OPEN ACCESS

Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Case Report

Primary Plasma Cell Leukemia: A Case Report and Literature Review

Imane Benbella[1, 5], Jihade Elamouri[1, 5*], Khalil Lemhouer[1, 5], Zineb Azzine[1, 5], Fatima Zahra Benatiya[1, 5], Fatima Elboukhrissi[2, 5], Imane Tlamçani[3, 5], Mustapha Mahmoud[1, 4, 5]

[1]Biochemistry unit, Central University Hospital Hassan II, Fès, Morocco
[2]Biochemistry unit, Military Hospital Moulay Ismail, Meknès, Morocco
[3]Hematology Unit, Hassan II Central University Hospital, Fès, Morocco
[4]Head of the Biochemistry unit, Central University Hospital Hassan II, Fès, Morocco
[5]Faculty of Medicine, Pharmacology and Dental Médecine, university Sidi Med Ben Abdellah, Fès, Morocco

DOI: 10.36348/sjm.2023.v08i04.001 | **Received:** 13.02.2023 | **Accepted:** 27.03.2023 | **Published:** 04.04.2023

***Corresponding Author:** Jihade Elamouri
Faculty of Medicine, Pharmacology and Dental Médecine, university Sidi Med Ben Abdellah, Fès, Morocco

Abstract

Primary plasma cell leukemia (pPCL) is a rare lymphoproliferative disease characterized by a malignant proliferation of plasma cells in the bone marrow and peripheral blood. It is either primary (in 60% of cases) or a secondary complication of multiple myeloma [1]. In this context, we report the case of a 37-year-old patient with respiratory distress, whose bone marrow smear showed the presence of 64% of dystrophic plasma cells. A serum protein electrophoresis with immunofixation was performed, revealing results in favor of pPCL. A cytogenetic study was not performed due to lack of resources. The patient was put on multidrug therapy with a favorable evolution.

Keywords: Primary plasma cell leukemia, monoclonal gammopathy, case report.

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INTRODUCTION

Plasma cell leukemia (PCL) is a malignant proliferation of plasma cells defined by a blood plasma count greater than 2 G/L or a plasma cell count greater than 20% of the white blood cell count. The primary form (pPCL) occurs de novo in a patient whereas the secondary form (sPCL) consists of the leukemic transformation of an already known Multiple myeloma (MM). pPCL has a relatively poor prognosis due to its very aggressive nature. Indeed, it is accompanied by bone marrow failure, hemolysis by destruction of red blood cells, and lytic bone lesions, and the most important non-bone marrow organ damage is liver and spleen damage [2].

Treatment includes immunomodulators, proteasome inhibitors, stem cell autotransplantation, and autologous stem cell transplantation. The median survival after rigorous chemotherapy and transplantation does not exceed three years [3].

The aim of this work is to report a case of PCL in order to highlight the diagnostic, therapeutic and evolutionary difficulties in our context and to encourage practitioners to think about it when faced with blood blastosis in young subjects and to systematically perform immunophenotyping for a rapid management due to its severity.

CASE REPORT

A 38 years old patient was admitted to the emergency unit for a respiratory distress. This distress came as a complication of a previous anemic syndrome (asthenia, shortness of breath, loss of hair) that the patient suffered from for several months, and for which he did not consult with doctors. The patient's anamnesis revealed no pathological history.

The patient's clinical examination found a mucocutaneous pallor compatible with the anemic syndrome reported by the patient, no associated hemorrhagic syndrome signs were found and a bilateral rib pain was noted on palpation.

The initial biological workup revealed a renal failure with a plasmatic creatinine at 365 UI and a plasmatic urea at 2.3g/l. Hypercalcemia and hyperprotidemia were found with a corrected calcemia and protidemia at respective values of 29 mmol/l and 114g/l.

A normocytic normochromic anemia associated with thrombocytopenia at 69.000 elements/mm3 and hyperleukocytosis at 23.000 elements/mm3 was found. Initially a diagnosis of MM was suspected and an additional workup was performed with an LDH and β2 microglobulin assay with respective values of 296 IU/l and 95.96 mg/l. A blood smear and bone marrow count were also performed and found respectively: circulating dystrophic plasma cells and 64% plasma cells with evidence of marrow infiltrating dystrophy (Figure 1 & 2) therefore a diagnosis of PCL was confirmed. Radiologically, our patient has no radiological evidence of multiple myeloma.

