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Plasma Cell Leukemia-Behind a Disguise

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Abstract

Plasma cell leukemia is a variant form of multiple myeloma with its own unique form of presentation. It may have a presentation resembling a lymphoproliferative disorder which if not investigated in detail can lead to misdiagnosis and thus completely different line of investigation. Our patient presented to us with disturbed dietary regimen, significant weight loss and was a known case of hypothyroidism since 2009 for which he was on medications. At the other centre, complete blood picture showed bicytopenia with hyperleucocytosis while bone marrow biopsy performed showed a diagnosis of lymphoproliferative disorder with a morphological diagnosis of Hairy cell leukemia. At our center, his complete blood count showed bicytopenia with leucocytosis as before but the morphological examination of his peripheral smear showed the presence of 80% plasma cells. The immunophenotyping showed CD23(+) and CD56(+) while the immunohistochemistry showed CD23(+), CD56(+) and CD138(+). Cytogenetics showed the presence of t(4;14) in 5% of the cells examined. Based on the above mentioned investigations, a diagnosis of Plasma cell leukemia was reached and the patient was placed on a treatment regimen including Lenalidomide, Bortezumib and Dexamenthasone. His blood counts came within the normal range within a week of starting the treatment. Bone marrow biopsy accounts for one of the many steps that should be taken to reach a correct diagnosis. Keeping in mind the variable presentation a disease can show, as many investigative tools should be undertaken as is clinically and economically possible for reaching at a correct diagnosis and thus the decision of the eventual treatment plan for the patient.

Keywords: Hairy cell leukemia; Plasma cell leukemia; Flow cytometry

Introduction

Plasma cell leukemia is a rare form of clonal plasma cell dyscrasia and is known to have an aggressive nature amongst all monoclonal gammopathies. It is defined by the presence of absolute plasma cell count of greater than 2×10^9/l in the peripheral blood. The leukemia is graded into primary or secondary type depending on its occurrence being de novo or whether it was a leukemic transformation from relapsed or refractory multiple myeloma respectively [1]. The primary type has an incidence of 60-70% while the rest of the 30-40% is the secondary subtype [2]. It can morphologically present itself as a completely different haematological disorder which can be misdiagnosed if appropriate investigative tools are not utilized and thus can lead to mismanagement and incorrect treatment regimen.

A 44 years male was referred to us from a different tertiary care hospital. His presenting complains at that centre were disturbed diet and significant weight loss of more than four kg within a two months period. The patient was a known case of hypothyroidism since 2009 and was on treatment for this ailment. His Complete Blood Count showed Hemoglobin (Hb)-10.2 g/dl, Total leucocyte count (TLC)-69.3 $\times$ 10^9/L (Differential: Neutrophils-12%, Lymphocytes-10% and Monocytes-83%) and Platelets-49 $\times$ 10^9/L. Bone marrow biopsy was performed on the patient and the features were consistent with lymphoproliferative disorder while morphologically the proposed diagnosis was Hairy Cell Leukemia.

On arrival at our centre, Complete Blood Count showed the following counts: Hemoglobin (Hb)-9.0 g/dl, Total leucocyte count (TLC)-99.9 $\times$ 10^9/L (Differential: Neutrophils-5%, Lymphocytes-10% and Monocytes-83%) and Platelets-51 $\times$ 10^9/L. His Serum Lactate Dehydrogenase level was 699 µ/l (Reference Range: 230-460 µ/l). His Serum immunoglobulin levels were performed and the findings were as follows: Serum IgA – 0.21 G/L (0.7-4.0 G/L), Serum IgM – 0.08 G/L (0.4-2.3 G/L), Serum IgG – 5.24 G/L (7.0-16.0 G/L). His general examination was unremarkable while his systemic examination showed no presence of lymphadenopathy or visceromegaly. The ultrasound of the abdomen as well as chest X-ray was performed which showed no positive findings. The peripheral sample, when examined morphologically showed ovoid, small to medium sized abnormal cells with irregular cellular outline and cytoplasmic circumferential fine projections. Nuclei were round, eccentrically placed had clumped chromatin pattern and inconspicuous nucleoli. Many cells also exhibited perinuclear hof. The plasma cell percentage in the peripheral blood amounted to 80% (Absolute count: 79.5 $\times$ 10^9/L) (Figure 1).

