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Case Report

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Synchronous polycythemia in a patient of relapsed multiple myeloma- An extremely unusual finding

Jatin Sarin[1], Rimpi Bansal[2], Akshita Sarin[3], Sumit Kaura[4]

1 *Consultant Medical Oncologist, Chandigarh Cancer and Diagnostic Centre, Chandigarh, India*
2 *Consultant Pathologist, Chandigarh Cancer and Diagnostic Centre, Chandigarh, India*
3 *Student, Government Medical College and Hospital (GMCH), Chandigarh, India*
4 *Medical Officer, Chandigarh Cancer and Diagnostic Centre, Chandigarh, India*

Abstract

Multiple myeloma is a common hematological malignancy in elderly population. Proliferating plasma cells destroy the normal marrow cells. Anemia (most common), leucopenia and thrombocytopenia are known occurrences in myeloma. Contrary to these usual features, occasionally myeloma may result in anomalous increased RBC or WBC production, resulting in polycythemia and neutrophilia respectively. Increased RBC production may be a part of a paraneoplastic syndrome TEMPI, in which there is excess secretion of erythropoietin. It can also be due to coexistent JAK2 positive polycythemia vera. In an occasional case there is no known etiology for polycythemia. But the polycythemia resolves with the treatment of underlying multiple myeloma. Only three such cases have been reported in literature so far. We present a case of polycythemia, in a patient who is a known case of myeloma, which manifested in the relapsed disease. The patient was on follow-up for a period of almost two years, when he developed symptoms of weakness, dyspnoea, numbness and inability to bear weight on lower limb. Investigations revealed relapsed disease along with elevated hemoglobin levels. The possible pathogenesis of polycythemia could be due to hypoxic damage to kidneys and lungs resulting from deposition of light chains.

Keywords: Polycythemia, Multiple myeloma, Bortezumib.

INTRODUCTION

Multiple myeloma (MM) is a BM-based, multifocal plasma cell neoplasm associated with an M-protein in serum and/or urine. It constitutes 1% of all malignant neoplasm and 10-15% of hemopoietic neoplasm [1,2]. Overall age-standardized incidence is 2.1 per 100,000 persons. Multiple myeloma was responsible for 2.1 million (95% UI, 1.9-2.3 million) DALYs (disability adjusted life years) at the global level in 2016, with an age-standardized rate of 30.5 (95% UI, 27.4-33.9) DALYs per 100,000 person-years [3]. Multiple myeloma has a myriad of presentation, but the most common symptoms are due to end organ damage (CRAB – hypercalcemia, renal insufficiency, anemia and bone lesions) [1].

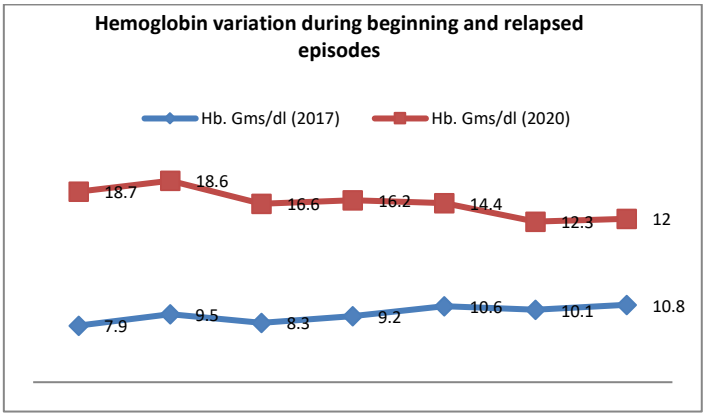
Proliferating plasma cells destroy the normal marrow cells. Anemia (most common), leucopenia and thrombocytopenia are known occurrences in myeloma. Anemia is caused by marrow suppression by proliferating plasma cells, immune mediated destruction, cytokine production from tumor cells and suppressed erythropoietin production from diseased kidney. Contrary to these usual features, occasionally MM may result in aberrant increased RBC or WBC production, resulting in polycythemia and neutrophilia respectively. Increased RBC production may be a part of a paraneoplastic syndrome TEMPI, in which there is excess secretion of erythropoietin [1,4]. It can also be due to coexistent JAK2 positive polycythemia vera (PCV) [5]. In an occasional case there is no known etiology for polycythemia [6]. But the polycythemia resolves with the treatment of underlying multiple myeloma. Only three such cases have been reported in literature so far. We present another case of polycythemia in a patient of MM, which manifested in the relapsed disease.

