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PLASMA CELL LEUKAEMIA: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Plasma cell leukaemia (PCL), a variant of multiple myeloma, is characterized by high levels of circulating plasma cells (PCs) in peripheral blood. It is very rare, very aggressive in nature and hence characterized by poor outcome. This is a case report of a 68-year-old man who presented to us after two years of being managed for back pain with analgesics in a peripheral facility and found to have anaemia, hypercalcaemia and renal failure. The plasma cells count in peripheral blood in absolute terms of (6.480 $x10^9$/L) was greater than 2 x 10^9/L and equally >20% (24%) of total white cell count. The bone marrow showed heavy infiltration of about 90% of abnormal plasma cells. This is the first documented case of PCL in this tertiary hospital and only adds to 2 cases (0.05%) of haematological malignancies documented in a ten year review at University of Ilorin, Nigeria in 2008. The overall presentation of this case is more in keeping with secondary PCL than primary PCL. Also the aggressive nature and poor prognosis of the disease was well demonstrated because the patient succumbed to the disease within one month of therapy. PCL is an aggressive disease with many important differentials. It's occurrence in this 68 year old is associated with very poor outcome especially in resource poor Countries like ours where late presentation is common and prompt intervention with bortezomib based chemotherapy with/out ASCT remains very difficult to achieve.

KEYWORDS: Plasma cell leukaemia; peripheral smear; bone marrow; monoclonal IgG; renal failure; hypercalcaemia, bone disease.

INTRODUCTION

Plasma cell leukemia (PCL) is a distinct entity in the array of plasma cell dyscrasias. It is a rare and aggressive malignancy characterized by the presence of more than 20% circulating plasma cells of the differential white blood cells and/or greater than 2 x 10^9/L absolute clonal plasma cells in the peripheral blood.[1,2] It accounts for about 1% to 2% of all plasma cell dyscrasias and can be seen in two forms, primary and secondary PCL.

Primary PCL (pPCL) represents approximately 60-70% of all PCL cases and presents de novo in the leukemic phase, without a prior diagnosis of multiple myeloma (MM), it is characterized by an aggressive clinical course though there is now a slight improvement in the outcome with the use of novel therapies. Secondary PCL (sPCL) accounts for the remaining PCL cases and indicates a leukemic transformation of end stage MM in approximately 1% of previously diagnosed and treated MM patients. Both forms of PCL have poor outcomes, however, prognosis for patients with pPCL is slightly better than for sPC.[3,4,5]

Given the rarity of this disease and paucity of information on its treatment and outcome in our environment, we present the first case report of a 68-year-old retired pilot managed in our centre. This case illustrates the aggressive clinical course of sPCL. In this case report, we discuss the pathogenesis and presentation of sPCL and provide recommendations for how to treat patients with this high-risk variant of MM. We also compare pPCL and sPCL to show the key differences between these two entities.

CASE REPORT

68year old pilot who was referred to us on account of a two-year history of bilateral hip pain and two-week history of generalized body weakness and loss of appetite. Pain started from the left hip, moderate to severe in intensity and requiring the use of analgesics, radiates down the leg and subsequently involved the right hip joint with associated difficulty in walking, numbness and weakness of both leg. There was no preceding history of trauma, fever nor weight loss, no sphincteric dysfunction.

He developed poor appetite with associated nausea and vomiting about a week prior to presentation at our facility, associated constipation and generalized body weakness and dizziness which progressively worsened hence, the presentation. He has long standing palpitations and diabetes for which he is on medications.

Significant finding on examination was tachycardia with occasional missed beats and haemic murmur, tenderness over the left iliac crest posteriorly. He was pale but not in obvious distress, anicteric, no lymphadenopathy and no pedal oedema. Abdominal examination and Ultrasound did not show hepatosplenomegaly.

A full blood count (FBC) revealed anaemia (PCV 15%), leucocytosis (WBC 27,400/mm^3) with WBC differential of Neutrophil 48%, Lymphocyte 26%, Monocyte 25%, and a platelet count of 163,000/mm^3. Peripheral blood film review (Fig 1) showed marked rouleaux formation of red cells and circulating plasma cells of about 24% (The so called monocytes by the cell counter).

Erythrocyte sedimentation rate (ESR) was 150mm1hr. Bence Jones Protein (by heat method) was Negative. The electrolytes, urea and creatinine (EUCr) showed marked electrolyte derangement (Na = 142, K = 6.7, Cl = 120, HCO_3 = 10mmol/L, Urea = 118mg/dl, Cr = 3.9, Corrected Ca = 11.8, eGFR= 14.9ml/min/1.73m^2. Total protein was elevated (11.1g/dl), Albumin 3.1, hence high globulin of 8g/dl and albumin: globulin ratio of 0.4. Urinalysis shows mild proteinuria and haematuria.