Immunophenotyping of the blasts in the peripheral sample showed the following results:

CD45 (Dim+), CD5 (Dim partial +), CD23 (+), CD38 (+), CD3 (-), CD4 (-), CD7 (-), CD8 (-), CD10 (-), CD19 (-), CD20 (scattered + in about 4.4% of these cells), CD22 (-), CD25 (-), CD79a (-), FMC7 (-) and ZAP70 (-). The sample showed 0.76% benign B-Lymphocytes, 7.5% benign T-Lymphocytes and 7.39% granulocytes.

The immunohistochemistry of the sample showed: CD5 (-), CD 20(scattered +), CD 23(+), CD 56(weak +), CD 138(+), PAX5 (-), TRAP (-), Annexin A1 (-), Kappa (-), Lambda light-chain restriction pattern (scattered +) and Cyclin D1(-). Bone marrow cytogenetics was also advised (Figure 2).

Protein Electrophoresis although not necessary for the confirmation of the diagnosis was also performed and the results are shown in Figure 3 and Table 1.

Protein electrophoresis pattern showed hypogammaglobinemia with no presence of monoclonal bands.

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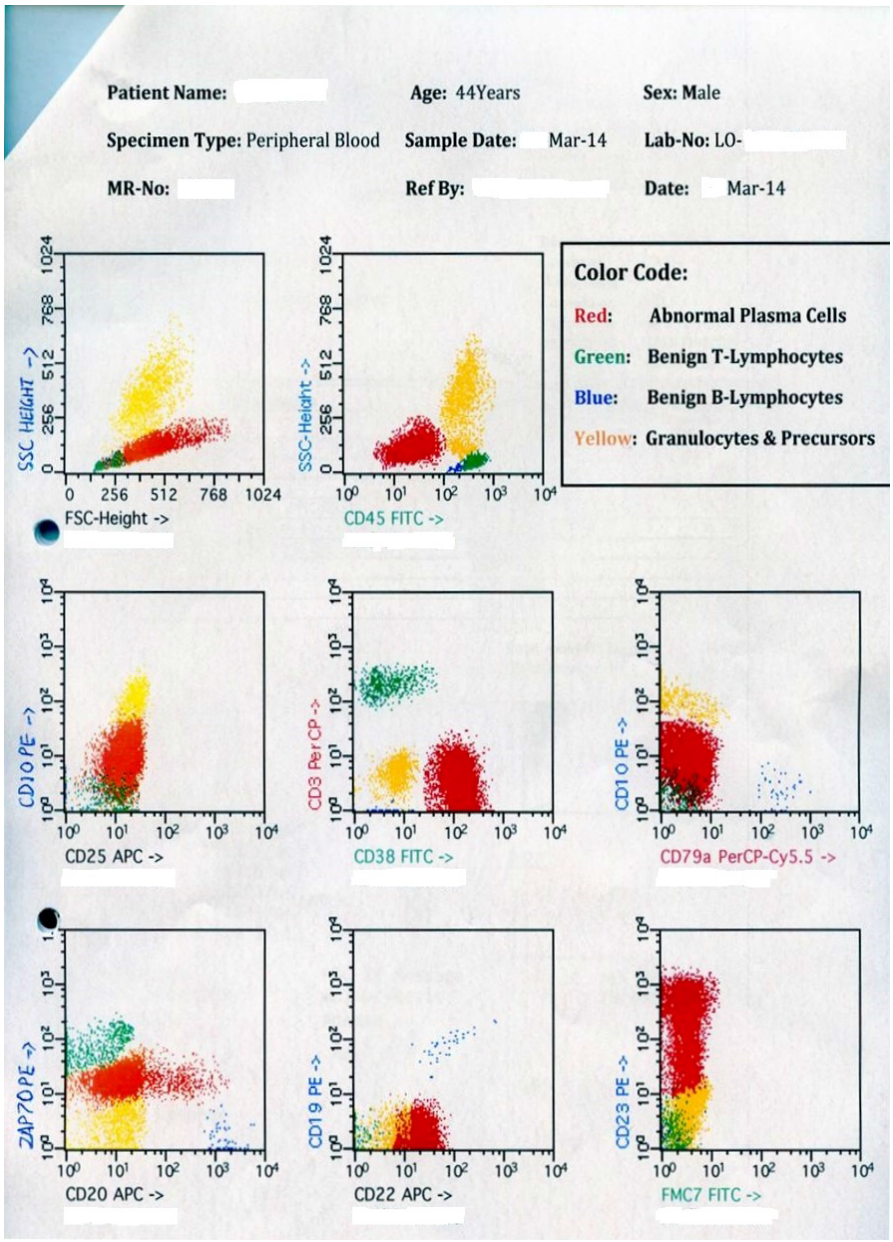


