brief communication

Plasma cell leukemia: Clinicopathologic, immunophenotypic and cytogenetic characteristics of 4 cases

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Plasma cell leukemia (PCL) is defined by the presence of more than $2 \times 10^9$/L peripheral blood plasma cells (PC) or plasmacytosis accounting for 20% of the differential white cell count. Primary PCL is malignant PC proliferation that is first diagnosed in the leukemic phase, while secondary PCL corresponds to the leukemic transformation of a previously diagnosed multiple myeloma (MM). The incidence of PCL ranges between 2–4% of patients with MM and 0.9% of patients with acute leukemia. In this case series, we describe the clinicopathologic, immunophenotypic, and cytogenetic findings for four patients diagnosed with PCL within a 10-year period (2002–2012) at King Faisal Specialist Hospital and Research Centre (General Organization), Riyadh, Saudi Arabia.

KEYWORDS: Leukemia; Plasma cell; Plasma cell leukemia; Multiple myeloma

Plasmas cell leukemia (PCL) is a rare hematologic malignancy with very poor outcome. It is defined by the presence of $>2 \times 10^9$/L plasma cells or >20% plasmacytosis of the differential white cell count in the peripheral blood. Primary PCL is first diagnosed in the leukemic phase, while secondary PCL corresponds to the leukemic transformation of a previously diagnosed multiple myeloma (MM). The incidence of PCL ranges between 2–4% of patients with MM and 0.9% of patients with acute leukemia. In this case series, we describe the clinicopathologic, immunophenotypic, and cytogenetic findings for four patients diagnosed with PCL within a ten-year period (2002–2012) at King Faisal Specialist Hospital and Research Centre (General Organization), Riyadh, Saudi Arabia.

CASES REPORT

Case 1
A 52-year-old male patient was initially referred for evaluation and treatment of MM. He was known to have bipolar disorder and initially diagnosed as stage III IgG kappa MM. He presented with renal impairment, for which he was started on dexamethasone with a good response. Later on, the patient was started on thalidomide 100 mg orally every other day in addition to dexamethasone as an induction treatment. Unfortunately after two cycles, he developed dexamethasone-induced psychosis and he was kept on thalidomide at a dose of 150 mg/d. Because of suboptimal response he was started on Velcade but there was no improvement, and therefore, dexamethasone was added. He completed four cycles but unfortunately the disease was refractory and his laboratory tests started to show circulating plasma cells. He was
started on VAD chemotherapy (vincristine, cyclophosphamide, and adriamycin) as his disease evolved to PCL. An abdominal ultrasound showed mild hepatosplenomegaly, and skeletal survey confirmed multiple bone lesions.

Laboratory findings at the time of transformation to secondary PCL shows white blood counts (WBCs) of 17.10 × 10^9/L (reference range (RR), 5–10 × 10^9/L) with 21% PCs, hemoglobin (Hb) level of 78 g/L (RR, 140–180 g/L), and platelets (PLT) were 62 × 10^9/L (RR, 150–450 × 10^9/L). Other laboratory studies included serum creatinine of 141 μmol/L (RR, 46–115 μmol/L); Ca, 2.26 mmol/L (RR, 2.1–2.55 mmol/L); lactate dehydrogenase (LDH), 407 U/L (RR, 135–225 U/L); and β2-microglobulin, 5.56 mg/L (RR, 0.7–1.8 mg/L). Serum protein electrophoresis (SPE) and immunofixation revealed IgG-kappa with 75.5% M-spike of total protein and 99.2% of total gamma globulin. Urinalysis was positive for Bence Jones protein (BJ protein).

Bone marrow (BM) examination demonstrated diffuse involvement by more than 80% PCs, of which some were binuclear and few had prominent nucleoli. Flow cytometry showed that PCs were positive for CD138, CD38, and cytoplasmic Kappa. Cytogenetic analysis revealed complex karyotyping of 45,XY,+i(1)(q10),add(2)(q33),add(6)(q23),t(8;14)(p21;q32),-11,t(12;22)(p13;q13),-13,-14, add(19)(q13.4),+22[cp4]/46.XY[9].

The patient continued receiving VAD, but had no response, and PCs in the peripheral blood fluctuated between 30% and 45%. The patient ultimately died from refractory plasma cell dyscrasia progression, 10 months after diagnosis of PCL.

