

TEMPI Syndrome: A Rare Plasma Cell Paraneoplastic Syndrome That Mainly Characterized by Telangiectasias, Monoclonal Gammopathy, Elevated Erythropoietin Level and Erythrocytosis

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TEMPI syndrome; Telangiectasias; Monoclonal gammopathy; Erythrocytosis; Intrapulmonary shunting

1. Abstract

TEMPI syndrome is a rare plasma cell paraneoplastic syndrome that mainly manifests as telangiectasias, monoclonal gammopathy, elevated erythropoietin levels and erythrocytosis, perinephric fluid collection and intrapulmonary shunting. To our knowledge, only 26 cases have been reported worldwide, and 4 cases have been reported in mainland China. The objective of this clinical case report was to highlight this unusual syndrome to avoid incorrect diagnosis. We herein present a case of a 69-year-old man with a 1-year history of erythrocytosis. In addition to erythrocytosis, he had telangiectasias, IgG-lambda monoclonal gammopathy, and intrapulmonary shunting. We believe that this is a rare case that is consistent with TEMPI syndrome.

2. Introduction

TEMPI syndrome is a rare multisystem disease characterized by 5 main features: (1) telangiectasias; (2) elevated erythropoietin levels and erythrocytosis; (3) monoclonal gammopathy; (4) perinephric fluid collection; and (5) intrapulmonary shunting. It was first described in 2011 by Sykes et al. in the *New England Journal of Medicine* [1], and like POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy or M proteins, and skin abnormalities), is considered “plasma cell neoplasm with associated paraneoplastic syndrome” in the World

Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, 4th edition [2]. As of June 2021, a total of 26 patients with TEMPI syndrome have been reported worldwide, many of whom have been described in individual case reports [3-13], with only four cases from mainland China [12,13]. Due to the complexity and rarity of the syndrome, the diagnosis may be missed in some patients. TEMPI syndrome may also be misdiagnosed as polycythemia vera and/or monoclonal gammopathy of unknown significance. According to reports, TEMPI syndrome can be treated as a plasma cell diseases, so timely diagnosis is very important. In this case report, we describe a TEMPI patient with polycythemia as the main complaint, hoping to provide new inspiration for clinicians.

3. Case Report

This case report was in accordance with the principles of the Declaration of Helsinki. The study procedures were approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University, China. Informed consent was obtained from the patient and his daughter for the publication of this case report and the accompanying images. A 69-year-old male nonsmoker presented to our hospital with polycythemia for 1 year. He reported no headache, dizziness, fever, cough, or chest tightness. His medical history included hypertension, diabetes, and

cerebral infarction. On physical examination, the patient was afebrile. His heart rate was 76 beats per minute, blood pressure was 126/92 mm Hg, respiratory rate was 18 breaths per minute, and oxygen saturation was 94% while he was breathing ambient air. Multiple flaky telangiectasias were seen on the front chest skin (Figure 1), without other obvious positive signs. The patient underwent an extensive laboratory evaluation. The complete blood count values were as follows: erythrocyte count, $5.92 \times 10^{12}/L$ (normal reference value $4.3\text{--}5.8 \times 10^9/L$); hemoglobin, 206 g/L (normal reference value 133.0–175.0 g/L); HCT, 58.2% (normal reference value 40–50%); leukocyte count, $6.6 \times 10^9/L$ (normal reference value $3.5\text{--}9.5 \times 10^9/L$); and platelet count, $218 \times 10^9/L$ (normal reference value $125\text{--}350 \times 10^9/L$). Further investigation revealed an elevated erythropoietin level of 716.3 mIU/mL (normal reference value 2.59–18.5 mIU/mL). Hepatic function, renal function, serum electrolytes, tumor markers and a panel of antinuclear antibodies (ANAs) were normal. Urinalysis was unremarkable. The hypothalamic-pituitary-adrenal axis and thyroid function were also normal. Ultrasound of the abdomen, veins of both lower extremities and the heart showed no obvious abnormalities. Ultrasound of the arteries of both lower extremities showed atherosclerosis and plaque formation in both lower extremities. Chest computed tomography and nerve conduction test findings were normal. Serum protein electrophoresis revealed a monoclonal band, and

