Clinical Case Report

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A case report of cerebral infarction caused by polycythemia vera

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Abstract

Rationale: Polycythemia vera (PV) is a cloned erythrocytotic disease manifested by high proliferation and apoptosis in the bone marrow. The clinical symptoms of PV are occult. In practice, patients with cerebral infarction caused by PV are prone to misdiagnosis and missed diagnosis.

Patient concerns: Here, we report a misdiagnosis of PV leading to cerebral infarction. The patient was a middle-aged woman who was diagnosed with acute cerebral infarction in the outpatient hospital. After treatment, the patient still had left hemiplegia, dizziness and other symptoms and was admitted to our hospital.

Diagnosis: We did not find sufficient evidence of atherosclerotic processes in the brain infarction. However, the patient's signs and laboratory examination indicated a high suspicion of PV. A series of further examinations confirmed the final diagnosis.

Interventions: Bone marrow suppression medications (oral hydroxyurea and subcutaneous injection of interferon) were given and subsequent prevention of cerebral infarction was implemented.

Outcomes: Routine blood reexamination was normal and no further cerebral infarction occurred.

Lessons: Patients with acute cerebral infarction should be considered comprehensively, and rare causes should not be ignored. It is crucial that PV be diagnosed and treated as early as possible, which can significantly improve the prognosis of patients.

Abbreviations: PV = polycythemia vera, RBC = red blood cell, WBC = white blood cell.

Keywords: cerebral infarction, polycythemia vera

1. Introduction

Polycythemia vera (PV) is characterized by increased red blood cells (RBCs) in peripheral blood, mostly due to cancer gene mutations, such as the JAK2 V617F mutation.[1] PV is easily ignored at an early stage because of occult clinical symptoms. It can cause thrombotic diseases,[2] especially cerebral infarction. A previous study revealed that in more than 15% of patients, PV is first manifested as cerebral infarction.[3] Based on the characteristics of PV, it is often missed as routine cerebral infarction. Here, we report our case of PV. This study was approved by the Medical Research Ethics Committee of Dongfang Hospital, Beijing University of Chinese Medicine. The patient provided informed consent for publication of the case.

2. Case report

The patient is a 64-year-old female who was admitted to our hospital on March 28, 2018. The patient complained of left limb dyskinesia and dizziness for more than 4 months. Magnetic resonance imaging (MRI) showed hyperintensity lesions on the right side of the basal ganglia and lateral ventricle (Fig. 1), suggesting the diagnosis of acute cerebral infarction. After treatment, the patient's clinical symptoms did not resolve. The patient had no history of risk factors such as hypertension, hyperlipidemia, diabetes, coronary heart disease, or smoking. No history of trauma, poisoning, surgery, blood transfusion, infection, or family history of heredity was found. The results of the physical examination were as follows: temperature (T): 36.4°C, pulse rate (P): 74 times/min, respiration (R): 20 times/min, and blood pressure (BP): 120/80 mmHg; the face and hands were obviously red, and the superficial lymph nodes throughout the body were not enlarged. Cognitive function was normal. The left side of the upper limb muscle was III+, the left side of the lower limb muscle was level IV, the right upper limb muscle was level V, and the right side of the lower limb muscle was level V. The left muscle tension was slightly lower, and the right muscle tension was normal. The Babinski sign was positive on the left. The results of auxiliary examination on March 29, 2018, were as follows: whole blood cell analysis: 18.65 *10^{e9}/L; white blood cell (WBC) count: lymphocyte percentage, 13.1%; neutrophil percentage, 78.3%; RBC count, 5.8 *10e12/L; hemoglobin content, 182 g/L; RBCs, 55.2%; platelet count, 409 *10e9/L;

