Early relapse after complete remission of primary plasma cell leukaemia manifesting clonal evolution: A case report

Wint Wint Thu NYUNT¹, Darnina ABDUL JALIL², Nur A’asyirah Bt ZAKARIAH², Noralisa ABDUL KARIM¹, Mohd Razif MOHD IDRIS¹, Dian Nasriana NASURUDDIN², Salwati SHUIB², Hajifa ALAUDDIN², Nor Rafeah TUMIAN³, Chooi Fun LEONG², S Fadilah S ABDUL WAHID¹

¹Pusat Terapi Sel, ²Department of Pathology, ³Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia.

Abstract

Introduction: Plasma cell leukaemia (PCL) is a rare variant of multiple myeloma. We report a case of PCL to demonstrate the clonal evolution, resulting in disease relapse after achieving complete remission, and its aggressive nature of the disease, leading to poor clinical outcome. Case Report: A 69-year-old man presented with a three-day-history of worsening generalized body weakness, poor oral intake, nausea, significant loss of weight and lower back pain. He was diagnosed as primary PCL, based on hypercalcaemia, renal insufficiency, anaemia, thrombocytopenia, lytic bone lesions, 24% abnormal plasma cells in peripheral blood, immunophenotype of clonal plasma cells which were positive for CD38, CD138 and CD56 markers with kappa light chain restriction, 49% abnormal plasma cells in bone marrow, monoclonal paraprotein (IgG kappa) in serum and urine, and positive IGH rearrangement (Fluorescence in-situ hybridisation, FISH). He achieved complete remission after four cycles of Bortezomib-based therapy. There was a plan for high-dose therapy plus autologous haematopoietic cell transplantation. A month later, the disease relapsed, as evidenced by 94% abnormal plasma cells in his bone marrow aspirate, complex karyotype and abnormal FISH results. He passed away a few days later, from severe septicaemia. Time-to-progression of disease was 1 month and overall survival was 5 months. Discussion: This case report illustrates the clonal evolution and aggressive nature of primary PCL with older age at presentation, leading to a shorter duration of remission and overall survival.

Keywords: Bortezomib, complex karyotype, fluorescence in-situ hybridisation, multiple myeloma, plasma cell leukaemia

INTRODUCTION

Plasma cell leukaemia (PCL) is a rare, but aggressive variant of multiple myeloma (MM) and is characterised by the presence of more than 20% and/or an absolute number of more than 2×10⁹/L plasma cells circulating in the peripheral blood.¹ PCL can be primary PCL (pPCL) (de novo) or secondary PCL (sPCL) (leukaemic transformation of pre-existing multiple myeloma). PCL accounts for 2-4% of patients with MM.²,³ We report a case of PCL to demonstrate the clonal evolution, resulting in disease relapse after achieving complete remission, and its aggressive nature of the disease, leading to poor clinical outcome.
examination revealed no focal neurological deficit.

Full blood count showed Hb 9.7 g/dL, MCV 94.3 fl, MCH 32.6 pg, white cell count 5x10⁹/L, platelet 19x10⁹/L. Full blood picture (FBP) showed 24% plasma cells, neutropenia, mild left shift with occasional myelocytes and true thrombocytopenia (Fig. 1). Liver function test revealed total protein 84 g/L, albumin 25 g/L (reversed A:G ratio). There were hypercalcaemia (corrected calcium 4.25 mmol/L), acute renal failure (Creatinine 528 µmol/L, Urea 40.2 mmol/L) and compression fracture with lytic lesions at L2, L4, L5 (lumbosacral X-ray).

FIG. 1 Full blood picture and bone marrow biopsy findings (a-f) plasma cell leukaemia at diagnosis. (g-l) relapsed plasma cell leukaemia. (a) full blood picture (Wright stain x40) abnormal circulating plasma cells (b) bone marrow aspirate [MGG (May-Grünwald Giemsa) stain x40] abnormal plasma cells (c) bone marrow trephine biopsy [Haematoxylin & Eosin (H&E) stain x40] increased number of abnormal plasma cells, (d) immunohistochemistry (x40) positive for CD138 (e, f) kappa light chain restriction (in-situ hybridisation x40) (g) full blood picture (Wright stain x40) abnormal circulating plasma cells (h) bone marrow aspirate (MGG stain x40) abnormal plasma cells (i) bone marrow trephine biopsy (H&E x40) increased number of abnormal plasma cells, (j) immunohistochemistry (x40) positive for CD138 (k, l) kappa light chain restriction (in-situ hybridisation x40)
He received the initial management for hypercalcaemia. Further investigative work-up was performed. His bone marrow aspirate sample showed 49% abnormal plasma cells, displaying small to moderate in size, moderate amount of cytoplasm, round nuclei, perinuclear halo, with some abnormal plasma cells exhibiting binucleation and trinucleation (Fig. 1). Immunophenotyping of neoplastic plasma cells revealed a malignant clone which was positive for CD38, CD138 and CD56 markers with kappa light chain restriction and negative for CD19, CD79a, and CD117.