immunofixation electrophoresis revealed IgG-lambda monoclonal immunoglobulinemia. Arterial blood gas revealed pH 7.45, pCO_2 36 mmHg, PO_2 76 mmHg (normal range: 80 to 100 mmHg), O_2 saturation 93.9% on room air, and hematocrit 52%. Bone marrow cytology of the iliac bone showed active bone marrow hyperplasia, suspicious for polycythemia. Flow cytometry showed that the proportion of myeloid blasts was not high, the phenotype of T lymphocytes was not significantly abnormal, and there were no obvious abnormal monoclonal B cells and plasma cells. The BCR/ABL1 mixed qualitative test was negative. Bone marrow pathology showed that under the condition of low bone marrow hyperplasia, granular red giant trilineage cells were seen with an increased proportion of erythroid cells, no obvious abnormalities in the morphology and number of megakaryocytes, scattered small lymphocytes or focal distributions, and a small number of plasma cells scattered or distributed in small clusters. MPN-related mutations, including JAK2, MPL and CALR, were negative. Bone marrow cytology of the sternum showed that plasma cells accounted for 2% of nucleated cells. Immunophenotype showed abnormal monoclonal plasma cells that accounted for 1.9% of nucleated cells, expressing CD38, CD56, CD138, CD27, CD28, and cLambda and not expressing cKappa. Based on these findings, we diagnosed the patient with TEMPI syndrome. Unfortunately, this patient refused further treatment and was thus discharged.



Figure 1. Telangiectasias were the most prominent on the skin on the front of the chest.

4. Discussion

TEMPI syndrome is a rare and recently described multisystem disorder that is thought to be caused by clonal plasma cells and monoclonal proteins. The early diagnosis of TEMPI syndrome is

essential because therapies targeting the underlying plasma cells can lead to a dramatic response. Bortezomib-based chemotherapy, daratumumab monotherapy, and autologous hematopoietic stem cell transplantation can result in the reversal of most man-

ifestations and prolonged survival. Nevertheless, the diagnosis of TEMPI syndrome remains a very great challenge due to its rarity and the complexity of clinical presentations. TEMPI syndrome is often misdiagnosed as other causes of erythrocytosis, resulting in a delayed diagnosis and further clinical deterioration, such as life-threatening pulmonary compromise [14]. The pathogenesis of TEMPI syndrome is still unclear. Sun et al. reported that the expression of the macrophage migration inhibitory factor (MIF) gene was significantly upregulated in 3 patients with TEMPI syndrome. The level of serum MIF in one patient with TEMPI syndrome was significantly decreased after treatment with plasma cell-directed therapy (VCD regimen). Their study provides insights on the genomic landscape and suggests that MIF plays a role in the pathophysiology of TEMPI syndrome [13]. Based on the patient characteristics observed to date, David B. Sykes et al. have proposed diagnostic criteria that include three major criteria (telangiectasias, elevated erythropoietin and erythrocytosis, and monoclonal gammopathy), two minor criteria (perinephric fluid and intrapulmonary shunting) and other conditions (venous thrombosis) [12]. Among these factors, pulmonary shunting is accompanied by a decrease in resting oxygen saturation. Our patient's blood oxygen saturation was reduced without other causes of this condition, so we believe that it was caused by an intrapulmonary shunt. Our patient presented with four of the five hallmark characteristics of TEMPI syndrome, including telangiectasias, erythrocytosis, monoclonal gammopathy, and intrapulmonary shunting. Our patient lacked perinephric fluid collection, which is common in patients with TEMPI syndrome. This patient requires close follow-up, and it is possible that as the disease progresses, perirenal effusion may appear. In our patient, the initial iliac bone puncture did not find monoclonal plasma cells, which was not consistent with monoclonal gammopathy of undetermined significance. However, we considered TEMPI syndrome as a possible diagnosis, and we performed a sternal puncture. Further flow cytometry provided evidence of plasma cell clonality. TEMPI syndrome is extremely rare and complex. It is a monoclonal plasma cell disorder that causes a paraneoplastic syndrome, but the specific pathogenesis is still unclear. The aim of the present case report was to present the clinical features of TEMPI syndrome, highlighting the differential diagnosis. Patients with long-term and unexplained polycythemia accompanied by elevated EPO and monoclonal immunoglobulin should be considered for TEMPI syndrome, carefully checked for the presence of telangiectasia, and imaging tests should be performed to assess perinephric effusion. Doctors are like detectives. In the process of disease diagnosis and treatment, each detail cannot be overlooked, the cause of the disease can be determined, and the diagnosis can be made through the tracking of "clues". By reading more books and the scientific literature, a doctor's knowledge can become more comprehensive, and the nature of diseases can be discovered more rapidly.

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