Skeletal survey (Fig 3) showed marked generalized osteopaenia, healed right iliac crest fracture and not displaced communited fracture of the left iliac crest. Bone marrow aspiration (fig 2) revealed heavy infiltration of abnormal plasma cells of more than 90%.

Serum Protein Electrophoresis showed a monoclonal gammopathy with severe immune-paresis (alpha 1 globuln of 5, alpha 2 globuln of 8, beta 1 globuln of 3, beta 2 globuln of 1g/L low, gamma globuln of 2 (low), M component of 47g/L,). Immunoglobulin quantitation values are as follows: IgG = 60.9(7-16), IgA = 0.4(0.7-4.0), IgM= 0.2(0.4-2.3) g/L. Serum free light chain kappa = 19.8mg/dl (3.3-19.4). Serum free light chain lambda = 6250 mg/L (5.71-26.3). K/L ratio = < 0.1(0.26-1.65). Beta 2 microglobulin = 9.7mg/L (<2.4).

A diagnosis of Plasma cell leukaemia with renal failure was made and he was commenced on supportive therapy with blood transfusion, electrolyte correction and rehydration, he also had oral allopurinol and intravenous Zolendronic acid 4mg stat. He was then commenced on combination chemotherapy of Melphalan, Thalidomide and Prednisolone in a 28day cycle.

He was noted to have developed right sided, dull chest pain on day 18 of chemotherapy, associated chest wall tenderness. A repeat chest X-ray was suggestive of fractured right 2nd to 4th ribs anteriorly with bilateral multiple osteolytic lesions on the ribs.

Patient management was complicated by recurrent electrolyte derangement requiring electrolyte correction and anaemia requiring multiple blood transfusions. He had a total of 6 units of blood transfused during this short period of hospital admission. Patient was however referred to an ancillary hospital close to his home on his request on day 24 of chemotherapy where he died shortly after.

In summary this patient presented with advance features of the disease which include severe anaemia, leucocytosis with heavy plasmacytosis, elevated ESR, marked roulaux, elevated M-band (IgG) and free light chain, immune paresis, elevated beta 2 microglobulin, K: L ratio of <0.1 and electrolyte imbalance in keeping with renal failure multiple osteolytic lesions, ostopaenia and pathological fracture,

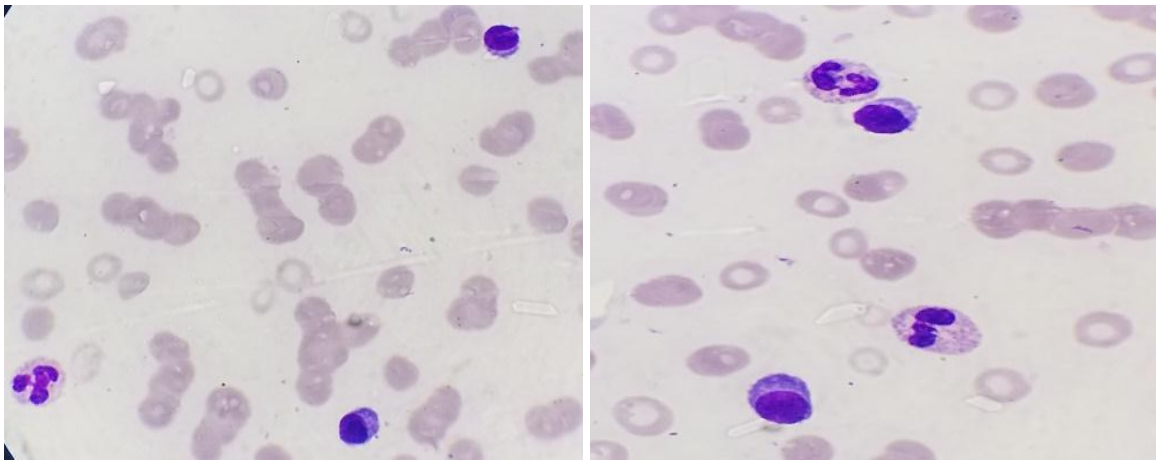

Fig 1: Peripheral blood film at diagnosis showing 24% plasmacytosis.

