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LETTER TO THE EDITOR

Relapsed multiple myeloma as TEMPI syndrome with good response to salvage lenalidomide and dexamethasone

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Dear Editor,

A new disease entity, TEMPI syndrome, characterized by the combination of telangiectasia, erythrocytosis and elevated serum erythropoietin level, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting, is included in the 2016 revised World Health Organization classification of tumors of hematopoietic and lymphoid tissues [1]. It is hypothesized to be a result of abnormal plasma cell clones; however, its exact mechanism is unknown. Patients with TEMPI syndrome frequently suffer from distressing symptoms, and management is difficult since the standard treatment is yet to be elucidated. Herein, we report a case of a patient with TEMPI syndrome, who presented with severe fluid accumulation bilaterally in the perinephric space and polycythemia at the time of IgA-kappa multiple myeloma relapsed, and responded dramatically to lenalidomide and dexamethasone.

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A 46-year-old non-smoking male was diagnosed about two and a half years ago with multiple myeloma, IgA-kappa, International Staging System stage I. The bone marrow biopsy revealed plasmacytosis of 40.6 %. He demonstrated a partial response to induction bortezomib and dexamethasone, but he declined autologous stem cell transplantation. He was lost to follow-up for one and a half years; subsequently, he presented with abdominal fullness and bilateral flank pain for 2 weeks. He did not have tingling or paresthesias of hands or feet. On examination, his vital signs were relatively stable. A hemogram revealed an elevated hemoglobin level of 17.4 g/dL and a hematocrit of 51.1%. Erythropoietin level was 142 mIU/mL (reference ranges, 4.3–29.0). Bone marrow evaluation was not performed and JAK2 V617F mutation status was not examined. IgA level was 1230 mg/dL. Abdominal ultrasonography revealed no hepatosplenomegaly, and computed tomography (CT) revealed fluid accumulation bilaterally in the perirenal space (Fig. 1a). Fluid drainage revealed the presence of transudate, which was negative for malignancy. A diagnosis of TEMPI syndrome was considered based on the presence of elevated erythrocytosis and erythropoietin level, monoclonal IgA-kappa gammopathy, and perinephric fluid collections. The patient was treated with bortezomib and dexamethasone, but the perinephric fluid did not resolve after the first cycle. He underwent surgical marsupialization for diverting the perinephric fluid to the peritoneal cavity, and needed frequent paracentesis for symptomatic relief. In the meantime, the bone pain worsened, and the IgA levels became progressively elevated. The patient was

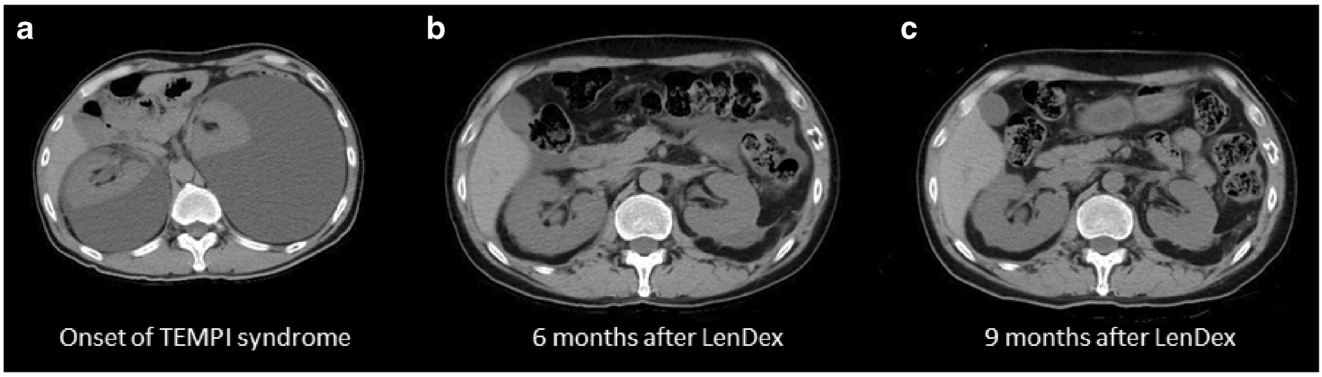

Fig. 1 Computed tomography scans of the abdomen showing (**a**) bilateral perinephric fluid collections and a severely displaced left kidney, **b** nearly complete resolution of the perinephric fluid collection after 6 months of treatment with lenalidomide and dexamethasone (LenDex), and **c** no recurrence of perinephric fluid collection after 9 months of treatment with LenDex

transferred to our institution due to the progressive evolution of the myeloma. Levels of erythropoietin and IgA were 474 mIU/mL and 1430 mg/dL, respectively. Due to disease progression while on bortezomib treatment, we decided to use lenalidomide (at a dose of 25 mg on days 1 through 21 of a 28-day cycle) and weekly dexamethasone as salvage therapy. His abdominal fullness improved significantly, and paracentesis was no longer needed after 2 weeks on lenalidomide. The IgA level decreased gradually, and an abdominal CT scan about 6 months later showed almost complete resolution of the bilateral perinephric fluid collections (Fig. 1b). The erythrocytosis also regressed but the erythropoietin level increased to over 750 mIU/mL. At the last imaging follow-up (about 9 months after being on lenalidomide), perinephric fluid collections did not recur (Fig. 1c).