**Case 2**

A 71-year-old female patient presented with lower back pain, generalized weakness, and severe anemia. She was known to have hypertension, diabetes mellitus (type 2), hyperlipidemia and severe coronary artery disease with ejection fraction of 66%; status post cardiac catheterization. Eleven years ago, she was diagnosed with left breast cancer and received 5000 cGy of radiotherapy to the left breast over a period of three months. She had multiple lytic lesions noted by skull X-ray unrelated to her breast cancer as there was no evidence of disease activity elsewhere and skeletal survey showed generalized osteopenia (Image 1). No evidence of organomegaly was detected.

Laboratory studies revealed a WBC count of 7.15 × 10^9/L with 35% circulating PCs, HGB level of 76 g/L and PLT count was 78 × 10^9/L. Serum creatinine was 102 μmol/L Ca 2.11 mmol/L and β2-microglobulin 6.04 mg/L. SPE revealed a hypogammaglobulinemia, and urine protein electrophoresis (UPE) was negative. BM examination showed diffuse infiltration by atypical lymphoid cells that accounted for about 40–50% of all nucleated cells. These cells were identified as PCs or lymphoplasmacytoid cells, which have very irregular cytoplasmic borders with eccentric nuclei and prominent nucleoli, with some showing cytoplasmic vacuolation. Flow cytometry confirmed that 55% of all cells were positive for CD38, CD138, and cytoplasmic Kappa, while negative for CD45 and CD56. This flow cytometry result is consistent with plasma cell dyscrasia. Fluorescent in situ hybridization (FISH) was positive, and in which 99% of 200 examined cells had both 13q14 and 13q34 deletion, reflecting −13. Also, 96% of the cells had trisomy ATM, indicating partial or complete trisomy for chromosome 11.

Because of her age, comorbid diseases, and heart failure, she was offered melphalan, dexamethasone, weekly doses of erythropoietin, and was continued on palliative treatment. She was lost to follow up, and most likely succumbed to her disease.

**Case 3**

A 53-year-old male patient was referred with anemia, thrombocytopenia, leukocytosis, and mild renal impairment. His abdominal ultrasound revealed a mild splenomegaly and skeletal survey demonstrated a well-defined lytic lesion seen at the right aspect of the occipital bone with collapsed T9 vertebral body. A complete blood count at the time of referral showed a WBC count of 16.15 × 10^9/L with 24% circulating PCs, HGB level of 96 g/L and platelet count was 10 × 10^9/L. Other laboratory studies included serum creatinine which was 309 μmol/L, calcium 2.55 mmol/L, and β2-microglobulin 17.10 mg/L. SPE revealed borderline hypogammaglobulinemia, and UPE was negative. The BM was diffusely infiltrated with PCs and some lymphoplasmacytoid cells which accounted for 30–40% (Image 2). Flow cytometry showed 26% monoclonal PCs with positivity for CD38, CD138, cytoplasmic Kappa, and negativity for CD56 and CD45. FISH was positive for deletion of both 13q14 and 13q34, suggesting −13, and 76% had IGH rearrangement; however, CCND1 (cyclin D1) was ruled out as fusion partner.

The patient received six cycles of Velcade/dexamethasone chemotherapy and achieved complete remission. He was mobilized for autologous stem cell transplantation (SCT) with cyclophosphamide and G-CSF protocol, and then received high dose melphalan and peripheral blood SCT. He was discharged in a
BM aspirate and biopsy for cases 3 and 4.

A. BM aspirate for case 3 appeared diffusely infiltrated with PCs and some lymphoplasmacytoid (Wright-Giemsa stain ×100).

B. BM biopsy for case 3 showing a sheet of plasma cells with the characteristic cogwheel chromatin arrangement (H&E stain ×100).

C. BM aspirate for case 4 markedly infiltrated by pleomorphic plasma cells (Wright-Giemsa stain ×100).

D. BM biopsy for case 4 showing many plasma cells containing intra-nuclear inclusions (Dutcher bodies `arrows in the image`) (H&E stain ×100).

Image 1. Case 2 skull X-ray showing multiple lytic lesions involving the skull vault, mainly the left parietal region.