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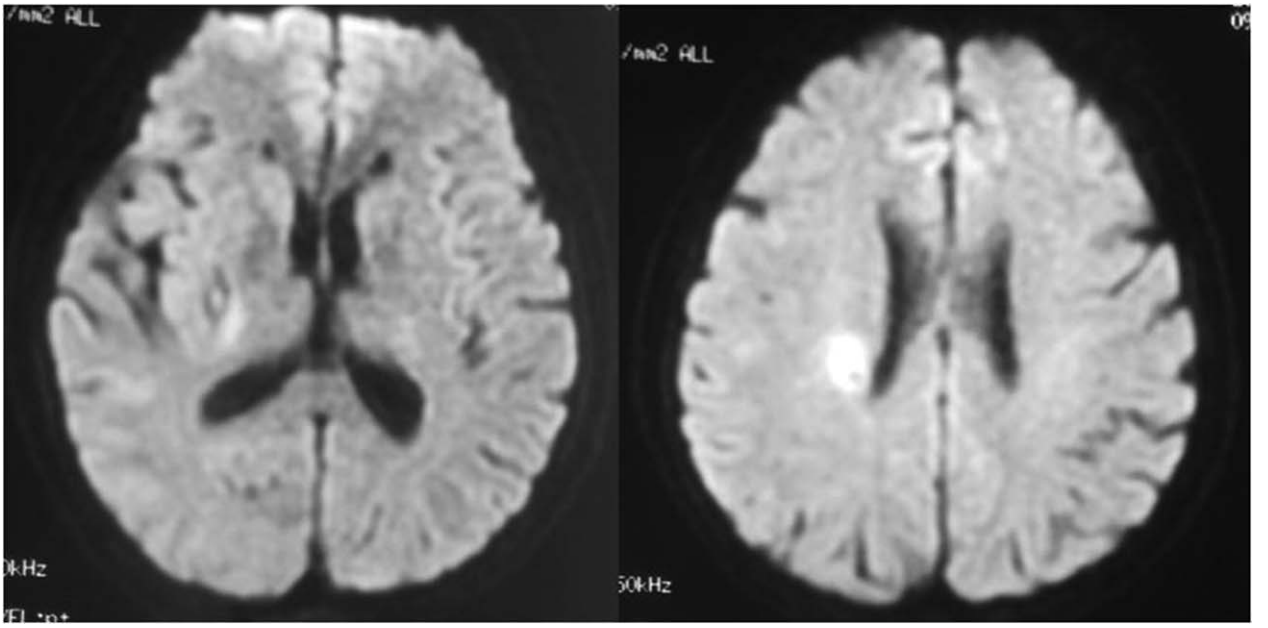

Figure 1. MRI shows acute cerebral infarction in right side of basal ganglia and lateral ventricle. MRI = magnetic resonance imaging.

monocyte absolute value, 0.63*10e9/L; eosinophil absolute value, 0.72*10e9/L; basophil absolute value, 0.24*10e9/L; and basophil percentage, 1.3%. The absolute value of neutrophils was 14.61*10e9/L and the platelet volume was 0.44%. The coagulation 4 + D dimer measures were an activated partial prothrombin time of 27.7 seconds, prothrombin ratio of 1.07, percentage prothrombin activity of 103.9%, thrombin officially standardized ratio of 1.07, fibrinogen coagulation time of 7.9 seconds, thrombin setting time of 19.7 seconds, D-dimer (quantitative) of 0.22 ug/mL, prothrombin time of 12.3 seconds, and fibrinogen content of 2.36 g/L. There was no obvious abnormality among the results for the remaining blood sampling: abdominal ultrasonography, large spleen; cardiac ultrasonography, 24-hour dynamic electrocardiogram: no obvious abnormality; intracranial and extracranial vascular ultrasound examination: no stenosis or unstable plaque was observed.

