TEMPI syndrome in a 57-year-old man: a case report

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European Journal of Medical Case Reports
Volume 5(9):274–278
https://doi.org/10.24911/ejmcr/173-1622838555

ABSTRACT

Background: The "TEMPI" syndrome consists of five distinct clinical features: telangiectasias (T), erythrocytosis with elevated erythropoietin (EPO) levels (E), monoclonal gammopathy (M), peri-nephric fluid collections (P), and intrapulmonary shunting (I). The etiology, pathogenesis, and prevalence of this ultrarare syndrome is still being elucidated.

Case Presentation: A 57-year old man was being investigated for secondary erythrocytosis. On examination he had telangiectasias over his trunk. His workup revealed high serum EPO levels, a monoclonal paraprotein band on serum protein electrophoresis and Immunofixation, peri nephric fluid on CT abdomen, and evidence of intrapulmonary shunting on arterial blood gas and an echocardiogram with bubble study. He fulfilled the diagnostic criteria for TEMPI syndrome. For reasons of worsening dyspnea, he initiated treatment and received two cycles of bortezomib, cyclophosphamide, and dexamethasone chemotherapy. Treatment was discontinued as he developed steroid induced myopathy. Planning is underway for the patient to receive daratumumab monotherapy.

Conclusion: Uptil now, 23 cases have been reported in the literature from different countries across the globe. Plasma cell directed therapies including bortezomib-based regimens, daratumumab monotherapy, lenalidomide, and autologous hematopoietic stem cell transplantation in few patients have resulted in dramatic clinical responses. Thoroughly investigating patients who present with secondary erythrocytosis along with other relevant findings can help us identify more patients with TEMPI syndrome. Case reports of this ultrarare disorder from across the globe can help us in better understanding and treatment of this disease.

Keywords: Case report, TEMPI, erythrocytosis, monoclonal gammopathy, peri nephric fluid, telangiectasias, intrapulmonary shunting.

Received: 04 June 2021 **Accepted:** 08 September 2021 **Type of Article:** CASE REPORT **Specialty:** Clinical Hematology

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Background

The "TEMPI" syndrome was first described in 2011 by Sykes et al. for a syndrome which consisted of five distinct clinical features: telangiectasias (T), erythrocytosis with elevated erythropoietin (EPO)levels (E), monoclonal gammopathy (M), peri-nephric fluid collections (P), and intrapulmonary shunting (I). So far, 23 cases have been reported in literature from different countries across the globe [1]. The etiology, pathogenesis, and prevalence of this syndrome is still being elucidated but as more patients were identified TEMPI syndrome was placed in category of "plasma cell neoplasms with associated paraneoplastic syndrome" in the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, fourth edition [2]. In a recent study a new pathogenesis for TEMPI as an autoimmune disorder have been described [3]. It is an acquired disorder that usually presents in third or fourth decade of life with no predisposition for any gender, ethnicity or any geographical location. Here, we describe a 57-year-old man who presented with unexplained erythrocytosis.

Case Presentation

A 57-year-old man, chronic smoker with co-morbid conditions including hypertension and anxiety, presented with pruritis and erythromelalgia to his local physician in 2017. He had no significant past medical history. His family history was notable for a father who had died of acute leukemia. His blood pressure was 160/90 mmHg, pulse 90/minute, respiratory rate 22/minute and oxygen saturation 97% on room air. On examination he had facial plethora and telangiectasias over both upper limbs and trunk (Figure 1). The remainder of the examination was unremarkable.

