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CASE REPORT

Secondary Polycythemia May Be an Early Clinical Manifestation of Multiple Myeloma: A Case Report

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Abstract: Multiple myeloma (MM) is a malignancy of plasma cells that can cause anemia due to renal failure and bone marrow failure. Secondary polycythemia (SE) is a clinically rare disease that involves the overproduction of red blood cells. To our knowledge, the association of multiple myeloma and polycythemia has been reported, but the association of SE and multiple myeloma is rare and has been infrequently reported in literature. In contrast to anemia, the presence of polycythemia in multiple myeloma patients is a rare finding. A patient of IgA-λ multiple myeloma with secondary erythrocytosis recently admitted to our department is now reported as follows and relevant literature is reviewed to improve clinicians' awareness of such rare comorbidities.

Keywords: multiple myeloma, secondary erythrocytosis

Introduction

Multiple myeloma (MM) is a malignant disease with abnormal proliferation of clonal plasma cells and is the second most common malignancy in the blood system.[1,2] Globally, an estimated 588,161 individuals are diagnosed with MM each year, at a median age of 70 years.[3,4] Erythrocytosis encompasses some diseases characterized by increased circulating red blood cells (RBCs), which can be classified as relative, primary and secondary polycythemia. Secondary erycytosis (SE) can be caused by a variety of causes, including kidney tumors, other kidney diseases and inappropriate erythropoietin production, but is rarely associated with oxygen transport defects, usually by abnormal haemoglobin (Hbs) with increased oxygen affinity. Most of these patients are in generally good health, but RBCs and hemoglobin levels in the blood are higher than normal.[5] Case reports of MM and SE are increasing, and Lee et al suggested that SE may be an early clinical manifestation of plasma cell tumors.[6] Therefore, clinicians should pay attention to this patient group and strive to clarify the correlation between these two diseases soon, so as to better serve the patients. Here, we report a case of MM coexisting with SE and an attempt to analyze the relationship between these two coexisting diseases.

Case Report

A 75-year-old retired man was admitted to the hospital with erythrocytosis detected during follow-up of cerebral arteriosclerosis. Physical examination after admission revealed Sanguineous appearance, but there were no other positive sign. The blood oxygen saturation measured in the no-oxygen inhalation state was 96% (normal range 95–100%). He had hypertension and cerebral arteriosclerosis which were controlled regularly by long-term oral treatment of aspirin and atorvastatin calcium tablets, and no vascular events before. He had no previous smoking history and had never lived at high altitude. He complained of no dyspnea, orthopnea and paroxysmal nocturnal dyspnea. There was no family history of polycythemia or any myeloproliferative disorder. We performed laboratory tests after the patient's admission (Table 1). Further examination revealed that IgA-

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Table 1 Initial Laboratory Test Data

Variable	Admission	Reference Range
White Blood Cell (cells/L)	5.28 $\times 10^9$	4.5–10.8 $\times 10^9$
Differential Count (%)	N:45.0, L:45.2, M:8.3, E:1.1, B:0.4	N: 41.0–74.3, L: 18.3–47.9, M: 4.2–15.2, E: 0.4–8.0, B: 0.0–1.2
Hemoglobin (g/L)	175.0	120–160
Hematocrit (%)	54.70	40.0–50.0
Platelets (cells/L)	104x10^9	100–400x10^9
Mean Corpuscular Volume (fL)	101.0	81.0–98.0
Lactate Dehydrogenase (U/L)	210	125–274
Urea Nitrogen (mmol/L)	10.05	2.50–7.50
Calcium (mmol/L)	2.33	2.08–2.60
Creatinine (μmol/L)	143.2	40.0–120.0
Sodium (mmol/L)	142.0	135.0–145.0
Potassium (mmol/L)	3.67	3.50~5.50
Total Protein (g/L)	75.3	60.0–85.0
Albumin (g/L)	38.9	35.0–55.0
Globulin (g/L)	27.4	20.0–40.0
Albumin/Globulin	1.07	1.5–2.5
Total Bilirubin (μmol/L)	16.2	3.4–20.5
Indirect bilirubin (μmol/L)	8.2	0.0–18.0U/L
Direct bilirubin (μmol/L)	5.3	0.0–6.84 U/L
Alanine aminotransferase (U/L)	16.0	0.0–40.0
Aspartate amino transferase (U/L)	33.0	0.0–40.0
Total bile acids (umol/L)	39.0	0.0–25.0
Immunoglobulin A (g/L)	7.63	0.82–4.53
Immunoglobulin G (g/L)	8.88	7.51–15.60
Immunoglobulin M (g/L)	0.67	0.40–2.74
Complementary C3 (g/L)	0.65	0.79–1.52
Complementary C4 (g/L)	0.15	0.16–0.38
KAP light chain (g/L)	8.48	6.29–13.50
LAM light chain (g/L)	6.59	3.13–7.23
C-reactive protein (mg/L)	1.31	0.0–8.0
Hepatitis B surface antigen (IU/mL)	Positive; 30.57	Negative; < 0.05
Hepatitis B virus (IU/mL)	2.41E+03	< 2.00E+01
Beta-2 microglobulin (mg/L)	2.73	1.0–3.0