In summary, we strongly suspected that the cause of cerebral infarction in this patient was PV. Bone marrow puncture was performed, and related genes were detected by bone marrow extraction and hematopoiesis. The results of the bone marrow image examination report on April 9, 2018, were as follows: 1. grade III bone marrow hyperplasia, with 63% granule system, 30% red system, and 2.1:1 granule/red system; 2. granule system: hyperplasia was active; early larval granulocytes could be observed; 3. red system: hyperplasia was active; early and late larval erythrocytes could be observed, with a slightly higher proportion of late larval erythrocytes; mature RBCs had normal morphology; 4. the proportion of lymphocytes was low, and the morphology was normal; and 5. there were 37 megakaryocytes and many platelets in the whole tablet. The conclusion was that bone marrow hyperplasia was active. The bone marrow pathology report (Fig. 2: bone marrow) showed that bone

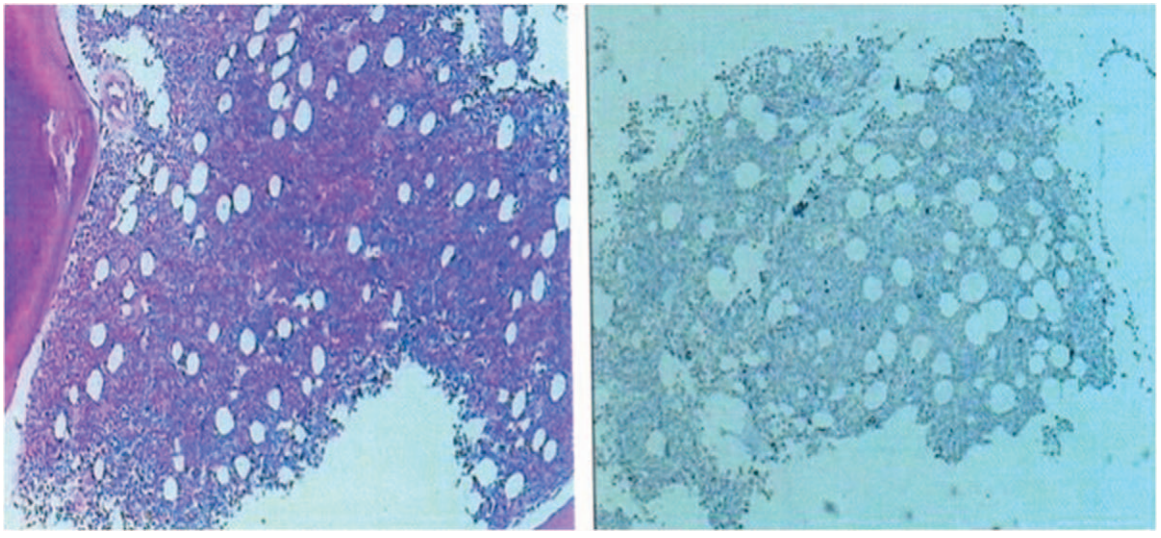

Figure 2. Bone marrow pathology shows hyperplasia of bone marrow.