His hemoglobin (Hb) was elevated at 19 g/dl (normal range 13.5-17.5 g/dl), hematocrit (Hct) 57% (normal range 40% to 54%) with a normal white blood count (WBC) 4.2 × 10^9/l (normal range 4-11 × 10^9/l) and platelet (Plt) count 256 × 10^9/l (normal range 150-400 × 10^9/l). Uric acid was 14 mg/dl (normal range 3.4-7.0 mg/dl), JAK2 V617F mutation testing was negative. His serum EPO was markedly elevated. (433.1 IU/l, normal range, 3-19 mIU/ml). He was given the diagnosis of secondary polycythemia and initiated a course of intermittent phlebotomies until 2018. In April 2018, he developed worsening shortness of breath and a respiratory tract infection and was seen in consultation by a pulmonologist. His arterial blood gases (ABGs) showed respiratory alkalosis with an increased Arterial- Alveolar (A-a) gradient, suggestive of a pulmonary embolism or an intrapulmonary shunt. His D-dimer was normal and a CT Pulmonary Angiogram (CTPA) showed no evidence of pulmonary embolism, confirming a diagnosis of intrapulmonary shunt as the reason for his increased A-a gradient. An echocardiogram with bubble study was also suggestive of microscopic pulmonary arteriovenous fistulae. His 2D-Echocardiography was otherwise normal. CT scanning of the neck, chest and abdomen showed peri-nephric fluid and fat stranding (Figure 2). No bony lytic lesions were seen.

In April 2018 his complete blood count revealed a WBC: 7.24 × 10^9/l, Hb: 14.9 g/dl, Hct: 50% (post 9 sessions of phlebotomy), Plt: 238 × 10^9/l, Reticulocyte count (Retic): 1%. He underwent a bone marrow biopsy; the morphological evaluation and immunohistochemistry (CD3, CD20, CD38, CD138, and CD56) were normal. There was an expansion of the erythroid population, consistent with his secondary erythrocytosis. Plasma cells were 2% with kappa light chain excess, consistent with Monoclonal gammopathy of undetermined significance (MGUS). Iron staining revealed iron deficiency secondary to his multiple therapeutic phlebotomies (serum ferritin 9.5 ng/ml, normal range 20-250 ng/ml). JAK2 exon 12 mutation testing was negative.