(*Continued*)

Table 1 (Continued).

Variable	Admission	Reference Range
Ferritin (ng/mL)	131.50	23.9–336.2
Haemopoietin (mIU/mL)	53.90	1.48–31.88
BCR::ABL1 P210/P190/P230	Negative	Negative
Mutation of JAK2/MPL/CALR/CSF3R	Negative	Negative
Serum free Kappa light chain (mg/L)	24.40	3.30–19.40
Serum free lambda light chain (mg/L)	68.82	5.71–26.30
Serum free kappa/free lambda (Ratio)	0.3545	0.2600–1.6500
Urinary free Kappa light chain (mg/L)	125.97	1.17–86.46
Urinary free lambda light chain (mg/L)	41.56	0.27–15.21
Urinary free kappa/free lambda (Ratio)	3.0310	1.8300–14.2600

λ was monoclonal with a M-spike of 5.65 g/L. The abdominal and urinary color examination showed no enlargement of the liver, spleen, kidney, and lymph nodes.Furthermore, a skeletal examination and magnetic resonance imaging of the spine showed no bone destruction. Bone marrow smear revealed 5.2% primary plasma cells (Figure 1). Flow cytometry further confirmed positive for λ chain, CD38 and CD138 in plasma cells (DxFLEX flow cytometer; Beckman Coulter, Inc). Bone marrow biopsy suggested the hyperplasia of nucleated cells in bone marrow is roughly normal (about 40% hematopoietic area); the granule/red ratio is roughly normal (Figure 2). Immunohistochemistry is shown CD138 (+), MPO (+), E-cad multicluster

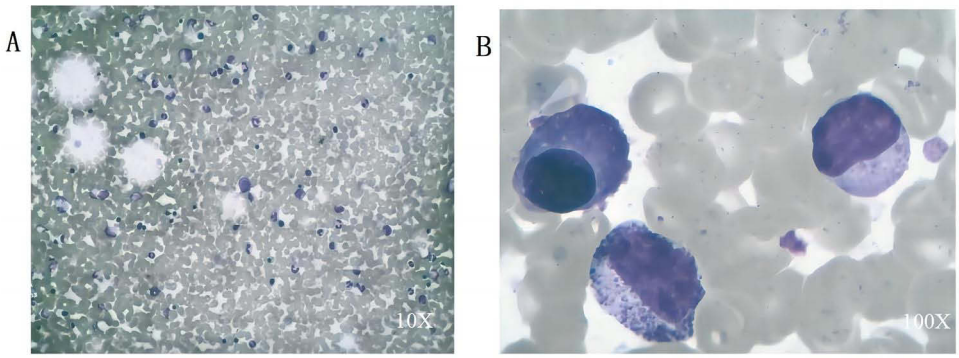

Figure 1 At the time of the MM diagnosis, the bone marrow was as above. (**A**) x10 magnification; (**B**) x100 magnification.