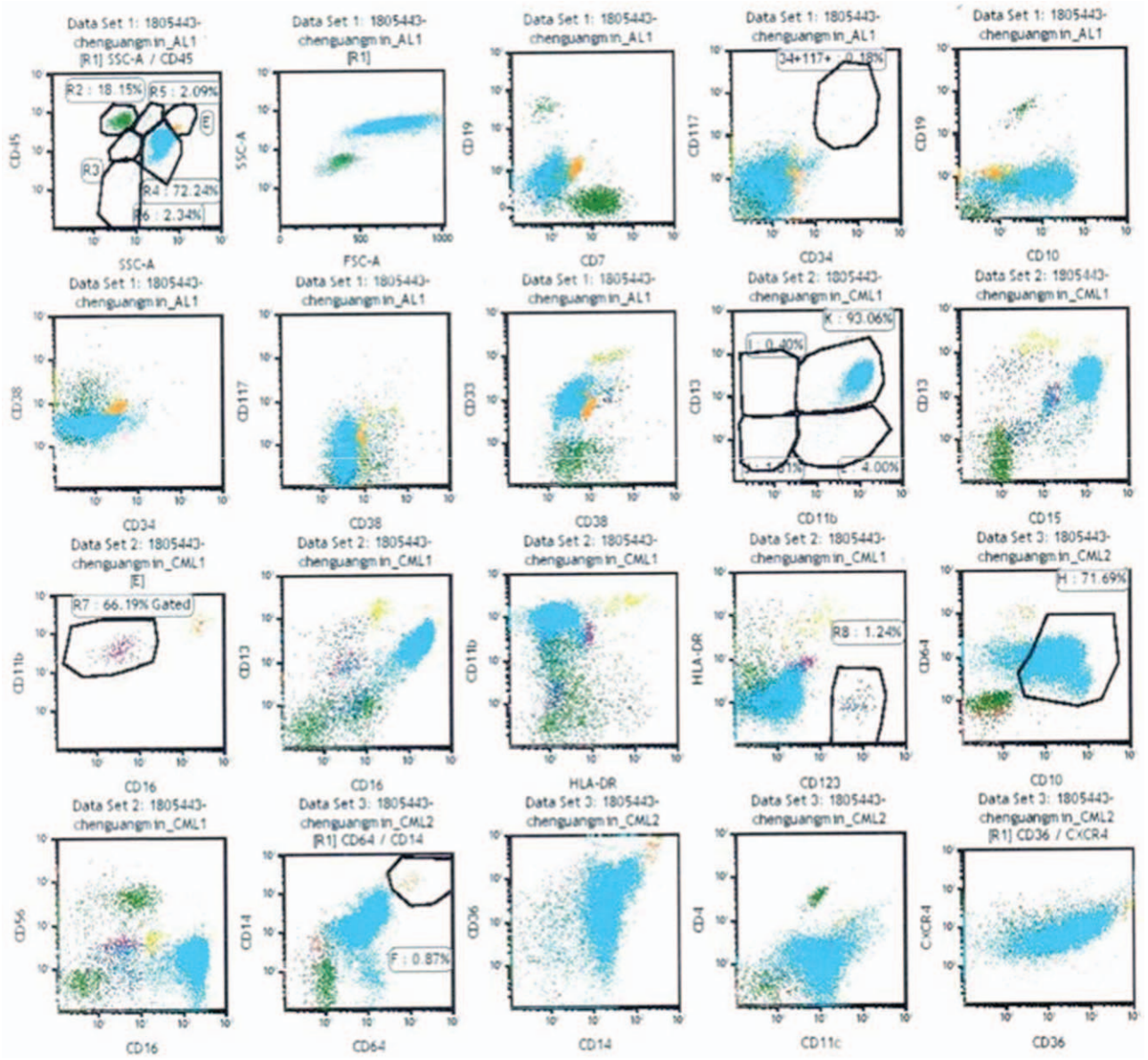

Figure 3. Immunotyping shows increased CD64 expression and abnormal phenotype.

marrow tissue was observed between bone trabeculae attached to fibrous cartilage, red pulp was relatively increased, yellow pulp was relatively decreased, the red and white system was common, and megakaryocytes were easy to see. Immunohistochemical expression on April 11, 2018, was as follows: CD38 (+), CD138 (+), CD31 (+), CD34 (+), MPO (+), TdT (+), CD235 (+), Ki67 (+ > 5%), P53 (+), and CD68 (+). The PCR gene test results were as follows: jak2-617 site V/F mutation (+), genotype G and T hybrid, CALR gene 9- exon mutation (-), MPLW515L/K mutation (-), JAK2-exon sequence mutation of gene 12 (-), and Quantitative rt-pcr (-) of bcr-abl (P210, P230, P190, and variant) fusion genes. The immunohistotypic report (Fig. 3) on April 13, 2018, was as follows: lymphocytes (P2) accounted for 18.15%, with a normal proportion, mainly mature T lymphocytes. Myeloid cells (P4) accounted for 72.24%, the proportion of CD10+ mature granulocytes was normal, the expression of CD64 was enhanced, and the phenotype was abnormal. Monocytes accounted for 0.87%, and no abnormal phenotype was observed. The proportion of nuclear red cells was reduced by 2.34%. CD34+ and CD117+ immature myeloid cells accounted for 0.18%, which was not high. Basophils accounted for 1.24% and acidophils accounted for 2.23%. Chromosome examination (G banding) (Fig. 4) on April 17, 2018, revealed the following: 46, XX [20]. In summary, the clinical diagnosis was clearly PV.