Image 2. BM aspirate and biopsy for cases 3 and 4. A. BM aspirate for case 3 appeared diffusely infiltrated with PCs and some lymphoplasmacytoid (Wright-Giemsa stain ×100). B. BM biopsy for case 3 showing a sheet of plasma cells with the characteristic cogwheel chromatin arrangement (H&E stain ×100). C. BM aspirate for case 4 markedly infiltrated by pleomorphic plasma cells (Wright-Giemsa stain ×100). D. BM biopsy for case 4 showing many plasma cells containing intra-nuclear inclusions (Dutcher bodies `arrows in the image`) (H&E stain ×100).
good condition after he recovered his peripheral blood on day 15 post-transplant. In his last outpatient clinic visit, he was still pancytopenic with WBC count of $2.29 \times 10^9/L$, HGB of 70 g/L and PLT was $43 \times 10^9/L$ with no PCs in the peripheral blood. His creatinine had normalized to 106 μmol/L, Ca to 2.11 mmol/L, but his β2-microglobulin was 7.72 mg/L.

The patient was still alive and in a good condition three years after auto-SCT and until the time this manuscript was written.

**Case 4**

A 70-year-old female patient was admitted with generalized bone pain over a period of about two weeks, weight loss, and renal impairment. She had a history of rheumatic heart mitral stenosis and aortic stenosis. She was on warfarin for chronic atrial fibrillation.

Radiologically, the patient was found to have hepatomegaly with no definite osteolytic lesions; however, diffuse osteopenia was noted.

At time of referral, WBC was $18.24 \times 10^9/L$ with 66% circulating PCs, HGB 78 g/L, and PLT was $85 \times 10^9/L$. Other laboratory studies included serum creatinine that was 187 μmol/L and calcium at 2.01 mmol/L. Testing for β2-microglobulin was not available. Serum protein electrophoresis and immunofixation revealed IgG-kappa (M-spike) of 51.4% of total serum proteins, and 92.3% of total gamma globulins (=58.60 g/L). UPE was positive for IgG-kappa and free kappa light chain monoclonal gammopathy.

The BM was markedly infiltrated by pleomorphic plasma cells of more than 90% (Image 1). Flow cytometry analysis revealed more than 55% clonal plasma cells with positivity for CD38, CD138, and cKappa. CD56 and CD45 were negative.

Chromosomal analysis could not be carried out because very few dividing cells were available, but FISH study was negative.

The patient was diagnosed with primary PCL and referred back to her local hospital with an arrangement to receive weekly Velcade 1.3 mg/m² and dexamethasone 20 mg weekly.

**DISCUSSION**

PCL needs to be diagnosed in a timely manner to immediately initiate therapy. The incidence of PCL ranges between 2–4% of patients with MM and 0.9% of patients with acute leukemia. The clinical and laboratory results for all four cases are summarized in Table 1. Three out of the four cases were primary PCL and one case was secondary. Secondary PCL occurs as a progression of disease in 1–4% of all cases of MM. The biology of dissemination of tumor cells out of the BM is not only related to changes in expression of adhesion molecules and chemokine receptors but also to the presence of several molecular aberrations, which contribute to BM microenvironment-independent tumor growth, inhibition of apoptosis, and escape from immune surveillance.

It has been reported that male to female sex distribution in both primary and secondary PCL are 3:2. The male to female ratio was equal (1:1) in our patients and the age range was 52–70 years.

Up to 15% of PCL patients will have hepatomegaly, splenomegaly or lymphadenopathy. Three out of our four patients had either hepatomegaly and/or splenomegaly, where none of the patients showed relevant lymphadenopathy. Bone lytic lesions were observed in three cases, and two cases were reported to have generalized osteopenia.

The majority of patients with PCL do not have clinical evidence of overt bone destruction and, because of extensive involvement of the bone marrow, they tend to show a higher prevalence of anemia and thrombocytopenia. This is evident in all of our patients with 78 g/L and $70 \times 10^9/L$ median hemoglobin level and platelets counts, respectively, at diagnosis.

Other laboratory findings include a higher prevalence of renal insufficiency, elevated β2-microglobulin and elevated LDH. In three out of our four cases, there was renal insufficiency; three tested patients showed high β2-microglobulin; and two out of three tested cases revealed high LDH.