CASE REPORT

A 72-years-old male patient presented in November, 2016 with complaints of weakness, dyspnoea, numbness and inability to bear weight on lower limb. Significant results in routine blood investigations were anemia, elevated ESR, LDH, creatinine, calcium and protein levels. A/G ratio was reversed. Skeletal survey showed multiple osteolytic lesions in skull bones, ribs, lumbar and sacral spine.

***Corresponding author:**
Dr. Rimpi Bansal
Consultant Pathologist, Chandigarh Cancer and Diagnostic Centre, SCO No. -23, SECTOR – 33-D, Chandigarh-160020, India
Email:
rimpijatinsarin@yahoo.com

Multiple vertebrae showed diffuse expansion of body. On further investigations bone marrow aspirate showed monoclonal population of plasma cells (73%) (Figure-1). Serum IgG was 84.10mg/dl, M-band was 8.27g/dl, kappa levels were 12,300 mg/L, k/l ratio 742.4 and beta2-microglobulin was 38,055 ng/ml. Multiple myeloma prognostic panel showed negative results for Del 13q14 /Del 17p 13.1 /t(4:14) /t(11:14) / t(14:16). Patient was diagnosed with IgG – kappa multiple myeloma. He was started on weekly bortezomib with dexona. Patient was clinically better, his renal functions improved, and M- band was absent on protein electrophoresis. He completed his treatment in April, 2017. He was then put on maintenance therapy with lenalidomide for one year. Since then he remained on regular follow up and was asymptomatic till December 2019. He developed complaint of acute loss of power in bilateral lower limbs and inability to bear weight. He also had a history of fall twice. He had episodes of irrelevant talking, dizziness, confusion and delusions. Blood parameters revealed elevated serum creatinine and protein levels. Hemoglobin (18.7gms/dl) (Graph -1) and hematocrit (56.8%) was also increased but platelet count was reduced. Serum IgG was 73.7 mg/dl, kappa levels were 10,300 mg/L, k/l ratio 730.50, M-band was 6.69g/dl and beta2-microglobulin was 23,455mg/L (Graph-2). He was diagnosed with relapsed myeloma. Initially we attributed increased hemoglobin to dehydration because the patient was not taking his diet properly. But even after giving him IV fluids the polycythemia did not rectify. He was a non-smoker and lives in plains. We investigated further to find the cause of elevated hemoglobin. Serum erythropoeitin levels were normal. JAK 2 mutation (both JAK2 617 and EXON 12) were negative. MRI of lower spine showed minimal vertebral retrolisthesis, diffuse bulges and bilateral neural foramina narrowing. Nerve conduction study was suggestive of mixed demyelinating (axonal) sensori motor polyneuropathy affecting lower limbs and upper limbs. We examined the patient thoroughly, there were no telangiectasias, bilateral air entry and heart sounds were normal. Ultrasonography of abdomen ruled out any fluid collection. To summarize, we ruled out all causes of primary and secondary polycythemia. The patient was diagnosed with relapsed multiple myeloma with aberrant polycythemia. He was restarted on weekly bortezomib (2mg) and dexona. After three cycles of therapy the serum electrophoreseis level showed a decline. Simultaneously there was significant reduction noted in hemoglobin (12.2 gms/dl) and hematocrit (36.9%) levels. Currently patient is on treatment for relapsed multiple myeloma.



Graph 1: Haemoglobin level variation seen at the time of diagnosis and during relapse of the disease

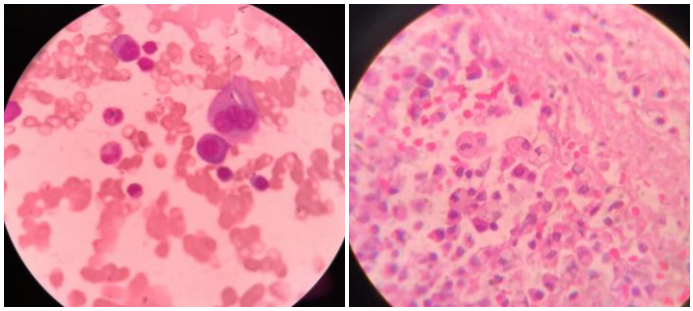
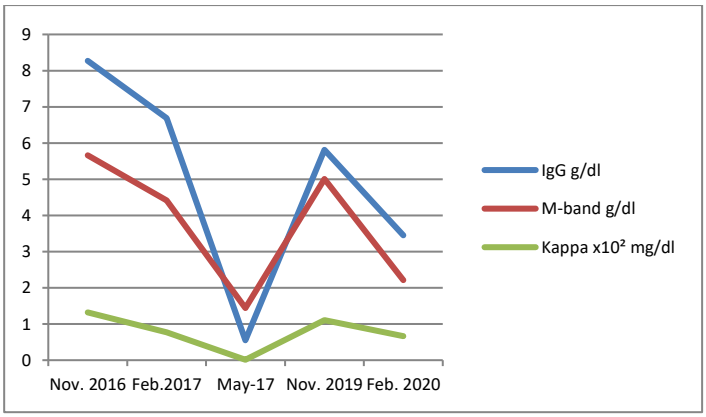