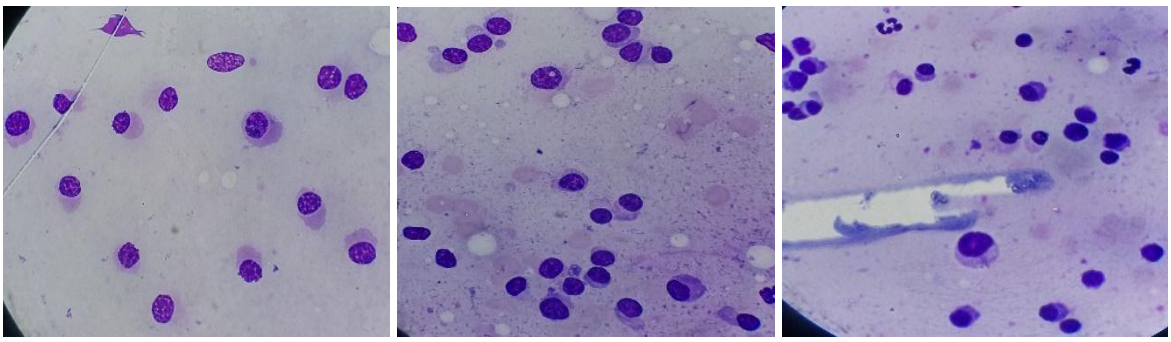

Fig 2(a,b,c): Bone marrow aspiration cytology showing more than 90% plasmacytosis.

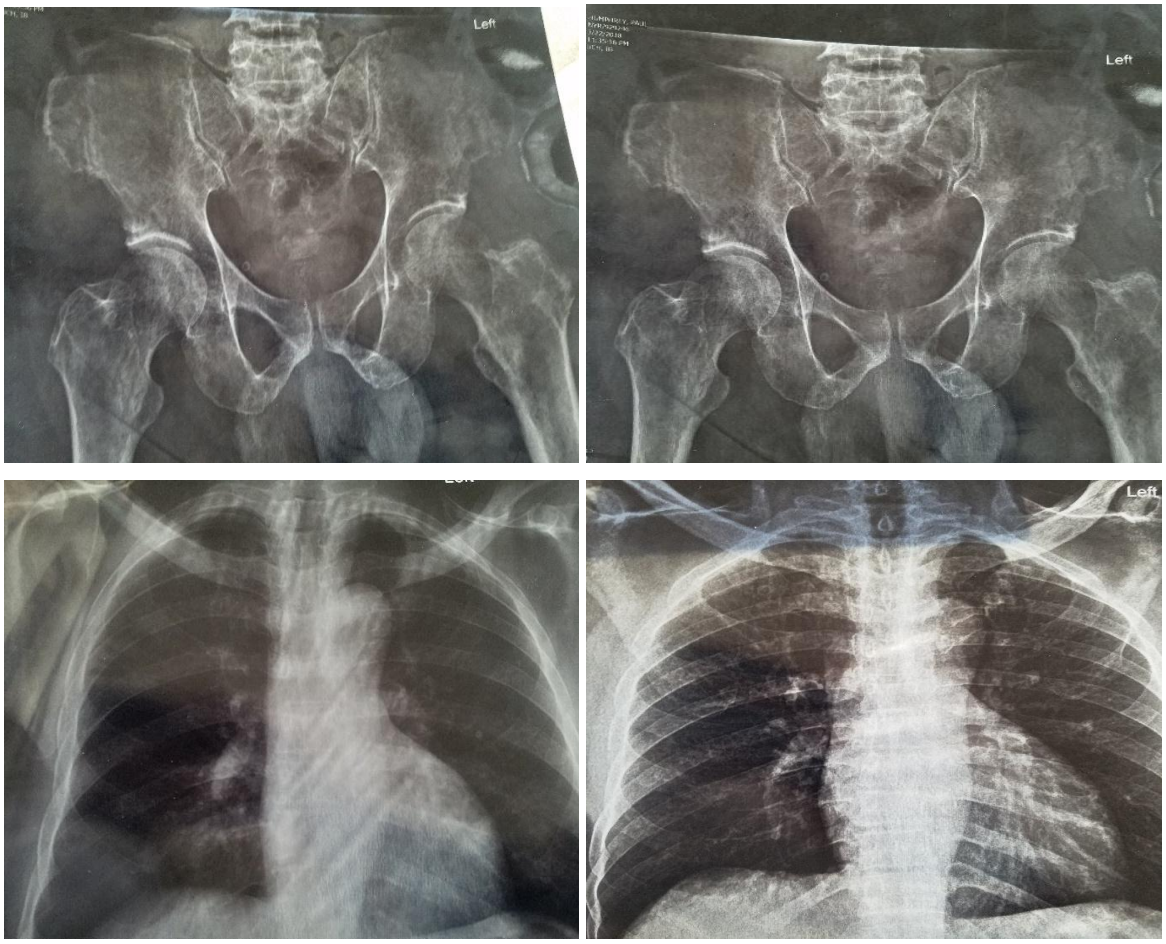

Fig 3 (a,b,c): X rays showing generalized osteopenia.