Treatment began on April 18, 2018, with aspirin enteric-coated metformin hydrochloride in 0.1 g Po Qd antiplatelet aggregation, on the basis of joint oral hydroxyurea; there was frequent adjustment of the dose of 0.5 g Po Bid, 0.5 g Po dar, 1 g Po Bid bone marrow suppression and sodium bicarbonate, and 0.5 g Po dar alkalized urine. The May 9, 2018, review of complete blood analysis revealed the following: WBC count, 7.90 *10e9/L; neutrophil absolute value, 5.55 *10e9/L; lymphocyte percentage, 20.5%; neutrophil percentage, 70.2%; RBC count, 5.71 *10e12/L; hemoglobin content, 177 g/L; RBCs, 53.10%; and platelet count, 122 *10e9/L. Giving the patient a larger oral dose of hydroxyurea was considered; however, RBC and hemoglobin

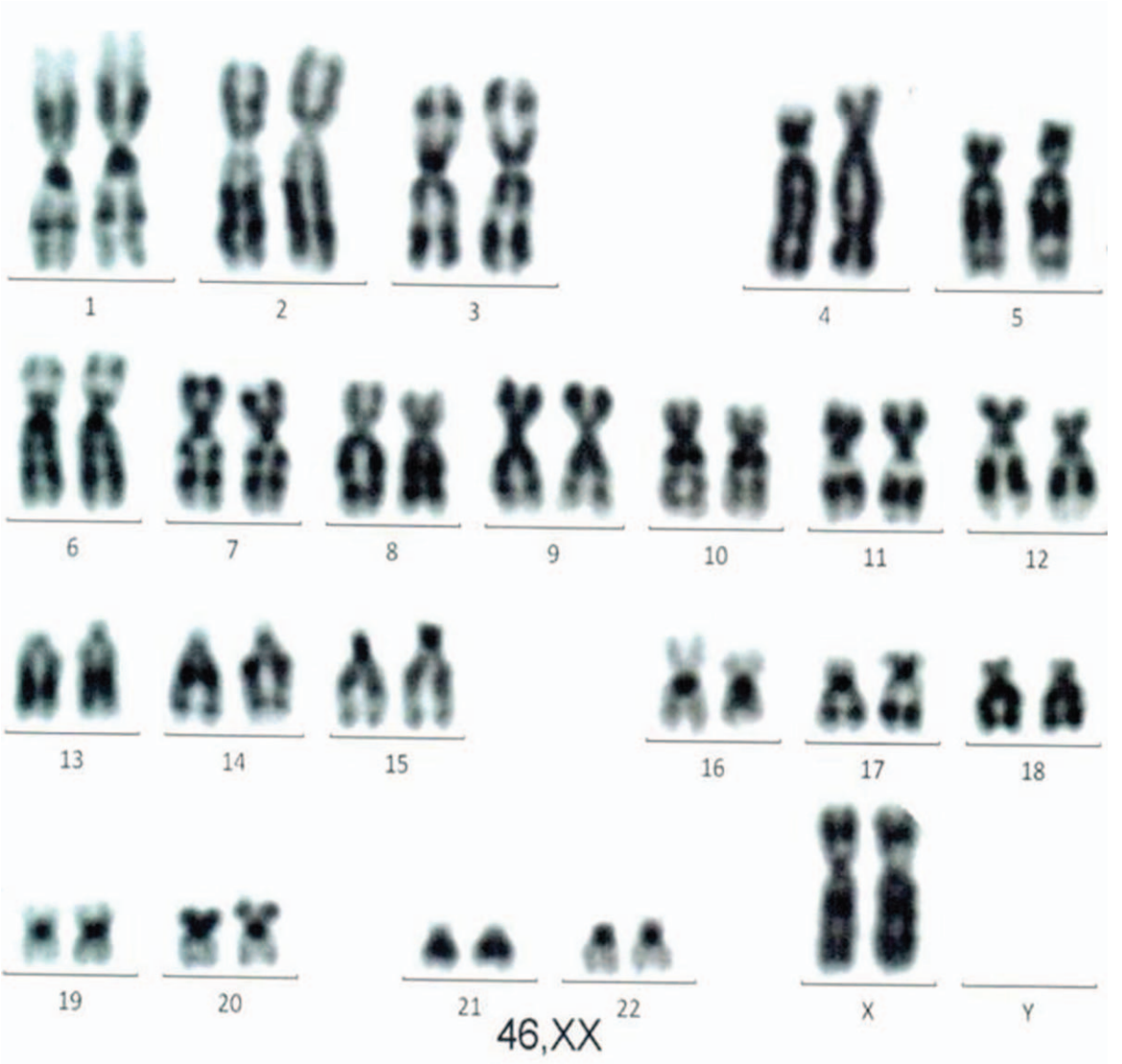

Figure 4. Chromosome examination (G band) shows 46, XX[20] abnormality.

values still were not normal, and there were significantly fewer platelets. Therefore, on May 10, 2018, oral hydroxyurea was stopped and changed to 2 bα human recombinant interferon injections; pseudomonas (3 million units: 1 mL) by subcutaneous injection was reduced from 3 times per week to 2 times per week. The results of the June 11, 2018, review of complete blood analysis were as follows: WBC count, 8.29*10e9/L; neutrophil absolute value, 5.36*10e9/L; lymphocyte percentage, 29.6%; neutrophil percentage, 64.6%; RBC count, 4.69 *10e12 at 11:45/L; hemoglobin content, 145 g/L; RBCs, 43.2%; and platelet count, 120*109/L. The patient was discharged from the hospital after improvement and was instructed to continue regular subcutaneous injection of interferon and routine blood evaluation.