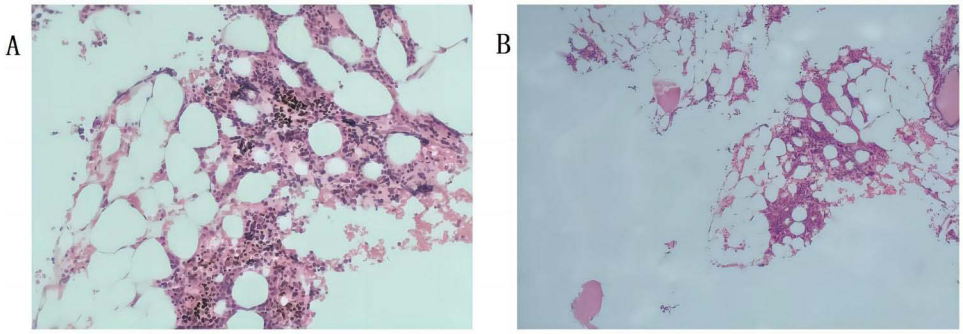

Figure 2 Bone marrow biopsy Immunohistochemistry: CD34 small vessel (+), occasional (+); CD11+ 17 occasional (+); CD61 megakaryocytes (+), sporadic (+); CD3 less (+); CD138 small cluster (+); MPO multiple (+); E-cad multicluster (+).

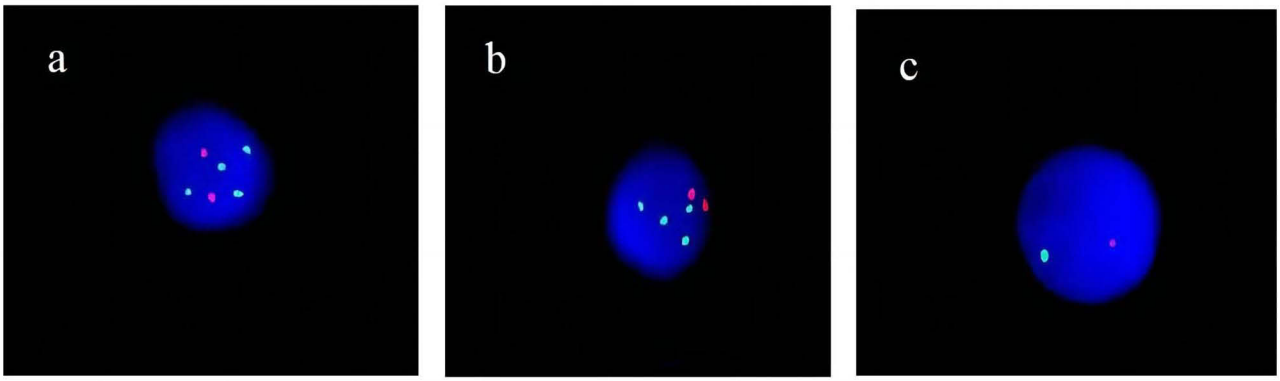

Figure 3 FISH: 1q21/1p32 (**a**), 13q14.3/(**b**), and 13q34 RB1(13q14) (**c**) genes are positive.

(+). Cytogenetic analysis revealed a normal female karyotype of 46 XX, while the mutation gene suggest that 1q21/1p32 13q14.3/13q34 RB1(13q14) genes are positive (Figure 3). Therefore, the patient was diagnosed with MM (IgA-λ DS Ia, ISS I, R-ISS I) (Durie-Salmon, DS; International Staging System, ISS; Revised International Staging System, R-ISS). He refused the associated treatment for SE (red blood cells were removed by apheresis), and now he is still asymptomatic.

Discussion

MM is a plasma cell monoclonal disorder derived from differentiated lymphoid B cells that causes uncontrolled growth, destructive bone lesions, kidney damage, anemia, and hypercalcemia. In contrast to anemia, the presence of polycythemia in patients with MM is rare, with only a few cases reported in the last 70 years.[7] In this patient, the concomitant polycythemia disappeared after myeloma treatment,[6–8] which may be related to the reduction of monoclonal light chain in the renal tubules.