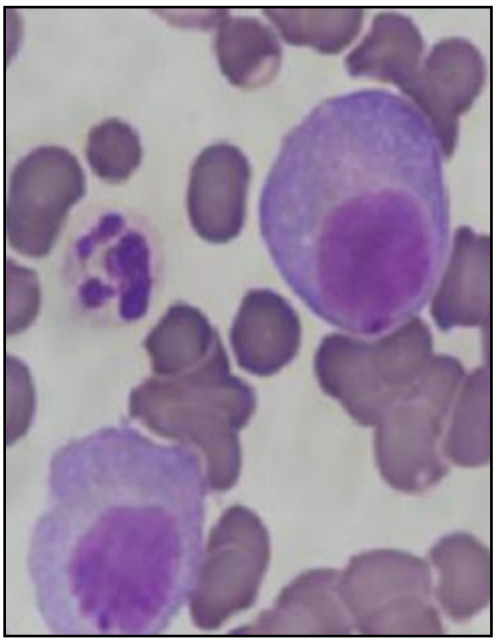

Figure 1: MGG-stained blood smear showing plasma cells (objective 100).

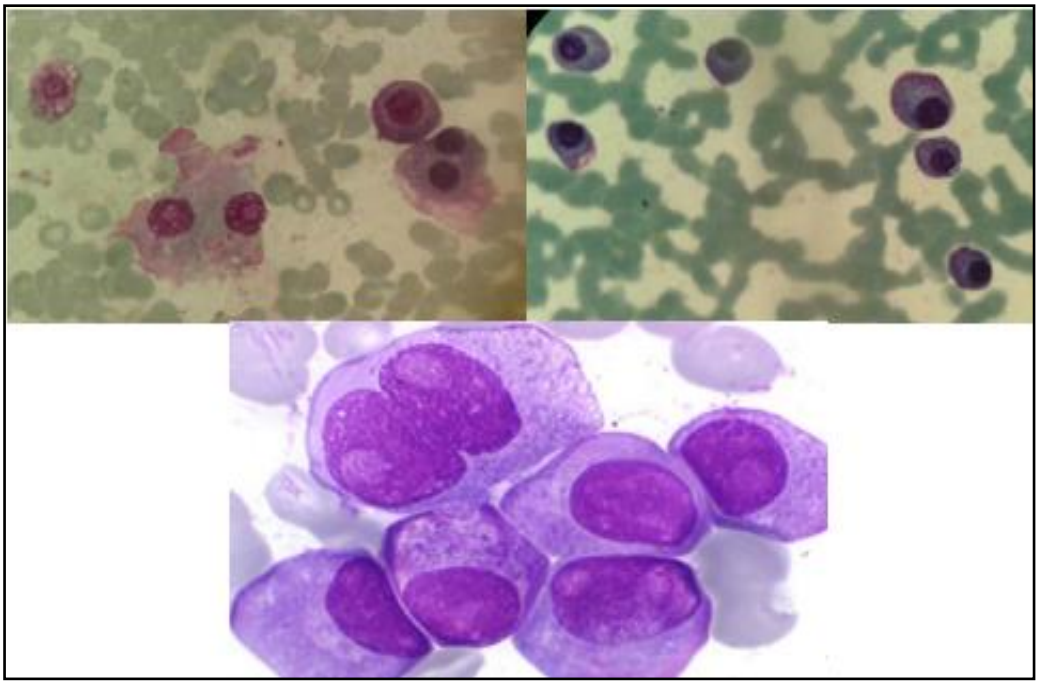

Figure 2: Apparence of Bone marrow at diagnosis: presence of a plasma cells infiltration in approximately 64%, cells with eccentric round nucleus and condensed chromatin, some of them multinucleated, basophilic cytoplasm. (objectivex100)

Serum protein electrophoresis showed a monoclonal peak in the gamma globulin zone with hypergammaglobulinemia at 68 g/l (Figure 3).