For CD38, CD138 and CD56 markers with kappa light chain restriction and negative for CD19, CD79a and CD117 (Fig. 2). Bone marrow trephine biopsy result was consistent with plasma cell leukaemia (Fig. 1). Conventional cytogenetic analysis showed normal male karyotype (46, XY) with no evidence of clonal abnormality in all 20 cells examined (Fig. 3). However, fluorescence in-situ hybridisation (FISH) analysis using Vysis LSI IGH Dual Color, Break Apart Rearrangement.

![Immunophenotyping (flow cytometry analysis) of bone marrow aspirate at diagnosis: plasma cell leukaemia. Immunophenotype of clonal plasma cells which were positive for CD38, CD138 and CD56 markers with kappa light chain restriction and negative for CD19, CD79a, and CD117.]

![Conventional cytogenetic analysis (karyotyping). (a) At diagnosis of PCL: normal male chromosome (46,XY) with no evidence of clonal abnormality in all 20 cells examined (b) At relapse: abnormal male chromosome 36~45, X, -Y[8], -1[8], add(4)(q21)[8], del(6)(q21)[8], add(8)(p23)[5], -8[2], -10[6], -12[8], -13[8], -14[3], -15[8], -15[8], -17[5], -20[2], -21[5], -22[4], +mar[2], +3mar[5], +5mar[2] with both structural and numerical chromosomal abnormalities in all 10 cells examined.]

FIG. 2

FIG. 3
FIG. 4 Fluorescence in-situ hybridisation (FISH). (a-c) At diagnosis of PCL. FISH result was abnormal and positive for IGH rearrangement in 12% of the cells analyzed. No evidence of 13q14.3 and 13q34 deletion. No evidence of 17p deletion. (d-h) At relapse. FISH result was abnormal and positive for IGH rearrangement, deletion of 13q14.3 and deletion of 17p detected in 99%, 53% and 76% of the cells analyzed, respectively; IGH-FGFR3 rearrangement, t(4;14) in 80%, three copies of IGH and MAF in 7% and no evidence of IGH-MAF rearrangement in all the cells analyzed.

Probe, Vysis TP53/CEP17 FISH Probe Kit and Vysis D13S319/13q34 FISH Probe Kit (Abbott Molecular Vysis) showed abnormal result, i.e., positive for IGH rearrangement in 12% of the cells analyzed; and no evidence for deletions of chromosome 17p13.1, chromosome 13q14.3 and chromosome 13q34 in all the cells analyzed (Fig. 4).

Serum and urine protein electrophoresis (SUEP) revealed monoclonal paraprotein (IgG kappa) in serum (32.2 g/L) and urine (49.3 mg/L) (Fig. 5). Erythrocyte Sedimentation Rate (ESR) was high (>120 mm/hour). Lactate dehydrogenase (LDH) was high (307 U/L) (normal range: 125-220 U/L). Magnetic resonance imaging (MRI) whole spines showed multiple compression fractures (T4, T12, L1, L2, L4, L5 vertebral bodies) and multiple lytic bone lesions (Fig. 6).

In summary, he was diagnosed as primary PCL, based on target organ damage (hypercalcaemia, renal insufficiency, normochromic normocytic anaemia, lytic bone lesions), >20% abnormal plasma cells in peripheral blood, immunophenotype of clonal plasma cells, >10% abnormal plasma cells in bone marrow and presence of monoclonal paraprotein in serum and urine.