Based on the etiology, erythrocytosis can be classified as polycythemia vera (PV), SE, and idiopathic polycythemia (IE).[9] The differential diagnosis of secondary polycythemia is extensive, but the most common etiology is chronic hypoxia.[10,11] Chronic hypoxia causing secondary polyred cell disease may be associated with multiple factors such as smoking, lung disease, living at high altitude, carbon monoxide exposure, hemoglobinopathy and sleep apnea.[7] After detailed history inquiry and examination, our patient quickly excluded the above reasons. The compensatory increase of erythropoietin (EPO) caused by various hypoxia, the increase of pathological EPO production and the increase of exogenous EPO production. EPO is composed of 165 amino acid residues, and its gene is located in the long arm 22 region of chromosome. The main function of EPO is to promote the proliferation, differentiation of late erythroid progenitors and their maturation, accelerate the release of reticulocytes and enhance the activity of antioxidant enzymes on the erythrocyte membrane.[12] It has been reported that SE of various reasons is related to the increase of EPO level.[13] The decrease of EPO level supports the diagnosis of PV, and the increase of EPO level is mostly SE.[14] In particular, under the negative condition of the JAK2 V617F mutation, EPO level is of great value in distinguishing PV from SE. This patient had a monoclonal immunoglobulin and 5.2% mature plasma cells, with occasional deformed nucleoplasma cell myeloid image, which was considered as focal onset of multiple myeloma lines. According to the diagnostic criteria of MM, the patient was diagnosis with MM, but no anemia occurred. In contrast, it showed increased RBCs from the currently known chronic bone marrow. As the results of genetic testing for proliferative tumors shown that, no mutations were detected in the JAK2-V617F gene, the JAK2 gene exons 12~15, the MPL gene, the CALR gene or exons, so polycythemia vera can be excluded. Polycythaemia caused by EPO-secreted tumors (e g, intracranial hemangioblastoma, hepatocellular carcinoma, renal cell carcinoma) was also ruled out by imaging studies. After a comprehensive systematic evaluation, the cause of polycythemia in this patient has not been clarified. We speculate that there may be an association between polycythemia and multiple myeloma in this patient.

The co-existence of polycythemia and multiple myeloma is rare, and some mechanisms may explain the association: ① Dominant or subclinical renal injury caused by monoclonal light chains in the renal tubules can lead to local hypoxia

and increased EPO generation.[8] Under normal oxygen tension, HIF-alfa is hydroxylated by EGLN 1 (PHD 2) and is targeted by VHL for ubiquitin-mediated degradation, resulting in the nonproduction of EPO.[15] Under hypoxia, the hydroxylase activity is inhibited. Thus, the EGLN 1 protein cannot hydroxylate HIF-alfa, thus enabling it to escape recognition and subsequent degradation by the VHL protein.[15] ② In recent years, it has been found that some tumors that do not originate from endocrine tissue can secrete one or more hormones and cause the corresponding excessive hormone excessive symptoms, which is called ectopic (source) hormone syndrome or associated hormone syndrome. Ectopic (source) erythropoietin or erythropoietin-like substances can lead to erythrocytosis.[16] In clinical practice, the appearance of this ectopic (source) hormone phenomenon can precede the symptoms of the tumor itself, which can be used as a diagnostic clue. ③ Other researchers have proposed that some tumors produce EPO or its predecessor,[17] which stimulates bone marrow hematopoietic tissue to produce more red blood cells, which requires further studies to confirm. ④ Notably, both elevated and decreased EPO levels have been reported in myeloma patients relative to the degree of anemia and renal dysfunction. Tumor cells (tumor polycythemia) have been described in uterine leiomyoma, hemangioblastoma, pheochromocytoma and so on.[7] Since malignant plasma cells do not produce EPO, this mechanism is unlikely to occur in polycythaemia-associated myeloma. ⑤The recently described TEMPI syndrome (Telangiectase, Erythrocytosis with elevation of erythropoietin, Monoclonal gammopathy, Perirenal effusion and Intrapulmonary shunting) may provide clues to the pathogenesis of polycythemia complicated with multiple myeloma.[18] Our patient was not eligible for the diagnosis of TEMPI syndrome owing to he did not have peri-renal effusion, telangiectasia and intrapulmonary shunt. However, polycythemia owing to exogenous EPO produced by myeloma cells is unlikely. His serum EPO levels were indeed elevated, and it could be speculated that, as with TEMPI syndrome, his erythrocytosis was due to monoclonal immunoglobulin increased HIF-1 α function and increased EPO production. Further studies may potentially clarify the association between MM and polycythemia.

Conclusion

MM incorporation of SE is rare, but the specific link between them is unclear. As the disease progresses, all patients eventually develop symptoms of anemia, which may be associated with high tumor burden, destruction of normal hematopoietic tissue in the bone marrow, or reduced generation of endogenous EPO. Therefore, we should closely monitor the condition of these patients, and need timely treatment once the patient has the treatment indication.