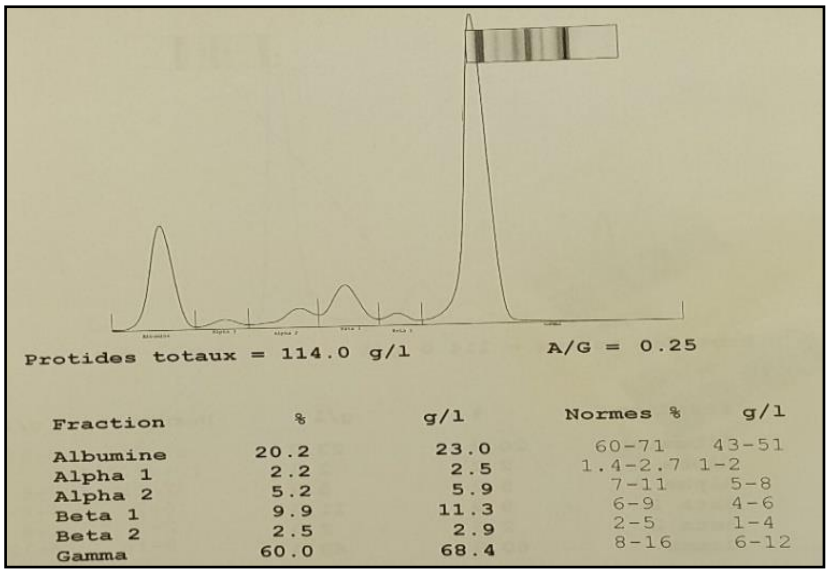

Figure 3: A monoclonal peak in the gamma globulin area with hypergammaglobulinemia on serum protein electrophoresis

Moreover, the realization of an immunofixation and a weight dosage allowed to identify the immunoglobulin clone, it was a biclonal profil with an immuglobuline G with a biclonal free chain lambda at a rate of 42.6g/l (Figure 4).

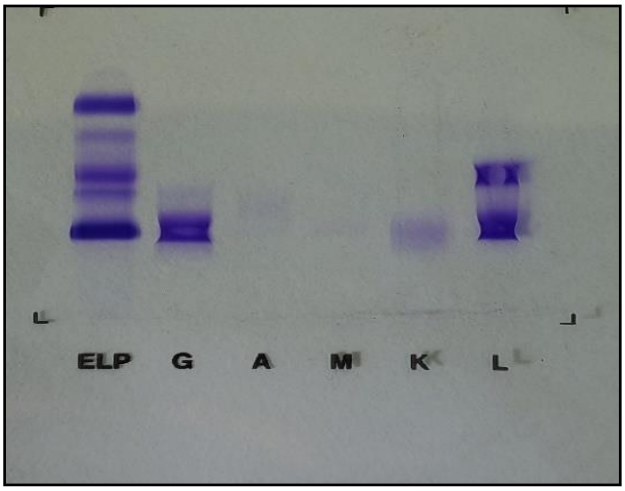

Figure 4: Profil biclonal avec une immuglobuline G avec une chaîne libre lambda biclonal

Due to its appearance on blood smear, protein electrophoresis and immunofixation and its rapid evolution, the diagnosis of pPCL became obvious. The cytogenetic study is still pending due to the patient's lack of means. However, the patient was treated with transfusion support in erythrocyte and platelet concentrate and a bolus of corticosteroid therapy under cover of antibiotic therapy associated with forced diuresis in order to correct hypocalcemia and improve renal function. The patient is clinically stable under VCD chemotherapy protocol (vecade, cyclophosphamide, dexamethasone).

DISCUSSION

PCL accounts for 2-4% of patients with plasma cells [4-7]. It is a malignant plasma cell proliferation of clonal origin. pPCL is a rare form of leukemia that occurs immediately, in contrast to sPCL, which corresponds to the unfavorable evolution (in 2-4% of cases) of advanced MM. Among PCL, 60-70% are pPCL and 30-40% are sPCL [8]. More recent data suggest an increase in the proportion of sPCL around 50% [7].

The pathophysiological basis is more or less the same. In MM, tumor cells are mainly localized in the bone marrow and are partly dependent on the microenvironment for their development, survival and protection against therapy-induced apoptosis. Whereas in PCL, plasma cells also accumulate in the bone marrow but have an increased ability to migrate into the peripheral bloodstream, which explains the extramedullary manifestations. This blood circulation is the result, on the one hand, of a modification of surface molecules and cytokine receptors but also of an inhibition of apoptosis and an escape from the immune

surveillance system. Loss of expression of a number of adhesion molecules appears to be involved in the pathophysiology of PCL, whether primary or secondary. For example, t (14; 16) is thought to lead to increased synthesis of the metalloprotease MMP-9, which is responsible for the destruction of the extracellular matrix [9].

pPCL is observed at a younger age, the median age of diagnosis of PCL is 55 years old, while it is 65 years old for multiple myeloma [7]. These results are similar to those reported in our case where our patient was 37 years old. Also, the majority of sPCL affect men with a sex ratio of about 3:2 [7].

The clinical aspect of PCL is more aggressive than that of MM. Patients may present extra marrow plasma cell infiltration responsible for a tumor syndrome that may associate hepatomegaly, splenomegaly, peripheral lymphadenopathy, neuromeningeal invasion, pulmonary involvement or other tissue localizations, generally in a higher proportion than in MM. On the other hand, bone lesions are less described in pPCL than in MM or sPCL [7]. Renal failure and hypercalcemia are more frequently found in pPCL than in MM, which may be partly explained by a higher proportion of light chain disease [7, 13]. A similar results were found in our patient.