Peripheral blood examination in PCL should show circulating tumor cells, and typically a leukoerythroblastoid blood picture in up to 67% of patients. BM biopsy typically demonstrates extensive BM involvement by PCs that disrupt the normal hematopoiesis. In some cases, the tumor cells resemble normal plasma cells with basophilic cytoplasm, prominent Golgi zone, and eccentric nuclei. Other cases have many lymphoplasmacytoid lymphocytes and only a minority of characteristic plasma cells as in case 2. Yet others have more primitive cells with a higher nucleocytoplasmic ratio, open chromatin, prominent nucleoli, and a less prominent Golgi zone (plasmablasts).

Sometimes, circulating plasma cells are difficult to classify by light microscopy alone, and differentiation from other conditions requires immunophenotypic analysis, which can also be useful to differentiate reactive from clonal plasma cells. The
Table 1. Characteristics of the four PCL patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>PCL type</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Organomegaly</th>
<th>Bone lesion</th>
<th>Ca, Total (mmol/L) N 2.1–2.55</th>
<th>Creatinine (μmol/L) N 46–115</th>
<th>LDH (U/L) N 135–225</th>
<th>Serum Protein Electrophoresis</th>
<th>Urine Protein Electrophoresis</th>
<th>β2microglobulin (mg/L) N 0.7–1.80</th>
<th>WBC (10^9/L)</th>
<th>Hg (g/L)</th>
<th>PLT (10^9/L)</th>
<th>PCs in PB (%)</th>
<th>PCs in BM (%)</th>
<th>Immuno-phenotyping</th>
<th>Cytogenetics</th>
<th>Immuno-phenotyping</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Secondary</td>
<td>Male</td>
<td>52</td>
<td>Hepatosplenomegaly</td>
<td>Multiple lytic lesions &amp; generalized osteopenia</td>
<td>2.26 (2.1–2.55)</td>
<td>141 (46–115)</td>
<td>407 (135–225)</td>
<td>IgG-kappa Hypogammablobulinemia</td>
<td>Trace of albumin is present</td>
<td>5.58 (0.7–1.80)</td>
<td>17.10</td>
<td>78</td>
<td>62</td>
<td>21</td>
<td>CD38+,CD138+,CD56+, cKappa+, CD45-, CD20-</td>
<td>45,XY,+i(1)(q10), add(2)(q33),add(6)(q23), t(8;14)(q21,q32), -11,-12,13,14, add(19)(q13.4),+22,46,XY[9]</td>
<td>CD38+,CD138+, cKappa+, DC56, CD45-, CD20-</td>
<td>13q14 &amp; 13q34 deletion, reflecting – 13 Trisomy ATM, indicating partial or complete trisomy for chromosome 11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Primary</td>
<td>Female</td>
<td>70</td>
<td>No organomegaly</td>
<td>Multiple lytic lesions in the skull &amp; generalized osteopenia</td>
<td>2.11 (2.1–2.55)</td>
<td>102 (46–115)</td>
<td>NA (135–225)</td>
<td>Hypogammaglobulinemia</td>
<td>No proteinuria</td>
<td>6.04 (0.7–1.80)</td>
<td>7.95</td>
<td>76</td>
<td>76</td>
<td>35</td>
<td>CD38+,CD138+, cKappa+, DC56, CD45-, CD20-</td>
<td>13q14 &amp; 13q34 deletion, suggesting – 13 Trisomy ATM, reflecting – 13 Trisomy ATM, indicating partial or complete trisomy for chromosome 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Primary</td>
<td>Male</td>
<td>53</td>
<td>Mild splenomegaly</td>
<td>Well defined lytic lesions seen at the right aspect of the occipital bone</td>
<td>2.55 (2.1–2.55)</td>
<td>309 (46–115)</td>
<td>412 (135–225)</td>
<td>IgG-kappa Hypogammaglobulinemia</td>
<td>No proteinuria</td>
<td>NA (0.7–1.80)</td>
<td>16.15</td>
<td>96</td>
<td>10</td>
<td>24</td>
<td>CD38+,CD138+, cKappa+, DC56, CD45-, CD20-</td>
<td>13q14 &amp; 13q34 deletion, suggesting – 13 Trisomy ATM, indicating partial or complete trisomy for chromosome 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Primary</td>
<td>Female</td>
<td>70</td>
<td>Hepatomegaly</td>
<td>Diffuse osteopenia but no osteolytic lesions</td>
<td>2.01 (2.1–2.55)</td>
<td>187 (46–115)</td>
<td>157 (135–225)</td>
<td>IgG-kappa and free kappa light chain monoclonal gammopathy</td>
<td>IgG-kappa</td>
<td>NA (0.7–1.80)</td>
<td>18.24</td>
<td>78</td>
<td>85</td>
<td>66</td>
<td>CD38+,CD138+, cKappa+, DC56, CD45-, CD20-</td>
<td>Too few dividing cells were available to establish a karyotype FISH is negative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCL: plasma cell leukemia; y: year; Ca: Calcium; N: normal; LDH: Lactate Dehydrogenase; NA: not available.
Peripheral blood smear in all cases showed more than 20% circulating plasma cells, which, by definition, is the percentage needed to diagnose PCL. Moreover, the BM was diffusely infiltrated by plasma cells disrupting normal hematopoiesis. The plasma cells displayed a spectrum of maturity, from small mature plasma cells to large, anaplastic, blastic or lymphoplasmacytic cells that were difficult to classify (Image 2).

