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LETTER TO THE EDITOR

A rare case of TEMPI syndrome (telangiectasias, erythrocytosis, monoclonal gammopathy and ascites) associated with IgM monoclonal gammopathy

Stavroula Asimakopoulou[a], Panagiotis Malandrakis[b], Aikaterini Kamiliou[a], Maria Gavriatopoulou[b], Konstantina Bafa[a], Vaios Samaras[c], Amalia Anastasopoulou[a], Eleni Variami[a], Eleftheria Lakiotaki[d], Penelope Korkolopoulou[d], Efstathios Kastritis[b], Meletios A. Dimopoulos[b] and Evangelos Cholongitas[a]

[a]First Department of Internal Medicine, Laiko General Hospital, Medical School of National & Kapodistrian University of Athens, Athens, Greece; [b]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital, Athens, Greece; [c]Department of Radiology, General Hospital of Athens "Laiko", Athens, Greece; [d]Department of Pathology, National and Kapodistrian University of Athens, Athens, Greece

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To the Editor,

A 67-year-old nonsmoking female was admitted to our Department due to abdominal discomfort of 10 days duration. Her physical examination was notable for telangiectasiason her chest, back and limbs and plethora. Shifting dullness test was positive. Laboratory evaluation showed polycythemia (red blood cell 7.3 x 10^{12}/L, hemoglobin 15.8 g/dL, MCV 76.7 fL, MCH 21.8 pg, MCHC 28.4 g/dL, RDW 27.7%) with normal white blood cells (8.9 x 10^{9}/L) and platelet counts. The presence of high serum levels of erythropoietin (EPO: 73.5 μIU/mL, normal ranges: 3.2–32) and absence of JAK2V617F mutation excluded the diagnosis of polycythemia vera. Arterial blood gas analysis (pH: 7.44, pCO_2: 27mmHg, pO_2: 97 mmHg, and HCO_3: 18 mmol/L) was normal, as well as her liver and renal function. Abdominal ultrasound demonstrated the presence of ascitic fluid and its analysis revealed a serum ascites albumin gradient (SAAG) of 3.6 gr/dL with 32/mm^3 neutrophils and low level of ascitic protein (0.76 g/dL), while chest and abdomen computed tomography (CT) showed no organomegaly or other abnormal findings, expect for the presence of amount of ascitic fluidand a significant amount of perinephric fluid collection (Figure 1). Liver biopsy did not show any evidence of cirrhosis, while extensive investigation did not reveal any cause of chronic liver disease (including Budd-Chiari syndrome). Serum protein electrophoresis and immunofixation revealed the presence of IgM-lambda paraproteinemia (Monoclonal protein level: 0.655 g/dL). Further investigation was conducted: a bone marrow biopsy showed a lymphoplasmacytic infiltration by clonal B cells (15% of bone marrow cells), and by clonal plasma cells (15% of bone marrow cells) with lambda light-chain restriction. Erythroid, myeloid and megakaryocytic lineages were both unremarkable. Testing for the MYD88 gene L265P mutation was positive. CXCR4 was not detected using Sanger's sequencing, TP53 status was not evaluated, neither by immunohistochemistry nor by molecular testing, (Figure 2) and we did not order NGS testing. There was no evidence or clinical signs of peripheral neuropathy or anyneuropathic symptoms, while electromyography/nerve conduction test and serum vascular endothelial growth factor (VEGF: 34 pg/μL, normal values <150) were normal, thus excluding POEMS syndrome diagnosis. Contrast-enhanced transthoracic echocardiography with agitated saline did not show the presence of intrapulmonary shunt. Interestingly, on the 2nd day of her hospital stay, left jugular vein thrombosis developed, confirmed by doppler ultrasound, leading to initiation of anticoagulation therapy. Based on the constellation of above findings, a diagnosis of TEMPI syndrome was made (telangiectasia, erythrocytosis with a high EPO level, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunt).

The patient received treatment targeting the lymphoplasmacytic clone with the combination of rituximab, cyclophosphamide and dexamethasone with the addition of bortezomib (V-DRC). After 6 cycles, IgM levels showed a gradual decrease, and the patient reached a very good-partial hematologic response (IgM: 162 mg/dL with a positive IgMλ immunofixation). Moreover, her clinical condition improved significantly, with a reduction in ascitic fluid, improvement of telangiectasias and a decrease in hemoglobin levels (Hb:13.3 g/dL), while EPO levels normalized (8 μIU/mL). The patient currently receives maintenance therapy with rituximab every eight weeks and bortezomib every two weeks, with no toxicities and a further decrease in IgM levels to 72 mg/dL, 18 months after the initial diagnosis (Table 1).