The diagnosis of pPCL is biologicaland based on blood count data coupled to the MGG-stained blood smear (Figure 1), which shows a blood plasma count greater than 2 G/L or a circulating plasma cell count greater than 20% of the white blood cell count. Plasma cells are sometimes difficult to identify on blood smears, so it is important that an experienced biologist examine the smear to ensure that the presence of plasma cells is not overlooked, and the use of immunophenotyping in ambiguous forms is essential for diagnosis. The workup is completed by a myelogram (Figure 1) or bone marrow biopsy [8].

Compared to MM, pPCL is more frequently responsible for bone marrow failure with anemic syndrome and thrombocytopenia due to a much higher bone marrow plasmacytosis [8].

PL blood plasma cell disease is distinguished from plasma cell disease reactive to an infectious or immunological event by its monoclonal character. In this context, flow cytometry has its place to demonstrate the clonality of plasma cells and to exclude other lymphoproliferative syndromes, notably lymphoplasmacytic lymphoma. Especially since the expression profile of CD38+ or CD138+ plasma cells is abnormal in CD19+ or CD56+ sPCL. With the exception of the plasma cell marker CD138 (also expressed in pPCL, sPCL, and MM), we find many differences in the expression phenotype in flow cytometry of pPCL and sPCL cells compared with MM. We observe a decrease in CD38 (plasma cell marker) expression between MGUS, MM and sPCL, suggesting a dedifferentiation of the plasma cell phenotype [15]. The CD56 antigen, also known as NCAM (neural cell adhesion molecule), plays an important role in plasma cell adhesion to the marrow stroma. A loss of expression of this antigen on primitive and sPCL can be observed, which may explain their migration into the peripheral circulation [5, 16, 17]. The cytogenetic abnormalities described in pPCL are quite heterogeneous, based on small retrospective studies. More than 80% of them show hypoploidism or diploidism [5], which is a poor prognostic factor.

The biochemical workup, complete the biological diagnosis and offers a more global picture regarding the prognosis. It often includes, a serum protein electrophoresis coupled to an immunofixation, a 24-hour urine protein electrophoresis. Also biomarkers assays are performed and include: serum protein, LDH, B2 microglobuline, renal function parameters, and phosphocalcique biomarkers mainly calcium [8].

PCL has a poor prognosis. According to studies, the survival of patients with PCL does not exceed a few months. Five-year survival is less than 10% in all series [7, 11, 12]. There is no specific prognostic score for PCL. Adverse prognostic factors for PCL are mostly common to those of MM, but their prevalence is higher than that of MM. They include low albumin, high β2 microglobulin and/or high LDH, hypercalcemia, advanced age, high number of S-phase cells [18]. Resistance to disease on initial treatment is also a very poor prognostic factor. which is consistent with the results obtained in our patient.

The prognostic value of cytogenetic abnormalities in PCL is based on small retrospective studies. A Chinese study (Qi Peijing *et al*.,) found that the presence of hypoploidism, complex karyotype, del (13q), del (17p), del (1q) are associated with decreased survival [12]. Tiedemann and al. describe a shorter survival in case of translocation involving chromosome 14q32 in pPCL and sPCL, a translocation involving the Myc oncogene is a poor prognostic factor in pPCL [7]. Despite the importance of the cytogenetic study by fluorescent hybridization technique (FISH) of the plasma cell population.Our patient could not benefit from a cytogenetic study or flow cytometry due to lack of resources.

The treatment of PCL will depend on the age, the clinical context, the extension work-up and the biological parameters. Treatment with melphalan-prednisone chemotherapy seems to be less effective (response rate 20-30%, median overall survival 4-8 months) than multidrug therapy using variable combinations (e.g. VAD protocol or vincristine, doxorubicin, dexamethasone) with a response rate of 40-60%, and a median survival of 10-20 months. Our

patient was put on a polychemotherapy with VCD protocol (vecade, cyclophosphamide, dexamethasone) with favorable evolution [6].

Recent preliminary data indicate that new drugs, in particular bortezomib, used as monotherapy or in combination with other chemotherapies, could significantly improve the clinical outcome of pPCL [6, 7].

CONCLUSION

PCL is a rare condition with a poor prognosis. It shares common features with MM but also has clinical, biological and prognostic particularities. PCL requires intensive treatment which now includes combinations with new therapies such as proteasome inhibitors and thalidomide analogues. Intensified autologous and allogeneic transplantation therapy in young patients has contributed to the improvementof the prognosis.

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