Flow cytometry analysis using CD38 and CD138 antigen expression is an excellent PC marker. However, it does not differentiate between MM and PCL. Typically, primary PCL tumor cells are more likely to express CD20, CD45, CD19, CD27, and CD23, while CD56, CD71, CD117, and HLA-DR are less often positive. Flow cytometry immunophenotyping examination for our patients was positive for plasma cell associated antigen CD38 and CD138 and non-expressed B cell associated antigen (CD19 or CD20).

Compared with MM, tumor cells from primary and secondary PCL patients have reduced expression of the adhesion molecules NCAM (neural cell adhesion molecule/CD56) and LFA-1 (leukocyte function-associated antigen-1), which may contribute to the extramedullary accumulation of tumor cells in PCL. Kraj et al. compared primary and secondary PCL and found that their immunophenotypic profiles were comparable, except for CD56 expression, which was more often present in secondary PCL, and was only detected in case 1.

All four cases expressed monocytic immunoglobulin light chain, which is cytoplasmic Kappa light chain.

Chromosomal and cytogenetic analyses focus on positivity for hypodiploidy, complex karyotype, del(17p13), del(13q), del(1p21), ampl(1q21), MYC translocations or amplifications, and the presence of 1q22 abnormalities; and they include: t(11;14) (q13;q32), t(4;14) (p16;q32), and t(14;16) (q32;q23). Chromosomal and cytogenetic analyses are therefore highly important for prognostication impact through their association with reduced OS.

The most prevalent IgH translocation in primary PCL is t(11;14) at a frequency of 25–65%, and these translocations are clearly associated with poor prognosis.

In our review, case 1 showed a complex karyotyping with monosomy 13, and cases 2 and 3 were found to have FISH results suggestive of monosomy 13 and/or 13q deletion.

Both primary and secondary PCL share a poor prognosis. Most series report a median survival not exceeding one year. The use of more intensive chemotherapy and SCT lead to a 20-month median survival.

In conclusion, PCL is a rare disease, and this was confirmed by our study. It is an aggressive form of plasma cell dyscrasias carrying a poor prognosis despite intensive chemotherapy, SCT, and the use of novel anti-myeloma agents. The morphology of the plasma cell could be highly misleading, and for that reason, comprehensive workup by immunophenotyping using flow cytometry is crucial for the diagnosis of PCL. Cytogenetic workup is substantial for prognostication. Prospective multicenter studies and more case reviews are required to reach a better understanding of the pathogenesis of PCL.

The authors declare they have no competing interests.

Dr. Nahlah AlGhasham made substantial contributions to the conception, design and acquisition of data. Dr. Nahlah and Dr. Randa Alnounou contributed to analysis, interpretation of data and to drafting the manuscript. Dr. Hazzaa Alzahrani and Dr. Fahad Alsharif were responsible for the critical revision of the manuscript’s intellectual content.

All authors read and approved the final manuscript.

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