CONTACT Evangelos Cholongitas cholongitas@yahoo.gr First Department of Internal Medicine, Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, AgiouThoma 17, 11527 Athens, Greece

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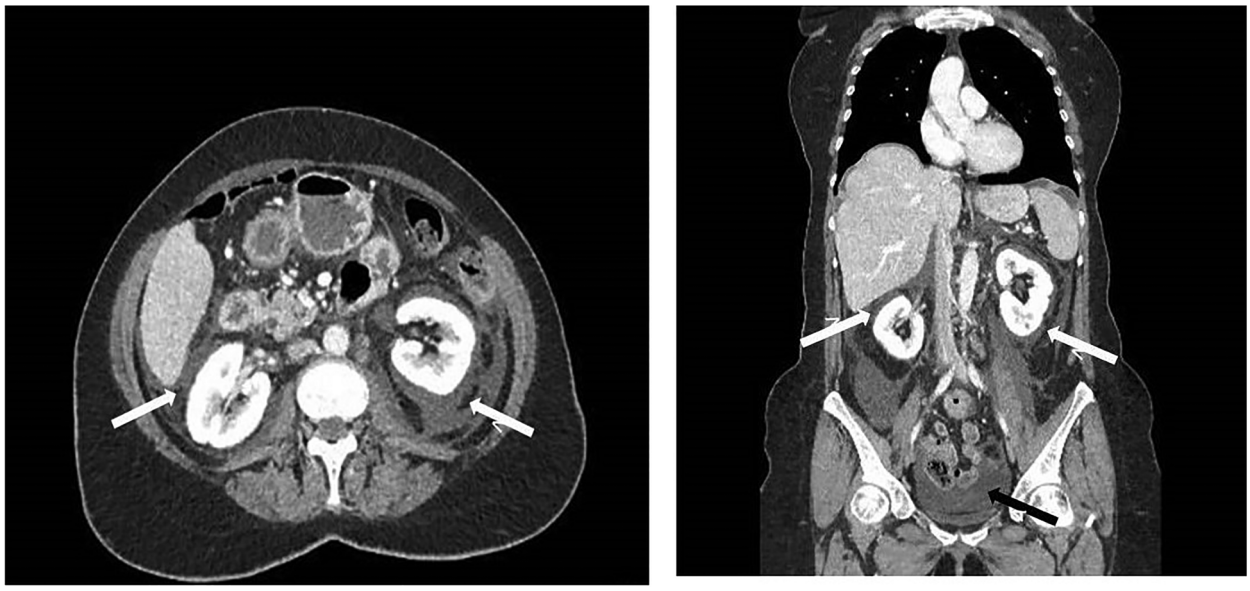


Figure 1. Enhanced computed tomography images showing bilateral perirenal fluid collections (white arrows), as well as ascites (black arrow).