He received 2 cycles of Bortezomib-Cyclophosphamide-Dexamethasone and 2 cycles of Bortezomib-pegylated Doxorubicin-Dexamethasone. There was a plan for high-dose therapy plus autologous hematopoietic cell transplantation (HCT) after completion of induction therapy. He achieved complete remission after four cycles of Bortezomib-based therapy, evidenced by no circulating plasma cells in peripheral blood, <5% plasma cells in bone marrow normal karyotyping, normal FISH result and no paraprotein in serum or urine. However, a month later, he presented again with lethargy, loss of appetite and loss of weight. FBP showed leucoerythroblastic picture with 2% plasma cells (Fig. 1). Bone marrow biopsy examination was done for reassessment of disease status. He was diagnosed as relapsed PCL with 94% abnormal plasma cells in bone...
FIG. 5 **Presence of monoclonal paraprotein (IgG Kappa) in serum and urine.** (a) serum protein electrophoresis, urine protein electrophoresis (b) immunofixation (left; serum, right; urine) (c) serum protein electrophoresis (densitometer tracing) (d) urine protein electrophoresis (densitometer tracing)

FIG. 6 **MRI (whole spines)** showing multiple compression fractures T4, T12, L1, L2, L4, L5 vertebral bodies and multiple lytic bone lesions
marrow (Fig. 1). Conventional cytogenetic analysis showed abnormal male chromosome with both structural and numerical chromosomal abnormalities in all 10 cells examined (Fig. 3). FISH analysis using the same probes (as at initial diagnosis) showed abnormal results: positive for IGH rearrangement, deletion of 13q14.3 and deletion of 17p detected in 99%, 53% and 76% of the cells analyzed, respectively. FISH analysis using Vysis LSI IGH/FGFR3 Dual Color Dual Fusion Probes and Vysis LSI IGH/MAF DF Probe Kit (Abbott Molecular Vysis) showed IGH-FGFR3 rearrangement, t(4;14) in 80%, three copies of IGH and MAF in 7% and no evidence of IGH-MAF rearrangement in all the cells analyzed (Fig. 4). LDH was high (1295 U/L). At that time, he was not keen for any further chemotherapy and he opted for the best supportive care. He passed away a few days later, from severe sepsisemia with underlying relapsed PCL. Time-to-progression of his disease was 1 month and overall survival was 5 months.

DISCUSSION

The spectrum of chromosomal abnormalities is comparable in PCL and MM, however, the incidence of chromosome abnormalities is higher in PCL than in MM. Poor outcome in PCL is related to high proliferative rate and multiple high-risk cytogenetic abnormalities [del(13q), del(17p), t(4;14), t(14;16)]. Our patient has IGH rearrangement at initial diagnosis. After four cycles of Bortezomib-based therapy, he achieved complete remission with cytogenetic remission evidenced by no circulating plasma cells in peripheral blood, <5% plasma cells in bone marrow, normal karyotyping and normal FISH result. Then, at relapse, he had high-risk cytogenetic abnormalities, del(13q), del(17p) (TP53 mutation) and t(4;14), which demonstrated the clonal evolution leading to disease relapse after achieving complete remission and contributed to his poor outcome with shorter duration of remission, faster time to disease progression and shorter overall survival. Even though he achieved the best response to treatment of his disease, i.e., complete remission, the duration of complete remission is too short that autologous HCT could not be carried out before he developed relapse. The reason could be the aggressive nature of disease and its clonal evolution. Even though the response was the best, the duration of the best response was not sustained long, highlighting the importance of the depth and duration of the best response, aiming for a cure. The research for newer novel agents to achieve complete remission as well as to sustain the duration of complete remission is enlightened. To our knowledge, there were case reports illustrating the clonal evolution into relapsed secondary plasma cell leukaemia from multiple myeloma.4,5 However, there was scarce data reporting about clonal evolution of relapsed primary plasma cell leukaemia.

In the study by Cifola I, et al.6, they performed the whole-exome sequencing of primary PCL cases and reported a remarkable genetic heterogeneity of mutational patterns. Upon identification of coding somatic variants in pPCL, they observed excess of C > T transitions and the presence of two main mutational signatures (related to APOBEC over-activity and ageing). They identified the candidate driver genes in pPCL, which were genes involved in cell-matrix adhesion and membrane organization (SPTB, CELA1), cell cycle and apoptosis (CIDEC), genome stability (KIF2B), RNA binding and degradation (DIS3, RPL17), and protein folding (CMYA5). Globally, cadherin/Wnt signaling pathway and G2/M cell cycle checkpoint pathway were the most affected functional pathways. In their study, sequencing results were finally combined with gene expression data to better elucidate the biological relevance of mutated genes. Our patient had TP53 mutation which was detected at relapse. Cifola I, et al.6 highlighted that TP53 was the most recurrently disrupted gene. The novel information presented by Cifola I, et al.6, contributed to the understanding of pathogenetic mechanisms associated with this aggressive and high-risk plasma cell leukaemia; and this may play an important role in the discovery of novel therapeutic agents for a better outcome.

