



Case Report

Monoclonal Gammopathy with Known Significance in TEMPI Syndrome: Case Report and Minireview of the Literature

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Abstract

TEMPI (telangiectasias, elevated erythropoietin level, and erythrocytosis, monoclonal gammopathy, perinephric fluid collections and intrapulmonary shunting) syndrome is a rare plasma cell neoplasm with associated paraneoplastic features. We diagnosed a new case with IgG kappa paraproteinaemia and a bone marrow plasma cell ratio not reaching the criteria of smoldering myeloma, but harboring translocation t(11;14). Unfortunately, the patient succumbed to central nervous system thrombosis and bleeding, therefore treatment results could not be reported. This sequence of events prompted a reevaluation of the currently available knowledge of TEMPI syndrome.

Introduction

In most cases, monoclonal gammopathy confers unknown significance, but it is occasionally responsible for distinct clinical symptomatology. It was reported as a key feature of the TEMPI syndrome named after the acronym that stands for telangiectasias, elevated erythropoietin level and erythrocytosis, monoclonal gammopathy, perinephric fluid collections and intrapulmonary shunting. This pentad was the main characteristic of the unsolved index patient [1] and additional 5 cases were identified by extensive literature review and international cooperation [2]. In 2011, TEMPI syndrome was called a “novel multisystem disease”, however, today it is already on the map of the World Health Organization as a member of “plasma cell neoplasms with associated paraneoplastic syndrome” alongside with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy/edema, monoclonal gammopathy, skin changes) [3]. To our best knowledge, our patient represents the 28th case. We hope that our patient description and the review will contribute to a better understanding of this extraordinarily rare disease, a monoclonal gammopathy of clinical significance.

Case Presentation

The 52-year-old woman with a history of well-controlled hypertension was referred to our center with polyglobulia (Hemoglobin: 197 g/l, Hematocrit: 58%). This condition was already discovered ten years earlier, but after a therapeutic phlebotomy and taking a single box of hydroxyurea, the patient did not turn up for further evaluation. When she finally returned years later to our institute, itching provoked by hot water was her only symptom, no shortness of breath or flank pain were reported. She was phlebotomized, and her evaluation in the direction of polycythemia vera was started. The non-smoker woman who did not live at a high altitude above sea level surprisingly exhibited a significantly elevated erythropoietin level (EPO: 165.8 mIU/ml, normal range: 3.3–16.6 mIU/ml). Polycythemia vera was ruled out, together with the negative results of the Janus kinase 2 (JAK2) V617F mutation and the wild type sequence of JAK2 exon 12. A monoclonal IgG kappa peak of 7.6 g/l was detected by serum protein electrophoresis and immunofixation. CT scan at this time did not show any possibly EPO producing neoplastic process or

renal artery stenosis. A 30 mm “cyst” was noticed on the upper pole of the right kidney. The research after the unusual triad of polyglobulia, higher EPO level and monoclonal gammopathy led to the suspicion of TEMPI syndrome. This highlighted the significance of the patient’s telangiectasias (Figure 1A), as the possible cutaneous manifestation of this syndrome. Bone marrow histology showed normocellular parenchyma and normal hematopoietic maturation with erythroid dominance (Figure

1C) and 5-10% of plasma cells of combined CD38+/CD56+ phenotype with a kappa light chain dominance (Figure 1D-E). The fluorescence in situ hybridization carried out after CD138 selection of plasma cells showed fusion of IGH-CCND1 signals as a result of a translocation t(11;14)(q13;q32). The 3-month control of the CT scan showed bilateral perinephric fluid collections (Figure 1B). Control EPO levels continued to increase to >500 mIU/ml. These results provided further support for the diagnosis of TEMPI syndrome.

