pPCL). If there is a prior history of MM then it is defined as secondary PCL (sPCL). sPCL may occur in 1% to 4% of MM patients over the course the disease.

In < 1% of patients of PCL, there may be severe leucocytosis, defined as >50 × 10^9/L). [3] Unlike classic MM, pPCL has very unique molecular pathogenesis and also very different clinical and laboratory presentation. pPCL carries poor prognosis with average overall survival (OS) of 7 months only. Hence, there is a need of prompt and novel intervention strategies to better the disease outcome.

1.1 Pathology of PCL:

Initially, MM plasma cells are sequestered in BM requiring BM microenvironment for growth and survival. In PCL too, plasma cells aggregate in BM but they have propensity to egress out of BM into the peripheral blood and ultimately into the end organs. Gene expression profiling studies find pPCL a distinct molecular entity among plasma cell neoplasms.[4] MM has often an early phase of MGUS which goes undetected in the majority of patients. There are also similar incidences of MGUS preceding the PCL, as highlighted in few case reports. [5] However, extent of such premalignant phase of MGUS preceding pPCL is unclear. It is also unclear if pPCL predominantly arises de novo.

1.2 Clinical and laboratory Features

pPCL and MM:

pPCL patients are usually younger (<60 yrs) as compared with MM patients (<80 yrs)[6] and more often develop end organ damage to liver, spleen, lymph nodes, and other soft tissues. pPCL also may present with malignant pleural effusion or CNS involvement.[7] pPCL also causes more frequent renal dysfunction due to light chain-only secreting disease as well as anemia and thrombocytopenia due to more diffuse and severe bone marrow involvement.[8] pPCL patients have more elevated serum lactic dehydrogenase (LDH) and increased β2 microglobulin. However, they less often have lytic bone disease than patients with MM.[9]

In pPCL, the clonal plasma cells appear more immature, or 'plasmablastic' in morphology. From a cytogenetics standpoint, patients with pPCL are less likely to be hyperdiploid in comparison with their MM counterparts. The t(11;14) is the most common cytogenetic abnormality, but deletion 17p, t(4;14) and CKSB1 duplication are also more commonly present than in MM. Whole-exome sequencing on pPCL clonal plasma cells demonstrates effects in the cadherin/Wnt signaling, extracellular matrix-receptor interaction, extracellular matrix organization and G2M cell cycle checkpoint. [10]

pPCL and sPCL:

sPCL is typically the terminal stage of preexistent MM, and this in part explains the higher prevalence of advanced bone disease compared with pPCL.[6] In contrast, extramedullary involvement may be less common in sPCL. Patients with sPCL present more often with renal failure than MM patients, but renal dysfunction is more common in pPCL.[8]

1.3 Hematological findings:

Peripheral blood examination in pPCL shows circulating tumor cells and typically a leuko-erythroblastic blood picture in up to 67% of patients. [6] BM biopsy typically demonstrates extensive BM involvement, disrupting normal hematopoiesis. In some cases, tumor resembles normal plasma cells, whereas in others, lymphoplasmacytoid or immature plasma cells predominate.[11] Sometimes the circulating plasma cells are difficult to classify by light microscopy alone and differentiation from other conditions, such as chronic lymphocytic leukemia, hairy cell leukemia, or marginal zone lymphoma with circulating lymphocytes requires immunophenotypic analysis, which can also be useful to differentiate reactive from clonal plasma cells.

The most striking immunophenotypic difference between newly diagnosed MM and pPCL is that pPCL tumor cells are less often positive for CD56, CD71, CD117, and HLA-DR, but more likely express CD20, CD45, CD19, CD27, and CD23. Both increased expression of CD20 and CD23 and down-regulation of CD56 may be related to the high incidence of t(11;14) in pPCL. Tumor cells are positive for CD38 and CD138 in both PCL and MM.[8] Interestingly, there is a progressive decrease in expression levels of CD38 from normal plasma cells to MGUS plasma cells, MGUS to MM, and finally MM to PCL, which probably reflects dedifferentiation into a more

immature phenotype. Immunophenotypic profiles of pPCL and sPCL are comparable, except for CD56 and possibly Cd28 expression, which is more often present in sPCL compared with pPCL.[12]

1.4 Diagnostic Approach

All patients with MM suspected of having pPCL must undergo a detailed history and physical examination. A comprehensive laboratory test evaluation of their blood should be performed, including at least a complete blood count with differential, peripheral blood smear; electrolyte panel; creatinine; liver enzymes; bilirubin; alkaline phosphatase; LDH; uric acid; β2 microglobulin; albumin; serum protein electrophoresis with immunofixation; and serum free light chain analysis. If possible, multiparameter flow cytometry should be performed on the peripheral blood to confirm the presence of clonal circulating plasma cells; they typically have immunophenotypes of Cd138+, CD38+, CD19–, and CD45+/–. Whole body imaging with either magnetic resonance imaging, computerized tomography (CT), or 18[F]fluorodeoxy- glucose positron emission tomography/CT to assess for both lytic bone lesions and extramedullary plasmacytomas is necessary. A 24-hour urine collection for electrophoresis, immunofixation, and total protein assessment should also be performed. Finally, it is essential to perform a bone marrow biopsy and aspirate to assess for morphology; proliferation rate, if possible; immunophenotyping; and cytogenetic analysis by fluorescence in situ hybridization (FISH). FISH is performed on the plasma cells from the bone marrow aspirate. The FISH probes should be directed on specific abnormalities, such as del(17p13), del(13q), del(1p21), and (1q21) amplification, and chromosome 14 abnormalities such as t(11;14), t(4;14), t(14;20) and t (14;16).[13]

