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Case Report

Primary Plasma Cell Leukaemia with Near-Tetraploidy: A Case Report

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Abstract

Plasma Cell Leukaemia (PCL) is an uncommon neoplasm of plasma cells, in which clonal plasma cells constitute > 20% of total leukocytes in the blood or the absolute count >2 × 109/L. It has an aggressive clinical course and poor outcome, even with current standard of care. It can occur de novo (primary PCL) or as a progression of multiple myeloma (MM). Here we report a case of plasma cell leukaemia in a 69-year-old Malay woman. She presented with a history of back pain for 3 months duration. On examination, she was pale but there was no organomegaly. Her peripheral blood count exhibited bicytopenia with leukocytosis and 50% circulating plasma cells. A diagnosis of Plasma Cell Leukaemia with Kappa clonality was confirmed through bone marrow aspirate, flow cytometry, and trephine biopsy together with immunohistochemistry. However, she only managed to receive one dose of Velcade (Bortezomid) as she succumbed to death due to multiorgan failure.

Keywords: Plasma cell neoplasm; Plasma cell leukaemia

Introduction

PCL is a clinical variant of plasma cell myeloma and it is the leukaemic transformation of relapsed or refractory MM [1-6]. The incidence of primary PCL is 2% - 4%, of which 60% - 70% of cases are primary and 30% - 40% are secondary [1]. The median age of patients diagnosed with primary PCL is younger than those with secondary PCL (52 – 65 years old versus 65 – 70 years old) [6]. Diagnosis is arbitrarily defined by Kyle's criteria as the presence of more than 20% circulating clonal plasma cells or an absolute plasma cell count greater than 2×10^9/L in peripheral blood [7]. In view of the aggressiveness of the clinical course as well as the poor outcome with a median overall survival (OS) ranging from 2 to 12 months, thus plasma cell leukaemia needs to be diagnosed early so that prompt treatment can be commenced. Despite the improvement of survival outcomes in patients with novel agents and Autologous Transplantation (ASCT) (OS is 5 months prior to novel therapy but has increased to 12 months with the introduction of novel chemotherapy), prognosis remains poor with mortality within the first months as high as 15% [7].

Case Presentation

We report a case of 69-year-oldMalay female who has underlying hypertension and dyslipidaemia. She presented with back pain for 3 months prior to admission. Her back pain was not associated with history of fall or trauma and she denied having any loss of weight or loss of appetite. Clinically, she was not pale, there were no hepatosplenomegaly, no palpable mass or lymphadenopathy, no obvious deformities seen at the lower lumbar region. Her peripheral blood count, full blood picture, bone marrow aspirate, and trephine biopsy findings were summarized in Table 1, Figures 1-3. The population of plasma cells analysed using flow cytometry showed negative for CD19, CD20 and CD117 with negative to dim expression of CD45. These plasma cells expressed CD38, CD138, CD56 (aberrant) and Beta - 2 microglobulin with Kappa clonality. She has hypercalcemia with a calcium level of 3.98 mmol/L, renal impairment with a creatinine of 237 µmol/L and urea of 13.4 mmol/L. There was no reverse A/G ratio; 1.22. The lactate dehydrogenase level was 1823 U/L. The cytogenetic analysis of marrow aspirate sample revealed complex karyotype pattern with near-tetraploidy in 84 ~ 86 chromosome, XX, del(6) (q13), del (13), t(12,14) (q24.3;q32), t(1;14) (p13;p13) and t(1;19) (q23;p13). Her cytogenetic result revealed complex cytogenetic abnormalities in all the metaphases analysed. The radiological investigations for this patient revealed that there were no obvious lytic lesion from chest (CXR) and thoracolumbar X-ray done, however old pathological fracture was seen at L1.

Treatment

She only managed to receive one dose of Velcade (Bortezomib), Thalidomide and Dexamethasone. Subsequently, she developed hospital-acquired pneumonia and progressively worsening in terms of her conscious level as well as renal functions.

Outcome

She was then intubated for airway protection. On day eleventh of admission, she succumbed to death due to primary plasma cell leukaemia with multiorgan failure.

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Table 1: Peripheral blood count.

Parameters	Value
Total White Cell Count	20.6 x 10^9/L
Neutrophil counts	3.41 x 10^3/µL
Lymphocyte counts	9.6 x 10^3/µL
Monocyte counts	8.8 x 10^3/µL
Eosinophil counts	0.11 x 10^3/µL
Basophil counts	0.06 x 10^3/µL
Plasma cell counts	13.19 x 10^3/µL
Haemoglobin	12.4 g/dL
Mean Corpuscular Volume (MCV)	93.6 Fl
Mean Corpuscular Haemoglobin Concentration (MCH)	32.2pg
Haematocrit (HCT)	35.90%
Platelet	77 x 10^9/L

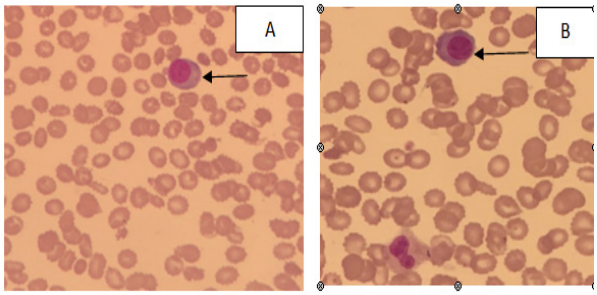

Figure 1: Full blood picture (A&B) showed circulating abnormal plasma cells (arrow) exhibiting eccentric nuclei, prominent nucleoli and flamed-shaped cytoplasm.