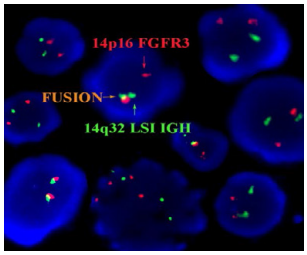
Figure 1: Flow cytometric results of the peripheral sample.

Fraction	%	Reference Range(%)	g/dL	Reference Range(g/dL)
Albumin	67.5	52.0-62.0	4.1	3.2-5.0
Alpha 1	3.4	1.5-4.5	0.1	0.1-0.4
Alpha 2	11.9	6.0-12.0	0.6	0.6-1.6
Beta	11.5	11.0-17.0	0.7	0.6-1.3
Gamma	5.7	11.0-19.0	0.3	0.7-1.5
Total Protein			6.1	6.0-8.0

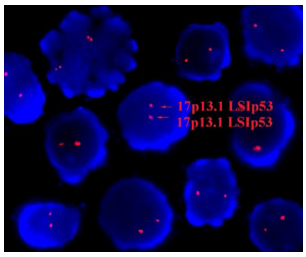
Total Protein A/G ratio: 2.2 (Reference Range: 1.15-1.65).

Table 1: Levels of serum protein.

All the investigations including peripheral blood morphology, immunophenotyping and bone marrow biopsy and cytogenetics that were performed led to the conclusion of Plasma Cell Leukemia. The treatment included Lenalidomide 25 mg × HS for 21 days, Bortezumib 2 mg × I/V weekly and Dexamethasone 8 mg × TDS for 4 days every week. Within a few weeks after the initiation of the treatment, the patient showed an improvement in the disease status as was evident in his complete blood count which showed an overall improvement



a)340 interphases were analyzed out of which 17 (5%) cells showed t(4;14) fusion signal pattern whereas 323(95%) cells showed normal signal pattern



b)250 interphases were analyzed none of which showed any evidence of deletion 17p53

Figure 2: Bone marrow cytogenetics by FISH. a) For t(4;14), b)For del17p53.

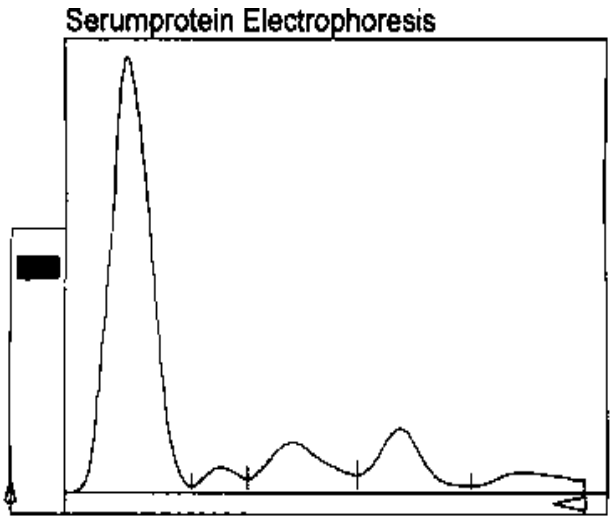


Figure 3: Serum protein electrophoresis image.

in all the three cell lineages which was as follows: Hb-13.5 g/dl, TLC-9.9 × 10^9/L (Differential: Neutrophils-88%, Lymphocytes-4%, Monocytes-5%, Myelocytes-3%) and Platelets-78 × 10^9/L and complete absence of plasma cells in the peripheral blood.