Figure 1: Bone marrow aspiration and biopsy done at the time of primary diagnosis of the disease, showing atypical plasma cells replacing the normal marrow elements. (400x Leishman stain and 100x Hand E)



Graph 2: Variation in levels of serum IgG and Kappa chain levels during primary presentation and relapsed disease

DISCUSSION

Polycythemia can be an incidental finding on routine health check-up. Occasionally the presenting sign could be skin plethora. In symptomatic patients, most common presentation is headache, dizziness, confusion, pruritis, blurring of vision, tinnitus, numbness, tingling, dyspnoea, tiredness and weakness. More severe symptoms due to thrombotic episodes could be myocardial infarction, GI bleed or CV stroke [7]. It is important to rule out secondary polycythemia before embarking on the diagnosis of primary or idiopathic polycythemia. Hutchison et al described 27 cases of polycythemia in patients of multiple myeloma in last 70 years, making it a very rare occurrence [8]. Antecedent polycythemia was a more common finding. Till date only three patients of synchronous polycythemia have been reported. In our patient polycythemia was diagnosed on relapse of disease [6,8,9].

The combination of polycythemia and myeloma is uncommon; there are rare syndromes that are characterized by both polycythemia / erythrocytosis and a monoclonal gammopathy. These syndromes include POEMS and TEMPI. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome is a rare syndrome with the following diagnostic criteria: Mandatory criteria -Polyneuropathy (typically demyelinating) , Monoclonal plasma cell-proliferative disorder (almost always λ); Major criteria- Castleman's disease, sclerotic bone lesions and vascular endothelial growth factor (VEGF) elevation; Minor criteria: organomegaly, extravascular volume overload, skin changes, endocrinopathy, papilledema, thrombocytosis, and polycythemia . A diagnosis requires the fulfillment of >=1 major criteria, along with at least one minor criterion [10]. It has been suggested that the manifestations of POEMS are the result of a marked activation of the proinflammatory cytokines IL-1beta, IL-6, and TNF-a, along with an associated decrease in the presumptive anti-inflammatory cytokine TGF-beta. Our patient was a known case of myeloma. Though he had

demyelinating polyneuropathy, but he did not fall in the category of POEMS.

Another rare syndrome with erythrocytosis and clonal plasma cells is telangiectasias, elevated EPO and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting (TEMPI) syndrome [1,4]. The pathogenesis of TEMPI syndrome is still not clear, but it is hypothesized that the abnormal protein leads to a paraneoplastic syndrome and increased erythropoietin production, similar to the mechanism seen in solid tumors [1]. The patient in the study had normal erythropoietin levels. Other diagnostic criteria were also absent.

Another cause of polycythemia in plasma cell neoplasms could be due to presence of concomitant JAK2 mutation positive PCV, which was ruled out in our patient [1,5,6] Few cases of leukocytosis and thrombocytosis have also been reported in patients of MM [11,12]. Badelita et al opine that cases of AL amyloidosis may be associated with pancytosis by amyloid related functional hyposplenism [13].

CONCLUSION

In our view, the probable explanation for paradoxical polyocythemia in patients of MM is due to end-organ damage in renal tubules and pulmonary parenchyma. There is deposition of monoclonal light chains in kidney tubules which lead to hypoxia. This, results in increased erythropoietin production. The deposition of light chains in tracheobronchial tree and alveolar septa also produces a state of hypoxia. The case mentioned above, in which treatment of the myeloma ameliorated the polycythemia too, are compatible with this theory. This is a hypothesis which needs in depth analysis of greater number of cases of coexistant polycythemia and myeloma.

Conflict of Interest

There is no conflict of interest.

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Nil.

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