Only 15 cases of TEMPI syndrome have been reported to date [2–12] (Table 1). Among the reported cases, many of the patients presented features of TEMPI syndrome before monoclonal gammopathy was detected, and IgG-kappa is the predominant monoclonal paraprotein. Our patient presented with TEMPI syndrome at the time of multiple myeloma progression, and his paraprotein was IgA-kappa. To the best of our knowledge, this is the first case of TEMPI syndrome with such unique presentation of disease evolution and presence of IgA-kappa paraprotein.

Another rare paraneoplastic disorder secondary to an underlying plasma cell dyscrasia is POEMS syndrome. Our patient was less likely to be suffering from POEMS syndrome, since he did not have the characteristic feature of peripheral neuropathy and the type of light chain seen in POEMS syndrome is almost always lambda [13].

Significant responses to a bortezomib [3, 6] and daratumumab [4] have been observed in several case reports on TEMPI syndrome, but reports regarding immunomodulatory agents are few. Our patient had a very promising response to lenalidomide, leading to the almost complete resolution of the bilateral perinephric fluid collections and concomitantly a good control of the myeloma. To the best of our knowledge, this is the first case of TEMPI syndrome involving a good response to immunomodulatory agents. However, the erythropoietin level increased despite the response to lenalidomide being good. Additionally, we are not sure whether the good clinical response was a result of the direct control of the myeloma or the immunomodulatory effect of lenalidomide.

Considering little is known about the pathogenesis of this rare syndrome, further studies are required to explore the mechanisms. Continued reporting of patients in the real world may help in providing the most effective treatment. We believe that our patient represents one of the rare cases of TEMPI syndrome, and the use of myeloma-targeted immunomodulatory agents is a new way to treat this condition.

Table 1 Features of patients reported with the TEMPI syndrome

Author	Patient no.	Age (years)	Gender	Onset of TEMPI	M protein	Plasma dyscrasia	EPO (mIU/mL)	Accompanying disorders	Treatment	Response
Sykes et al. [2]	1	42	Male	When MGUS detected	IgG-kappa	MGUS	> 5000	Venous thrombosis	Sirolimus Bortezomib	Progression NR
	2	36	Female	NR	IgG-kappa	MGUS	> 5000	Venous thrombosis, spontaneous intracranial hemorrhage	Thalidomide, bevacizumab Bortezomib	Progression Complete response
	3	39	Female	NR	IgG-kappa	MGUS	> 5000	Venous thrombosis, spontaneous intracranial hemorrhage	Bortezomib	NR
	4	35	Male	NR	NR	NR	> 500	NR	NR	NR
	5	56	Male	NR	IgG	NR	NR	NR	NR	NR
	6	36	Male	NR	NR	NR	NR	NR	NR	NR
Schroyens et al. [3, 4]	7	48	Female	NR	IgG-kappa	NR	6400	NR	Bortezomib Daratumumab	Complete response Complete response
Mohammadi et al. [5]	8	58	Female	Before MGUS detected	IgA-lambda	MGUS	134	Diarrhea, hepatic hemanigioma	NR	NR
Kwok et al. [6]	9	56	Female	Before SM detected	IgG-lambda	SM	100	Fatigue, diffuse pain	Bortezomib	Partial response
Viglietti et al. [7]	10	49	Male	Before MGUS detected	IgA-lambda	MGUS	78	Ascites, pleural effusion	NR	NR
Ryden et al. [8]	11	50	Male	NR	IgG-kappa	MGUS	433	Focal segmental glomerulosclerosis	Bortezomib	Clinical improvement
Jasim et al. [9]	12	61	Female	When MGUS detected	IgA-lambda	MGUS	134	Hypertension, hypothyroidism	Bortezomib	Clinical improvement
Kenderian et al. [10]	13	49	Female	Before MGUS detected	IgG-kappa	MGUS	8144	Iatrogenic iron deficiency anemia	Cyclophosphamide, bortezomib, and dexamethasone ASCT	Partial response Complete response
Belizaire et al. [11]	14	54	Male	Before MGUS detected	IgG-kappa	NR	5000	Iatrogenic iron deficiency anemia	Bortezomib, dexamethasone, and lenalidomide ASCT Daratumumab	Partial response Stable disease Complete response
Pascart et al. [12]	15	65	Female	When SM detected	IgG-kappa	SM	5000	Rheumatoid arthritis	Bortezomib	Clinical improvement

MGUS, monoclonal gammopathy of undetermined significance; NR, not recorded; SM, smoldering myeloma

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Authors' contributions SHL carried out the data gathering and drafted the manuscript. SPY provided the concept and data analysis. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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