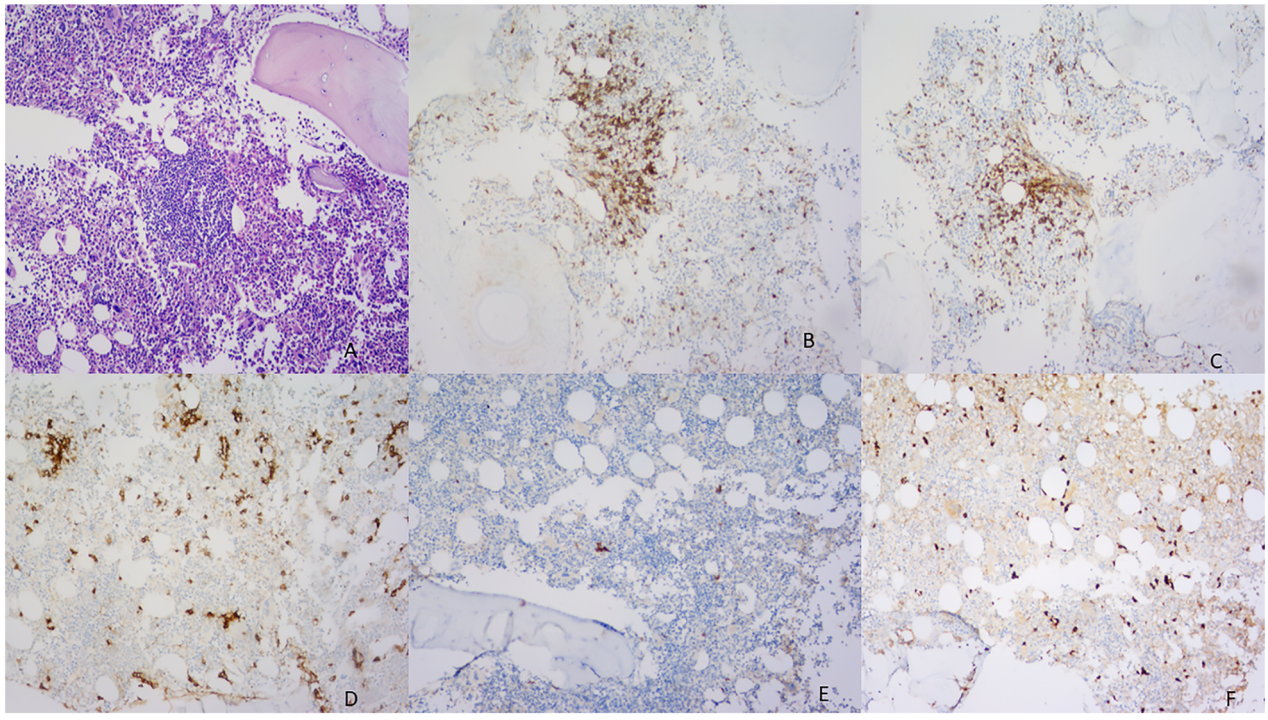


Figure 2. (A) hematoxylin-eosin stain (X100): Hypercellularity for the age of the patient; (B) CD20 immunostain (X100) and (C) CD3 immunostain (X100): Lymphoid aggregates of predominantly B cells (D) CD138 immunostain (X100): relatively increased number oof plasma cells E) kappa light chain immunostain (X100) and (F) lamda light chain immunostain (X100): plasma cells are monoclonal for lamda light chain.

TEMPI syndrome was first described in 2011 and in 2017 was classified under the category of plasma cell neoplasms with an associated paraneoplastic syndrome in the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues [1]. A limited number of patients with TEMPI syndrome have been reported in the English literature to date [2–4]: almost all had monoclonal gammopathy of usually IgG or less frequently IgA type, whilekappa monoclonality is predominant in the light chains (kappa-to-lambda ratio: 2.8). To our knowledge, only recently, Kubik et al. [5] described a case of a patient with an IgM lambda paraprotein and TEMPI syndrome with low grade B-cell lymphoma with plasmacyticdifferentiation (positive for the presence of MYD88 L265P mutation). Our patient had almost all the typical findings of TEMPI syndrome [1]. We didnot detect the presence of intrapulmonary shunts. However, in the literature, only 14 of 23 patients with TEMPI syndrome [3] had intrapulmonary shunting, while our patient fulfilled all the

Table 1. Laboratory results of our patient with TEMPI syndrome at the time of diagnosis, during treatment and six months after treatment.

Laboratory result (units)	Normal ranges	At the time of diagnosis	During treatment	6 months after treatment
Hemoglobulin (g/dL)	11.6–15	15.8	13.8	13.3
IgM (mg/dL)	50–300	655	162	72
Erythropoietin (μIU/mL)	3.2–32	73.5	12.1	8
Free lambda levels (mg/L)	5.7–26.3	34.7	NA	15.2
Free kappa levels (mg/L)	3.3–19.4	18.9	NA	9.48
kappa/lambda ratio	0.26–1.65	0.54	NA	0.62
M spike size (g/dL)	<1	0.643	NA	0
Urine protein (mg/24h)	<150	890	NA	272

NA: not applicable.

three proposed major criteria (i.e. telangiectasias, elevated EPO levels with erythrocytosis and monoclonal gammopathy), as well as two of the three minor criteria (i.e. perinephric fluid collection and venous thrombosis but not the presence of intrapulmonary shunt) for TEMPI syndrome [1]. The rarity and nonspecific signs and symptoms make the differential diagnosis of TEMPI syndrome broad, especially if not all the typical findings are present. In our case, we excluded POEMS syndrome, which can also be presented with ascitic and perinephric fluid accumulation, lambda light chain restriction and telangiectasia, based on the absence of neuropathy and low levels of VEGF.

Different therapeutic approaches have been reported in patients with TEMPI syndrome, such as proteasome inhibitors-PIs (bortezomib), immunomodulatory drugs-IMiDs (lenalidomide and thalidomide), antiCD38 monoclonal antibodies (daratumumab) and autologous stem cell transplantation. In our patient, due to the presence of a lymphoplasmacytic clone, we used a combination of DRC, typical for Waldenstrom macroglobulinemia, in which we added bortezomib. The role of PIs, and especially bortezomib in the HIF-1 pathway has led to the use of this regimen for TEMPI patients. Bortezomib affects the function of HIF-1α, by inhibiting HIF-1α–mediated inhibition of p300 recruitment. The reduction of HIF-1–mediated activation of VEGF and EPO gene expression contributes to the inhibitory effect on cell proliferation and hypoxic adaptation [6]. Since an IgM-related TEMPI with a lymphoplasmacytic clone is very rare in the literature, there are no data regarding the safety and efficacy of newer regimens such as BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib); however, may be a reasonable option for some patients.

In conclusion, TEMPI syndrome is a newly described hematolymphoid entity accompanied by (not always well-explained pathophysiological) paraneoplastic manifestations. Our case is different from the most other cases described to date, as our patient was diagnosed with lymphoplasmacytic lymphoma rather than a plasma cell neoplasm. Due to its rarity, the clinicians should be aware regarding this entity to avoid delay in the diagnosis and treatment aiming to reduce the appearance of new complications related with this syndrome and increase survival.

Author contributions

All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Disclosure statement

The study did not receive ethical approval by the local Institutional Review Board. Research ethics and patients' sensitive personal data were protected according to the 2017 Declaration of Helsinki.

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ORCID

Efstathios Kastritis http://orcid.org/0000-0001-8191-5832

Data availability statement

The data are available; Patient consent was received.

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