DISCUSSION

The case report presented demonstrates florid features of multiple myeloma with a spill over into circulation making it a secondary PCL. Protracted and refractory back pain was the main complaint, Peripheral blood smear showed rouleaux formation, there were clinical and laboratory features of renal failure and beta 2 microglobulin was elevated which fits well into previously documented features of sPCL.[6 ,7,8]

Bone marrow findings in the two forms of PCL are similar but higher plasma cell infiltration of the marrow are usually found in secondary PCL as depicted in this case presentation.[7]

Since many low grade lymphomas in leukaemic phase can mimick plasma cell leukaemias, it is important to employ immunophenotypic characteristics like CD38 and CD138 antigens expression which are similar findings in both MM and PCL. CD2, CD3, CD16 are noted to be consistently negative in both groups while clonal acquisition of CD28 antigen on Plasma cells correlates with increased proliferative rate and disease progression.[8] All these

immunophenotypic characteristics are of immense value in sorting out close differentials to PCL like B-cell chronic lymphocytic leukaemia (CLL), Hairy Cell Leukaemia (HCL), marginal zone lymphoma(MZL) with circulating lymphocytes and reactive polyclonal plasmacytosis due to infections or autoimmune disorders. However, we are seriously incapacitated in demonstrating immunophenotypic features in this index case.

Pathogenesis wise, tumour cells are usually localized in bone marrow (BM) and depend on the BM microenvironment for growth and survival initially in MM, however in PCL, although the tumor cells accumulate in the BM, they also have an increased ability to circulate in blood and has a higher propensity for extramedullary disease.[8] The spillage of tumour cells out of the BM is related to changes in expression of adhesion molecules, chemokine receptors, presence of some molecular abnormalities that contribute to BM microenvironment-independent tumour growth, inhibition of apoptosis and escape from immune surveillance.[9]

Several studies had shown that survival is short for PCL. It was reported that 28% of patients die in the first month after diagnosis[9,10,11] and this was what happened to this case being reported. Even though recent studies have shown survival improvement in pPCL within a large US population that maybe associated with the use of better therapeutic strategies[12], most of this agents are not readily available or affordable by our patients and we still have to rely on the more conventional chemotherapy options like Melphalan, Prednisolone and Thalidomide (MPT). Our index patient had a marked reduction in circulating plasma cells from 24% at diagnosis to 8% by second week of therapy with a reduction in blood transfusion need, however no significant improvement in renal parameter was noticed and subsequent fracture of the ribs detected could have occurred through several attempts in turning the patient in order to avoid bed sore. There was early mortality in this case (death $\leq$ 1 month). The fact that pPCL has a higher tumour burden, plasma cell proliferative index and a higher incidence of extramedullary involvement than sPCL confers the poor long-term survival rate.[12,13,14]

However, the use of autologous transplantation and or first generation novel agents e.g thalidomide, lenalidomide and Bortezomib based therapy has been found to improve response rate and overall survival, and allogeneic transplantation is potentially curative in young and fit patients even though there is a high mortality rate for this procedure.[12,13]

Secondary PCL represents the terminal stage of a pre-existing MM and hence, explains the higher prevalence of advanced bone disease compared with pPCL, less extramedullary involvement and a more frequent presentation with renal failure. Therefore, a prolonged history of bone disease in the index patient may be suggestive of a pre-existing MM. The treatment of sPCL, as for other forms of relapsed and refractory MM, depends on both patient- and disease-specific factors. Bortezomib-based treatment is the most effective treatment modality in sPCL.[13,14] Combination approaches like lenalidomide with bortezomib, participation in a clinical trial, may be considered in case of refractoriness. High-dose methylprednisolone and other novel agents may also be used. However, because most sPCL represents previously treated end-stage MM, patients are generally refractory to available treatment or have short response duration.[15,16,17]

Supportive care and effective palliation are very important following treatment failure.

CONCLUSION

PCL is an aggressive disease with many important differentials, occurring at advanced age with very poor outcome especially in resource poor Countries where late presentation occurs and prompt intervention with bortezomib based chemotherapy with/out ASCT remains very difficult to achieve even though it has been proven to confer a higher survival benefit. There is need for further research and development of newer therapeutic strategies and agents.

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