3. Discussion

Cerebral infarction is a serious threat to human health, and the most common cause is atherosclerosis; however, some more rare etiologies can also lead to brain tissue ischemia and hypoxia, such as arteritis, amyloidosis, erythrocytosis, and thrombocytopenic purpura. PV refers to the quantity of the unit volume of RBCs, and hemoglobin is higher than the reference value range: the adult male RBC count is > 6.0 * 10e12/L with hemoglobin > 165 g/L; the adult female RBC count is >5.5 * 10e12/L with hemoglobin >160 g/L. Erythrocytopenia is classified according to relativity and absoluteness. Relativity refers to the capacity to reduce plasma, intensifying the RBCs' relative increase in capacity, resulting in severe vomiting, diarrhea, excessive sweating, burns, diabetes insipidus, thyroid function hyperfunction, and diabetic ketoacidosis. The increase in absoluteness can be divided into 2 categories: primary and secondary. Idiopathic patients can also be divided into congenital and acquired. Congenital primary erythrocytopenia presents as increased erythrocyte production due to EPO receptor gene mutation. PV, a primary disease of growth in the number of RBCs, is a type of erythrocytosis hyperplastic bone marrow tumor currently thought to be caused by JAK pluripotent hematopoietic stem cells, specifically with the V617F mutation, as thrombotic events occur. Some scholars[4] analyzed the clinical characteristics of 70 patients with PV and found that 22.68% presented with cerebral infarction as the first symptom.