The patient received 16 cycles of Lenalidomide (25 mg × HS for 21 days), Bortezumib (2 mg × I/V weekly) and Dexamethasone (8 mg × TDS for 4 days every week). At the end of treatment, he underwen t bone marrow biopsy which showed the disease in remission. The immunophenotypic analsysis for the minimal residual disease (MRD) was found to be positive as there was the presence of 0.03% blasts which corresponded to >10^{-4}. The serum protein electrophoresis showed no monoclonal bands while the immunofixation study resulted in the absence of monoclonal gammopathy. His β2-microglobulin level was 3793 ng/ml. His echocardiographic evaluation performed about a month ago showed normal sized left ventricle with generalized dysfunction. Aortic and tricuspid valves were normal while degree of mitral regurgitation ranged from mild to normal.

The patient at present is on Lenalidomide (10 mg HS for 21 days) and Melphalan (8 mg/day for 4 days/month) and has been counseled for the autologous bone marrow transplantation.

Discussion

Plasma Cell Leukemia is a rare but aggressive variant of Multiple Myeloma. This leukemia is classified into the primary subtype which arises de novo and the secondary subtype which results at the end-stage transformation of refractory or relapsed form of multiple myeloma [1]. This leukemia can have an unusual presentation with abnormal cells that on morphology could appear as cells with hair-like projections.

Primary Plasma Cell Leukemia is a disorder that occurs in patients who are comparably younger from those who suffer from multiple myeloma or the secondary Plasma Cell Leukemia. The median age lies between 52 and 65 years for the primary subtype as opposed to the median age of 65-70 years for the patients of the secondary subtype [3] and myeloma [4]. Our patient was a young male of 44 years of age. The present diagnostic criteria of >20% circulating plasma cells or an absolute count of >2 × 10^9/L in the peripheral blood as given by Noel and Kyle [5] was met by our patient. The bone marrow shows an infiltration of abnormal plasma cells with lowered marrow reserve and increased incidence of anemia, thrombocytopenia and leucocytosis and similar findings were observed in our patient. Elevated Lactate Dehydrogenase levels was also observed in accordance to the literature. On immunophenotyping, CD38 and CD138 are the plasma cell markers and both were present in our patient [6]. Our finding of higher expression of CD20, CD45 and CD23 compared to CD56 was consistent with the published literature [7]. Cytogenetically, deletions and translocations are common features of Plasma Cell Leukemia. The IGH (14q32) translocation is the most common occurring and accounts for about 87% of the cases of Primary Cell Leukemia [8] t(11;14) which accounts for 25-65% [9-11]. However, this was observed for in our case. In our patients's case, t(4;14) was observed while del17p13.1 which is present in 50% of the cases of Plasma Cell Leukemia as reported in the literature was not detected [3]. Bortezumib seems to be an important drug in regards to the treatment of Plasma Cell Leukemia as it rapidly reduces the tumor load and studies have shown a 79% improved overall survival in Bortezumib-based therapy [12]. Lenalidomide in combination with dexamethasone seems to be another favorable treatment option for Plasma Cell Leukemia as this regimen have shown to give a partial response in 61% of the patients. Thus based on the literature and the favorable response achieved, combination of Bortezumib, Lenalidomide and Dexamethasone is recommended [13]. We used this drug combination and achieved a commendable response in our patient with a reduction in the tumor load in a very short period of time.

Thus, morphological examination although an important step in reaching to a diagnosis of Plasma Cell Leukemia is still only one of the many important steps. Bone marrow examination, immunophenotyping, immunohistochemistry as well as serum protein electrophoresis are other key steps that have to be taken in order to reach to a correct diagnosis and for the initiation of treatment in order to achieve a favorable response.

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