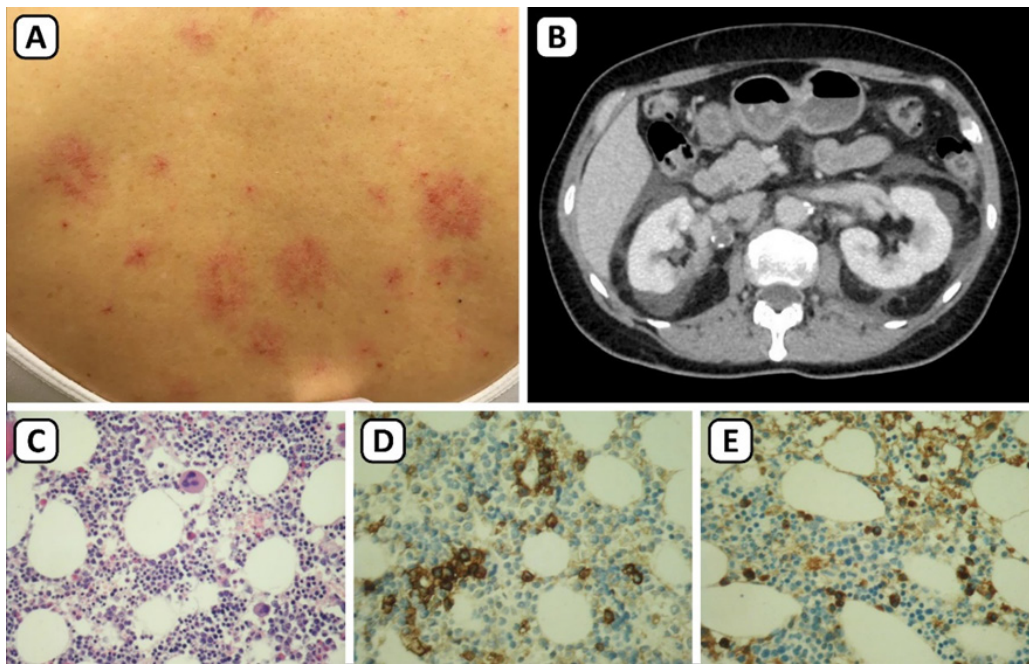


Figure 1: (A) Diffuse telangiectasias visible on the skin of the dorsal trunk. (B) CT scan revealing bilateral perinephric fluid collections. (C) Bone marrow histology: normocellular parenchyma and normal hematopoietic maturation with erythroid dominance, HE, 20x. (D) CD38 immunostaining showing patchy plasma cell infiltration, 20x. (E) kappa light chain immunostaining showing light-chain restriction of plasma cells, 20x.

The patient was immunized with 2 cycles of the SARS-CoV2 mRNA vaccine (Co-mirnaty®). To control the erythrocytosis and the perirenal fluid collection, and to prevent the possible further complications, initiation of a bortezomib-dexamethasone-cyclophosphamide (VCD) treatment regime was chosen and an autologous stem cell transplantation was also planned. One cycle of VCD was completed with a decrease in M-protein production (hematologic response not evaluable). Unfortunately, at her workplace, the patient developed sudden neurological symptoms (vertigo, dysarthria, right-sided hemiplegia with vomiting, and hypertension) with the background of left frontal and left cerebellar ischemia detected by MR angiography. Due to rapid impairment of consciousness, a control CT scan was performed which showed an acute bleeding component in the left frontal lesion. Despite

intensive therapy, aggressive dehydration, and decompressive craniotomy, the patient’s condition showed no improvement. MR angiography revealed a subacute thrombosis in the superior sagittal and left transverse sinuses. Reevaluation of the first MRI pictures revealed the signs of sinus thrombosis already present then. The condition of the patient unfortunately deteriorated and she died after 10 years of possible and 1 year of proven history of the TEMPI syndrome.

Discussion

Polyglobulia/erythrocytosis is frequently a presenting symptom and is one of the diagnostic criteria of TEMPI syndrome [4]. Prolonged histories of erythrocytosis treated by phlebotomies or hydroxyurea may occur with no effect on disease progression.

Erythrocytosis secondary to EPO overproduction is a well-known phenomenon, but it does not seem to be the primary motivator of this disease. Aspiration of the perinephric fluid collection [5], marsupialization [6] or decortication [7] of the affected kidney usually does not influence the other disease parameters either. Again, this supports the hypothesis that kidney involvement is not the primary causative factor of TEMPI. Interestingly, monoclonal gammopathy is kappa restricted in most TEMPI cases, whereas M-proteins are nearly exclusively of the lambda class in POEMS syndrome. The only effective treatments for TEMPI are based on targeting the underlying plasma cell population, which supports its central pathogenetic role. It is likely that some soluble factors secreted by the clonal plasma cells or their microenvironment are responsible for the diffuse symptomatology of TEMPI. In fact, a recent report drew attention to MIF (macrophage migration inhibitory factor), with its gene located on chromosome 22q11.23 [8]. This would be analogous to the role of VEGF in POEMS syndrome. To detect a possible amplification of the MIF1 gene, FISH testing with a MIF-specific probe was carried out, however, we found no gross aberration with thorough testing of 300 nuclei. Translocation t(11;14) detected in our case does not seem to be commonly occurring in this setting, although t(11;14) is known to be enriched in rare plasma cell disorders. Therefore, we consider the founding aberration of TEMPI remaining still undetermined, t(11;14) alone does not cause the TEMPI syndrome.