Plasma cell leukaemia can manifest as typical CRAB features of MM (hypercalcaemia, renal insufficiency, anaemia, lytic bone lesions) as well as features of leukaemia (anaemia, infection, thrombocytopenia, lymphadenopathy, hepatomegaly, splenomegaly). Other manifestations include extramedullary plasmacytoma, pleural effusion and neurological deficit. In this case, the patient had typical CRAB features of MM and manifestations of leukaemia (anaemia, thrombocytopenia). The initial presentation of our patient was typical presentation of MM, i.e., lower back pain, hypercalcaemia, renal insufficiency, anaemia and lytic bone lesions although he had circulating...
plasma cells exceeding 20% of total white cell count in FBP, which made his diagnosis to be pPCL. In the case report which was previously reported at our centre, there was one patient who was diagnosed as pPCL; and the initial presentation was progressive paraplegia, which was contributed by extramedullary mass.

The diagnostic evaluation of a patient with suspected PCL is identical to that of MM, with the importance of FBP and flow cytometry. The diagnosis of PCL is based on evaluation of FBP, bone marrow biopsy (BMB) examination and SUEP. Diagnosis of PCL is confirmed when the circulating abnormal plasma cells in peripheral blood exceed >20% of white blood cells or absolute plasma cell count in peripheral blood exceed \(2 \times 10^7\) cells/L. The findings of BMB are similar in PCL and MM, demonstrating an increased number of monoclonal plasma cells (>10%). In PCL, the bone marrow infiltration is usually extensive and consists of plasma cells with high proliferative index and anaplastic or plasmablastic morphology. The findings of SUEP are similar in PCL and MM, demonstrating the presence of monoclonal paraprotein. In our patient, the diagnostic criteria for PCL is fulfilled.

Our patient was diagnosed as pPCL since he presented as the first clinical manifestation without any previous history of plasma cell dyscrasia. Among the types of PCL, pPCL accounts for 60-70% and the incidence of sPCL is increasing in trend in this era because the overall survival of MM has been improved by therapy with novel agents.

Primary PCL presents at a slightly younger age at diagnosis (median age 55 years) compared to sPCL (66 years). Our patient presented at an older age (69-year-old) for pPCL.

Prognosis of PCL is poor. Median overall survival was only 4 to 11 months. In the study by Cha CH, et al., there was significant difference in survival between 3 groups (median survival of pPCL, sPCL and MM was 22.2, 1.3 and 36.4 months, respectively; \(p=0.048\)). The prognosis of pPCL was superior to sPCL but inferior to MM. Unfavourable prognostic factors of pPCL include low serum albumin, hypercalcaemia, elevated serum LDH, advanced age and high-risk cytogenetic abnormalities at the time of relapse, leading to adverse outcome.

There was no prospective randomised trial for treatment of PCL. The recommendation as the standard of care is induction therapy with Bortezomib-based regimen followed by high-dose therapy plus autologous HCT for transplant-eligible patients. Maintenance therapy with Lenalidomide is recommended rather than observation until relapse. For recurrent or refractory PCL, allogeneic HCT may be an option in eligible patients. At initial diagnosis, our patient was able to achieve complete remission after Bortezomib-based therapy, however, time-to-progression of his disease was so fast that he was not able to undergo autologous HCT; and he succumbed to his disease. Even though induction regimen with Bortezomib-based therapy can be effective to achieve complete remission, the consolidation regimen with high-dose (Melphalan) therapy followed by autologous HCT plays a significant role to overcome the poor prognosis by PCL.

The development of newer novel agents, such as Carfilzomib, Pomalidomide, Daratumumab, for treatment of MM in this era may provide the improvement in clinical outcome for PCL, which is one of the most challenging diseases for haematologists.

**CONCLUSION**

This case report illustrates the clonal evolution of pPCL leading to disease relapse after complete remission, and its aggressive nature with older age presentation leading to shorter remission duration, progression-free survival and overall survival.

**Conflict of interest:** The authors have no conflict of interest to declare.

**REFERENCES**