Ethics and Consent

The patient provided written informed consent for publication of this case report. This study is not required to obtain approval from the Ethics Committee of the First Affiliated Hospital for Jishou University.

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Disclosure

The authors declare that no conflict of interest exists in this work.

References

1. Wang S, Xu L, Feng J, et al. Prevalence and incidence of multiple myeloma in urban area in china: a national population-based analysis. *Front Oncol*. 2020;9:1513. doi:10.3389/fonc.2019.01513
2. Liu W, Liu J, Song Y, et al. Union for China leukemia investigators of the Chinese society of clinical oncology, union for China lymphoma investigators of the Chinese society of clinical oncology. Mortality of lymphoma and myeloma in China, 2004–2017: an observational study. *J Hematol Oncol*. 2019;12(1):22. doi:10.1186/s13045-019-0706-9
3. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364(11):1046–1060. doi:10.1056/NEJMra1011442
4. Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and management of multiple myeloma: a review. *JAMA*. 2022;327(5):464–477. doi:10.1001/jama.2022.0003
5. Pearson TC. Diagnosis and classification of erythrocytoses and thrombocytoses. *Baillieres Clin Haematol*. 1998;11(4):695–720. doi:10.1016/s0950-3536(98)80035-8

6. Lee SG, Lim G, Cho SY, et al. JAK2 mutation-negative secondary erythrocytosis in smoldering plasma cell myeloma: a case study and review of the literature. *Acta Haematol*. 2011;126(3):169–171. doi:10.1159/000328996
7. Hutchison EJ, Taverna JA, Yu Q, et al. Polycythaemia: an unusual presentation of multiple myeloma. *BMJ Case Rep*. 2016;2016:bcr2016216686. doi:10.1136/bcr-2016-216686
8. Yoon H-J, Kyung Baek S, Lee W-I, et al. {JAK2} mutation-negative secondary erythrocytosis in multiple myeloma: a case report follow up. *Exp. Hematol*. 2013;41:S46. doi:10.1016/j.exphem.2013.05.181
9. Finazzi G, Gregg XT, Barbui T, et al. Idiopathic erythrocytosis and other non-clonal polycythemias. *Best Pract Res Clin Haematol*. 2006;19 (3):471–482. doi:10.1016/j.beha.2005.07.006
10. Raaijmakers NJ, Bokma AHF, Eggen GG, et al. An unhealthy blush - secondary erythrocytosis due to waterpipe smoking. *Neth J Med*. 2020;78 (4):202–205.
11. Keohane C, McMullin MF, Harrison C. The diagnosis and management of erythrocytosis. *BMJ*. 2013;347:f6667. doi:10.1136/bmj.f6667
12. Lombardero M, Kovacs K, Scheithauer BW. Erythropoietin: a hormone with multiple functions. *Pathobiology*. 2011;78(1):41–53. doi:10.1159/000322975
13. Oymak O, Demiroğlu H, Akpolat T, et al. Increased erythropoietin response to venesection in erythrocytosic renal transplant patients. *Int Urol Nephrol*. 1995;27(2):223–227. doi:10.1007/BF02551324
14. Wille K, Sadjadian P, Griesshammer M. Differenzialdiagnose der Erythrozytose-Ursachen und klinische Bedeutung [Differential Diagnosis of Erythrocytosis-Background and Clinical Relevance]. *Dtsch Med Wochenschr*. 2019;144(2):128–135. German. doi:10.1055/a-0739-8340
15. Wilson R, Syed N, Shah P. Erythrocytosis due to PHD2 mutations: a review of clinical presentation, diagnosis, and genetics. *Case Rep Hematol*. 2016;2016:6373706. doi:10.1155/2016/6373706
16. Staszewski H. Hematological paraneoplastic syndromes. *Semin Oncol*. 1997;24(3):329–333.
17. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. *Leukemia*. 2009;23(5):834–844. doi:10.1038/leu.2009.54
18. Sykes DB, Schroyens W, O'Connell C. The TEMPI syndrome--a novel multisystem disease. *N Engl J Med*. 2011;365(5):475–477. doi:10.1056/NEJMc1106670