Some scholars have found that the pathogenesis of PV is related to the reduction of cerebral blood flow and abnormal platelet function caused by increased blood viscosity.[5] A large number of abnormal RBCs infiltrated the arterial wall for a long time in PV patients, resulting in increased blood viscosity, followed by a slower blood flow rate, leading to cerebral vascular obstruction, cerebral ischemia, and hypoxic necrosis. PV leads to cerebral infarction in the common locations of the basal ganglia, radiated corona, cerebellum, and so on.; it is also observed in the cortex, but large area infarctions are relatively rare.[6] Due to its occult character, the clinical symptoms are not typical, and early recognition is not easy. For this patient, after cerebral infarction occurred, the possibility of PV was not considered initially; therefore, there was a failure to treat the primary disease in a timely manner, which may lead to the occurrence of cerebral infarction and relapse.

At present, studies[7] have found that there is a certain relationship between leukocyte count and thrombosis and thrombosis recurrence. Data from PV patients have shown that the risk of thrombosis increased when the WBC count is $>9.5^{*}10$ e9/L. A WBC count $>12.4^{*}10$ e9/L is an independent risk factor for thrombosis recurrence in patients under the age of 60 following the first thrombus. Bonicelli et al[8] proposed that in patients with PV, the survival rate would decrease when the leukocyte count was $>13^{*}10$ e9/L.

Because most PV patients have V617F mutations in the JAK2 gene, those with a high clinical suspicion of PV should not only be examined for hematology and bone marrow but also be tested for genes to further confirm the diagnosis. JAK2 V617F mutation-positive patients with PV have a single nucleotide mutation, and mutations of guanine (G) and thymine (T) make the in situ valine missense coding for phenylalanine, resulting in JAK2 kinase activity, promoting self-phosphorylated activation, further activating downstream signal transduction pathways, and causing the endogenous cloned generation of RBCs.[9]

The patient was an elderly female patient who was admitted with cerebral infarction and was found to have obvious redness on her face and hands and splenomegaly on abdominal ultrasound. The imaging findings were consistent with the characteristics of PV secondary to cerebral infarction. After admission, the patient's blood routine indicated that hemoglobin was 182 g/L and all 3 lines (WBCs, RBCs, and platelets) were increased. A bone marrow examination revealed hyperplasia of the 3 lineages. Gene testing found that the JAK2 V617F mutation was positive, while the bcr-abl gene, CALR gene, and MPL gene were negative. According to the 2014 revision and recommendation criteria,[10,11] the clinical manifestations and laboratory examination results of this patient fulfilled the diagnostic criteria of PV.

For the treatment of PV combined with cerebral infarction, the current commonly used treatment method is control of vascular disease risk factors. Small doses of aspirin (0.1 g/d) are administered; patients with bleeding, stomach intolerance or other contraindications are excluded. There is also a blood test, and patients with hydroxyl urea resistance or intolerance to hydroxyl urea can be treated with artificial interferon (<65 years old) and baixiao tablets (>65 years old). The standard value is an RBC count below 45%.[1,12] The patient was finally effectively treated by subcutaneous injection with interferon. Routine blood testing is back to normal, and no thrombotic events have recurred.

This case suggests the following: if a patient presents with red and purple skin color and their RBC volume is increased significantly, we should pay special attention to possible PV. In cases of thrombosis, the possibility of PV should be highly suspected, further bone marrow-related examination should be performed,[13] and JAK2 gene testing should be performed if conditions permit. Patients with acute cerebral infarction should be considered comprehensively, and rare causes of infarction should not be ignored. Early diagnosis and treatment can significantly improve the prognosis of patients.

Author contributions

Data curation: Fang Gao.
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Writing – original draft: Shan Ren.
Writing – review & editing: Zhiqun Wang.

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