2. Case Presentation:

We hereby present a case to be published in accordance with the SCARE 2020 criteria. [14]

A 37 year old female developed difficulty in breathing from last 3 months. She was non smoker, non alcoholic. She was evaluated by a cardiologist. 2D Echo suggested Non-rheumatic mild TR, LV & LA dilated, LV global hypokinesia, mild PAH, PASP-38 MMHG + rap, Heart rate 113/min, moderate LV dysfunction, No LV/LA thrombus seen, LV global EF 42-44%.

In view of CHF and severe TR, she was referred to a tertiary hospital. There she was reviewed & ECHO findings suggested Restrictive Heart Disease. Classic symptoms of Amyloidosis were absent & Plasma cell disorder was then suspected.

She was then transferred to our hospital for Myeloma workup. On physical examination, liver was palpable 4 cm below right costal margin but spleen was not palpable. She was HIV, HbsAg, HCV Non-Reactive & Covid-19 TrueNAT was Not detected.

On blood investigations, she was found to have normocytic normochromic anemia with Hb 5.5gm/dl. TLC was 49000/mm^3 with leucoerythroblastic picture. Platelet count was 63000/mm^3. Peripheral smear showed rouleax formation. There were circulating plasma cells comprising of 30-40% of nucleated cells in the peripheral blood with 8-10% of NRBCs. Most of the plasma cells appeared mature with occasional cell showing typical paranuclear hoff. However, a few binucleated plasma cells and still other few with plasmablstic morphology were also seen.

She was then subjected to Bone marrow aspiration, FISH for Myeloma & Myeloma Flowcytometry panel. Bone marrow aspirate showed hypercellular preparations with mild erythroid hyperplasia with sheets and clusters of both mature and immature appearing plasma cells with occasional binucleation, comprising of approximately 70-80% of nucleated cells. While results of FISH are awaited, Flowcytometry showed clonal population of plasma cells with light chain restriction, constituting 80% of marrow hematopoietic cells.

The case was discussed with the patient and family members and was planned for BOR-LEN-DEX (Inj. BIODRONATE + Inj. BORTEZOMIB + Inj. CYCLOPHOSPHAMIDE + Tab Dexa) therapy after informed, written consent. The family has been advised for skeletal survey and PET-CT, however due to financial constraints she will undergo these investigations next time. She has been given C1D1 cycle of BOR-LEN-DEX and discharged from the hospital.

3. DISCUSSION:

The median age of diagnosis for pPCL is 55 yrs, a decade earlier than MM. But our case was still younger at 37 yrs. Extramedullary involvement is common in pPCL. Flowcytometry is crucial in formulating the diagnosis and assessing clonality of plasma cells. The diagnosis of pPCL is often based on bone marrow examination, flowcytometry, cytogenetic studies, serum and urine protein electrophoresis. Differential diagnoses need to be considered are Amyloidosis, MM and low grade B cell Non Hodgkin Lymphomas.

Plasma cell leukemia is a rare blood dyscrasia with an aggressive clinical course and dismal prognosis. There is a need for an effective early treatment with a durable therapeutic response. Recent advances in chemotherapeutic regimens particularly with the introduction of novel agents in combination with stem cell transplant have led to improved rate, quality of response, and median OS in patients with PCL. There remains a need for a more comprehensive diagnostic criterion. The presence of 5% circulating clonal plasma cells has been suggested to improve detection. More research is needed in exploring genomic variations which may potentially identify various novel biomarkers that may serve as prognostic markers. Overall clinical course remains poor, signaling a need for more agents, and effective management strategies.

4. Learning points

- Plasma cell leukaemia (PCL) is the most aggressive clinical presentation of all plasma cell dyscrasias.
- Prognosis is often dismal in primary PCL (pPCL) with the median overall survival as low as 7 months, if treatment is delayed.
- Early and accurate diagnosis and aggressive therapy remain cornerstones to improve survival in pPCL.
- Financial constraints & patient's compliance remain challenging & often daunting task for the treating team in developing countries.

Declarations

Contributors: GS carried out the literature search, clinical study, data acquisition, data analysis and drafted the manuscript. SS conceived of the study and participated in its design and coordination, edited and reviewed the manuscript. Both authors read and approved the final manuscript.

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