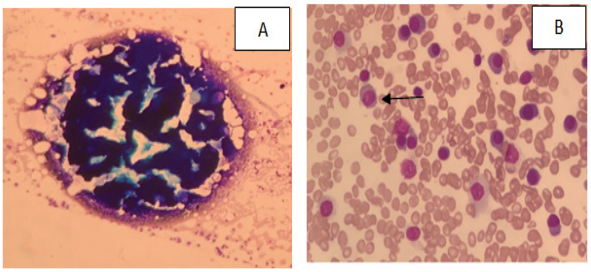

Figure 2: The bone marrow aspirate fragments (A) showed hypercellular fragments and the predominant cells in the cell trails (B) Some of the plasma cells exhibit plasmablastic morphology; dispersed chromatin & single prominent nucleoli (Fig. B;arrow: plasmablast).

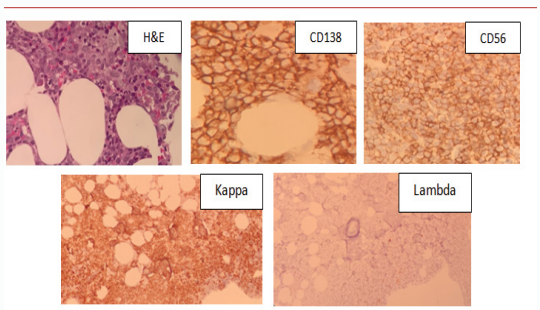

Figure 3: Bone marrow trephine biopsy (Haematoxylin and Eosin stain; H&E) showed hypercellular marrow infiltrated by plasma cells evidenced by positivity towards CD138, CD56 and with Kappa clonality.

Discussion

Plasma cell leukaemia is a rare blood dyscrasia; 0.6% of Multiple Myeloma (MM) with an aggressive clinical course and dismal prognosis [1]. The diagnosis of Primary Plasma Cell Leukaemia (pPCL) is made when PCL is detected at diagnosis de novo without prior history of MM. However, if PCL arises in a patient with a known history of MM, it is considered secondary PCL (sPCL) [2]. The diagnosis of PCL is made when there are presence of clonal plasma cell constitute >20% of total leukocytes in the peripheral blood or the absolute count is > 2 × 10^9/L. The bone marrow is extensively infiltrated by the neoplastic plasma cells [3]. The presence of 50% clonal plasma cells in our patient peripheral blood film together with the immunohistochemistry finding which showed Kappa clonality of the plasma cells; fit the diagnosis of PCL. PCL is clinically and biologically distinct from MM, with a younger age at diagnosis, higher propensity to show visceral and extramedullary involvement, and unique biologic, immunophenotypic and cytogenetic characteristics [2]. Biologically, the tendency of PCL to invade extramedullary sites (lymphadenopathy, hepatosplenomegaly, pleural effusion, skin and central nervous system involvement) compared to its counterpart; MM [7,8]. Additionally, osteolytic lesion is less seen in pPCL (35%) compared to sPCL which presented from a pre-existing MM (81%) [7,8]. Furthermore, a study done by Ramsingh G. et al. [3]; showed there is a lower likelihood of lytic bone lesion and bone pain presented in PCM compared to MM which was consistent finding with our patient. On top of that, PCL tend to have a higher prevalence of elevated Lactate Dehydrogenase (LDH) around 48% with only 9% in case of MM, anaemia with Haemoglobin (Hb) less than 8.5 g/dL and thrombocytopenia with platelet less than 100 × 10^9/L are more frequently seen in PCL. In addition, PCL cases more frequently seen with elevated beta-2 microglobulin, hypoalbuminemia, hypercalcemia and renal impairment compared to MM cases [7-11]. The laboratory findings in this patient include markedly elevated LDH (1823 U/L), thrombocytopenia with platelet of 77 × 10^9/L, hypercalcemia (3.98 mmol/L) and renal impairment (creatinine level of 237 µmol/L). Normally cytopenia from PCL is more profound compared to MM due to higher amount of bone marrow involvement. In addition lactate dehydrogenase (LDH) will increase because of the high tumour load and increased in beta-2 microglobulin level [12]. The Serum Protein Electrophoresis (SPEP) and Urine Serum Electrophoresis (UPEP) with immunofixation usually showed light chain only, IgE and IgD myeloma presented as PCL. In the full blood picture as well as the bone marrow aspirate, the clonal plasma cells appear more immature or plasmablastic in morphology [3]. Unfortunately, due to the rapid progression of the disease in our patient, the SPEP and UPEP were not managed to be sent. The full blood picture and marrow aspirate of our patient showed some of the plasma cells exhibit plasmablastic morphology (dispersed chromatin and single prominent nucleoli). The main role of Multi Parameter Flow Cytometry (MFC) is to distinguish between reactive, benign plasmacytosis versus clonal and potentially malignant Plasma Cells (PC) [13]. In general, plasma cells (normal and neoplastic) express CD38 (bright), CD138 and negative for CD20, while the normal peripheral blood plasma cells are CD45 positive but in bone marrow, there are two subsets of plasma cells: one major subset positive for CD45 and a smaller negative one [14]. The aberrant CD56 expression is identified in most patients with myeloma together with the bright CD38 expression and negative for CD19 expression are used as markers to detect abnormal populations of plasma cells by flow cytometry [3,14]. The abnormal population