Bortezomib alone [9] or in combination, autologous stem cell transplantation [10], and dexamethasone combined with

lenalidomide [11] or even daratumumab [12] were successfully used to treat TEMPI, with clinical regression of telangiectasias, renal symptoms, and erythrocytosis as well. The significance of the underlining plasma cell disorder presenting with monoclonal gammopathy seems to be inarguable, but its role in the pathogenesis is yet to be explored. Increased thromboembolic risk of MGUS is well known [13], although in TEMPI syndrome it is not well defined. Among the first case series published by Sykes et al [2], 3 patients were reported to have a thrombotic event and 2 of them had intracranial bleeding. No further thromboembolic events were reported. Though telangiectasias are commonly observed on the skin surface (mostly on the trunk and the hands), there are indications of similar vascular disorder on the meninges, and at least one case is published where telangiectasias resulted in gastrointestinal bleeding [4]. Bilateral renal fluid collections, telangiectasias, and intrapulmonary shunting were reported as possible results of polycythemia vera that harbors V617F mutation and without any sign of monoclonal gammopathy or EPO overproduction. This observation contests that EPO would have a triggering role behind the vascular features of TEMPI. In the context of monoclonal gammopathy, the detected t(11;14) translocation is unique (Table 1). The bone marrow findings described above for our case are consistent with the literature [14]. The association of IGH-CCND1 rearranged smoldering myeloma and polycythemia were described but lacked other features of the syndrome such as kidney, skin, and pulmonary symptoms [15].

Author	Telangiectasia	Erythrocytosis	EPO	M protein	perinephric fluid	pulmonary shunt	plasma cells	cytogenetics
Bazari et al [1]	yes	yes	>5000 mIU/ml	IgGκ	yes	yes	5%	N.R.
Sykes et al [2]	yes	yes	>5000 mIU/ml	IgGκ	yes	yes	>10%	N.R.
	yes	yes	>5000 mIU/ml	IgGκ	yes	yes	>10%	N.R.
Burton et al [16]	N.R.	yes	>500 mIU/ml	N.R.	yes	N.R.	N.R.	N.R.
Olerud et al [17]	yes	yes	increased	IgG	N.R.	yes	N.R.	N.R.
Shaheen et al [18]	N.R.	yes	38 mIU/ml	N.R.	yes	N.R.	N.R.	N.R.
Schroyens et al [19]	yes	yes	>8000 mIU/ml	IgGκ	N.R.	yes	N.R.	N.R.
Mohammadi et al [7]	yes	yes	134 mIU/ml	IgAλ	yes	no	10%	N.R.
Kwok et al [9]	yes	yes	100 mIU/ml	IgGλ	yes	N.R.	10-15%	N.R.
Viglietti et al [20]	no	yes	78 mIU/ml	IgAλ	yes	N.R.	N.R.	N.R.
Ryden et al [21]	yes	yes	433 mIU/ml	IgGκ	yes	yes	<10%	N.R.
Pascart et al [22]	yes	yes	>5000 mIU/ml	IgGκ	no	yes	10,5%	N.R.

Kenderian et al [10]	yes	yes	8144 mIU/ml	IgGκ	yes	yes	5-10%	N.R.
Belizaire et al [23]	yes	yes	5000 mIU/ml	IgGκ	yes	yes	N.R.	N.R.
Hutchison et al [24]	no	yes	32,4 mIU/ml	IgGκ	renal cyst	no	9-15%	+5p, +9, +15
Katerji et al [15]	no	yes	687 mIU/ml	IgDλ	no	N.R.	16%	t(11;14)
Debbaneh et al [25]	yes	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Liang et al [11]	N.R.	yes	142 mIU/ml	IgAκ	yes	N.R.	>10%	N.R.
Maquet et al [26]	yes	yes	525 mIU/ml	IgGκ	no	no	0,4%	-13, -X, +1q, -6q
Shizuku et al [27]	yes	yes	4468 mIU/ml	IgGκ	yes	no	3,1%	N.R.
Lor et al [28]	yes	yes	NR	IgGκ	yes	yes	N.R.	N.R.
Diral et al [29]	yes	yes	5428 mIU/ml	IgGκ	yes	yes	20%	N.R.
Sun et al [8]	yes	yes	106 mIU/ml	IgGκ	yes	yes	7%	N.R.
	yes	yes	676,16 mIU/ml	IgAκ	yes	yes	3%	N.R.
	yes	yes	741 mIU/ml	IgGκ	yes	yes	2,5%	N.R.
Ruan et al [16]	yes	yes	>750 mIU/ml	IgAλ	yes	yes	<10%	N.R.
Strobl et al [30]	yes	yes	537 mIU/ml	IgGκ	no	no	10%	N.R.
Harasztombi et al	yes	yes	165,8 mIU/ml	IgGκ	yes	N.R.	5-10%	t(11;14)

Table 1: Selected features of the cases available in the literature.

Our patient presented typical features of the TEMPI syndrome. Diffuse telangiectasias [16], erythrocytosis and elevated EPO, monoclonal gammopathy, and perinephric fluids are consistent with the previously described cases. Our case described along with others increases the awareness of TEMPI syndrome and raises questions concerning the possible increased risk of thrombosis and central nervous system bleeding associated with TEMPI syndrome.

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