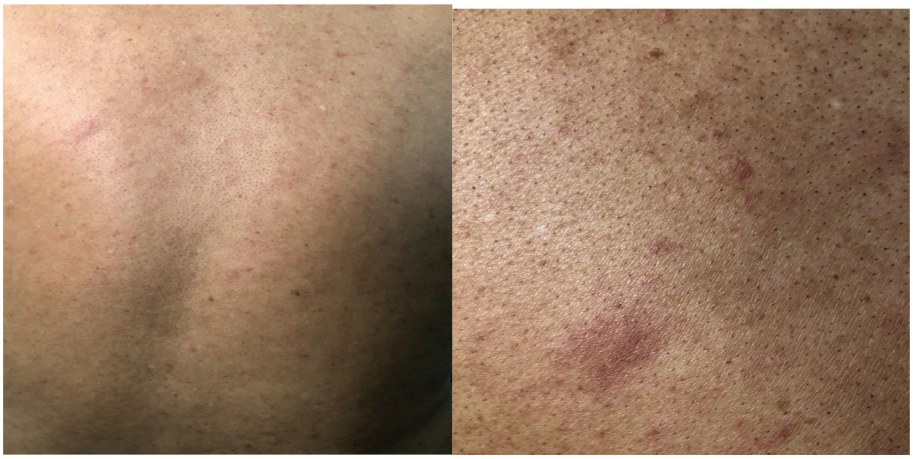

Figure 1. *Telangiectasias on back of patient.*

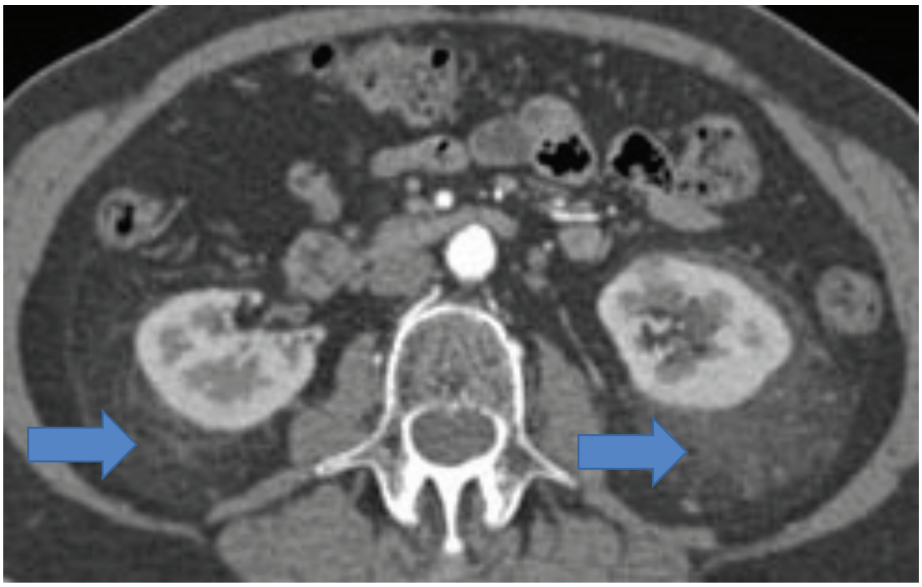

Figure 2. *Perinephric fat and fluid collection on CT scan abdomen and pelvis of the patient.*

Table1. *Diagnostic criteria for TEMPI syndrome [3].*

DIAGNOSTIC CRITERIA FOR TEMPI SYNDROME	CASE FEATURES	CRITERION FULFILLED
Major		
Telangiectasias	Present	✓
Elevated EPO and erythrocytosis	Present	✓
Monoclonal gammopathy	Present (IgG kappa)	✓
Minor		
Perinephric fluid	Present (confirmed twice on CT scan abdomen and pelvis)	✓
Intrapulmonary shunting	Present (confirmed on bubble study and increased A-A gradient on ABGs)	✓
Other		
Venous thrombosis	Absent	✗

Serum protein electrophoresis and Immunofixation revealed a monoclonal paraprotein band identified as an IgG Kappa with a concentration of 17.4 g/l. Serum B2 microglobulin was normal (1.95 mg/l). Urine Protein Electrophoresis showed no paraprotein. Kappa free light chain (FLC) was 30.41 mg/l, Lambda FLC was 0.95 mg/l, and his Kappa/Lambda ratio was 32.0. The serum EPO level was 543.1 IU/l

Further workup was done to rule out other the diagnosis of POEMS syndrome. Electromyography (EMG) and nerve conduction studies (NCS) were normal. Magnetic resonance imaging (MRI) brain with contrast was normal. Autoimmune, vasculitis, and paraneoplastic testing were all negative.

Based on the recently published diagnostic criteria [3], patient was diagnosed as having TEMPI syndrome (telangiectasias, erythrocytosis with elevated EPO levels, monoclonal gammopathy, perinephric-fluid collections, and intrapulmonary shunting) (Table 1).

There was no indication for immediate treatment though he was kept under regular surveillance. He was strongly advised to quit smoking. He was advised to monitor his oxygen saturation at home to assess the potential need for treatment in the case of worsening oxygen saturation. Furthermore, he was also advised that the development of clinical symptoms or worsening erythrocytosis may be indications for treatment.

In February 2020, he developed bilateral flank pains, muscle spasms, and exertional dyspnea. His complete blood count showed a Hb 17.4 g/dl and HCT 48% (post phlebotomy). His ABGs showed partial pressure of oxygen 62 mmHg, with further increase in the A-a gradient. His CT abdomen showed an increase in the size of perinephric collections. He was again strongly advised to quit smoking, and to repeat serum EPO levels 8 weeks post smoking cessation, and weekly phlebotomy to keep his Hct <45%. He remained stable with weekly phlebotomy and reduced frequency of smoking with subsequent decrease in serum EPO levels. However, within months, he had worsening dyspnea and initiated treatment with two cycles of bortezomib, cyclophosphamide, and dexamethasone (VCd). Treatment was discontinued when he developed severe steroid induced myopathy. Currently, his dyspnea persists with rising serum EPO levels. He is now scheduled for daratumumab monotherapy.