of plasma cells once identified should also exhibit cytoplasmic light-chain restriction (Kappa or Lambda) [3,14]. Immunophenotypically, PCL differs from other Plasma Cell Myeloma (PCM) by its frequent expression of CD20 and less of CD56 expression (80% of PCL has negative CD56) [3]. In our patient, her flow cytometry result revealed that the abnormal plasma cells were negative for CD19, CD20 and CD117 with negative to dim expression of CD45. These plasma cells expressed CD38, CD138, CD56 (aberrant) and Beta - 2 microglobulin with Kappa clonality. The common cytogenetics features that occur in PCL are hypodiploidy as well as complex karyotypes with multiple numerical and structural abnormalities involving chromosome 1,13,14 and the common translocations involving chromosome 14 are; t(11;14), t(14;16) and t(4;14) and deletions of 1p,6q,8p,13q,14q as well as 16q [10,15].Translocations of the immunoglobulin heavy chain locus 14q32 were highly prevalent in secondary and primary plasma cell leukemias (82% and 87%, respectively) [16]. Meanwhile, the most common mutations are involvingTP53, DIS3, NRAS, KRAS and BRAF. In our patient, her cytogenetic findings revealed complex karyotype pattern with near-tetraploidy in 84 ~ 86 chromosomes, XX, del(6)(q13), del (13), t(12,14)(q24.3;q32), t(1;14)(p13;p13) and t(1;19)(q23;p13). In the presence of del (13), according to Swerdlow, it will be stratified as intermediate risk with overall survival of 4 – 5 years [3].Throughout the literature search, as for now there was no plasma cell leukaemia case per se having near-tetraploidy but in multiple myeloma cases these chromosomal abnormalities will have 5 years survival rate of 34.6% in comparison to hypodiploid patients with only 10% of patients achieving 5 years survival rate [17]. As for the prognosis of del (6q) in multiple myeloma is highly variable as it also depend on karyotypic pattern where in the presence of near-tetraploidy karyotypes the median survival is 1.5 years, unfortunately there was no documentation regarding plasma cell leukaemia case with del (6q) [18]. As for now other chromosomal abnormalities; t(12;14)(q24.3;q32), t(1;14)(p13;p13) and t(1;19)(q23;p13) found in this patient can be novel findings in the case of plasma cell leukaemia. Survival is known to be poor in plasma cell dyscrasia with a complex karyotype, where 28% of patients dying in the first month following diagnosis. The prognosis of pPCL has generally been poor with reported median Overall Survival (OS) below 1 year. Cytogenetic abnormality t(11;14) has a more favourable prognosis [10,15]. There were few cases of pPCL achieved remission for more than 1 year [5]. An intensive risk adapted approach is encouraged when managing patients with PCL. Induction therapy with a triplet, novel agent-containing regimen that includes proteasome inhibitors and Immunomodulator Drugs (IMiDs) such as VRd (bortezomib, lenalidomide and dexamethasone) or KRd (carfilzomib, lenalidomide, and dexamethasone). In some patients with pPCL with an extensive burden of disease, more aggressive combination regimens such as VDT-PACE (bortezomib, dexamethasone, thalidomide or lenalidomide, cisplastin, doxorubicin, cyclophosphamide, and etoposide) can be utilized. For elderly or frail patients who may not be able to tolerate such an intensive regimen, CyBorD (cyclophosphamide, bortezomib, and dexamethasone) can be given [2]. In our patient she was planned to be given VTD (bortezomib, thalidomide- half of usual dose and dexamethasone) for 4 cycles, unfortunately she succumbed to death during the first cycle. The correct and timely diagnosis of pPCL is highly dependent upon the ability of haematopathologist to identify circulating plasma cells on a peripheral blood smear. The rapid progression of disease making the management of plasma cell leukaemia even more challenging.

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