Discussion

While being evaluated for secondary erythrocytosis, this patient was found to have features consistent with diagnosis of the rare entity TEMPI syndrome. Historically, in patients with TEMPI syndrome, telangiectasias developed mostly over the face, trunk, and arms with sparing of lower limbs just like in our patient [4]. Biopsies of these lesion have shown no unusual features [3].

Serum EPO levels tend to progressively increase over years and can be very high leading to secondary erythrocytosis which usually precedes the development of intrapulmonary shunting and perinephric fluid collection [3].

Monoclonal gammopathy is a hallmark of the TEMPI syndrome. Similar to other patients with TEMPI syndrome, our patient was found to have an IgG kappa light chain MGUS with <10% plasma cells on bone marrow biopsy [5].

Sampling of perinephric fluid collection has shown clear, aseptic, serous fluid having low levels of protein, few leukocytes, and no cholesterol or triglycerides in few of the patients [6].

Intrapulmonary shunting is microscopic, not detected on high-resolution CT scans, and accompanied with a decrease in resting oxygen saturation leading to hypoxia and need for supplemental oxygen [3].

Plasma cell directed therapies including bortezomib-based regimens, daratumumab monotherapy, and autologous hematopoietic stem cell transplantation (ASCT), have resulted in dramatic clinical responses, with reversal of most manifestations of TEMPI. The

first patients with TEMPI syndrome who were treated had partial to complete responses with bortezomib based regimens, one patient underwent successful ASCT while other patient achieved complete response with daratumumab monotherapy following ASCT [3]. Lenalidomide has also been reported to be successful in treating TEMPI syndrome in a recent study [3]. More recently a case of TEMPI syndrome refractory to both proteosome inhibitor and ASCT with fatal outcome has also been reported from Japan [7].

This is the second case report of TEMPI syndrome in a patient from Pakistan. The first case of TEMPI from Pakistan was reported in 2014 of a 37-year-old male who presented with bilateral perinephric collections, telangiectasias, polycythemia vera with normal serum EPO levels, and interpulmonary shunting [8]. He responded well to treatment with hydroxyurea with reversal of symptoms [8]. Our patient also responded well with bortezomib based chemotherapy (VCd) with significant improvement in his dyspnea and lowering of serum EPO levels. However, due to steroid induced myopathy his treatment was interrupted and now he is due for daratumumab monotherapy. Reversal of most and in some cases all of TEMPI syndrome manifestation with plasma cell directed therapies show that all these manifestations have a common pathological origin that is still unclear at the moment. An international registry and close collaboration are needed for further study of this very rare disorder.

Conclusion

There is currently no standard treatment for TEMPI syndrome. Further case reports of this syndrome from all over the globe will help us in understanding pathophysiology and management of this ultrarare disorder. It also further highlights the need of international registry and collaboration so research samples can be collected.

What is new?

TEMPI syndrome is a recently found entity which is classified under plasma cell disorders. So far, only 23 patients have been diagnosed from all over the globe. Our patient also forms part of this series who responded partly to plasma cell directed therapy.

List of Abb reviations

ABGs	Arterial blood gases
ASCT	Auto stem cell transplant
CTPA	Computed tomography pulmonary angiogram
EMG	Electromyography
EPO	Erythropoietin
Hb	Hemoglobin
Hct	Hematocrit
IFX	Immunofixation
MGUS	Monoclonal gammopathy of undetermined significance
MRI	Magnetic resonance imaging
NCS	Nerve conduction studies
Plt	Platelet
SPEP	Serum protein electrophoresis
VCd	Bortezomib, cyclophosphamide, dexamethasone
WBC	White blood cell count

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Written and informed consent was taken from patient to publish this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 57 years
2	**Final diagnosis**	TEMPI syndrome
3	**Symptoms**	Pruritis, erythromelalgias, dyspnea
4	**Medications**	Analgesics, antihypertensive, anxiolytics
5	**Clinical procedure**	CT abdomen and pelvis, CTPA, ABGs, bone marrow examination, Echocardiography, Bubble study, MRI brain, EMG /NCS study
6	**Specialty**	Clinical hematology, medicine