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【 CASE REPORT 】

The First Case of TEMPI Syndrome in Japan

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Abstract:
TEMPI syndrome, a disease entity comprising telangiectasia, erythrocytosis with high erythropoietin, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting, was first described by Sykes et al. in 2011. To our knowledge, only 15 cases have been reported worldwide, none of which were in Japan. We herein report a 47-year-old man who had intractable ascites for 2 and a half years and was referred to our department for a peritoneovenous shunt. In addition to ascites, he had telangiectasia, high erythropoietin, monoclonal gammopathy, and perinephric fluid collection. Thus, this is the first case of TEMPI syndrome in Japan.

Key words: TEMPI syndrome, erythrocytosis, monoclonal gammopathy, perinephric fluid collection

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Introduction

In 2011, Sykes et al. reported the first case of TEMPI syndrome (1). This syndrome has five characteristic features: telangiectasia, erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting. The World Health Organization classified this syndrome as tumors of hematopoietic and lymphoid tissues in 2016. TEMPI syndrome is more specifically categorized as a plasma cell disorder with paraneoplastic manifestations. To our knowledge, only 15 cases have been reported thus far, none of which were in Japan. Some patients may go undiagnosed because of this syndrome's complexity and rarity. TEMPI syndrome may also be misdiagnosed as a renal, pulmonary, or hematologic disorder, such as polycythemia vera and/or monoclonal gammopathy of undetermined significance. TEMPI syndrome can reportedly be treated in the same way as plasma cell disease, so it is important to diagnose it promptly.

Case Report

Two and a half years prior to his referral to our institution, a 47-year-old man developed left lower back pain for which he visited another hospital. Magnetic resonance imaging revealed perinephric fluid collection and ascites. However, no specific diagnosis was made. While his ascites and perinephric fluid collection were exhaustively investigated at two other hospitals, no definitive diagnosis was made. He had undergone fortnightly concentrated ascites reinfusion therapy for two and a half years before his referral to our hospital for the creation of a peritoneovenous shunt. Prior to his illness, he had been working in a rural area but had recently moved to our area. He was taking no medications and had been a smoker. He had drunk approximately 350 mL of beer every day prior to the development of his ascites.

On admission, his blood pressure was 119/81 mmHg, heart rate 85 bpm with sinus rhythm, and body temperature 36.8°C. Arterial oxygen saturation was normal. His only symptom was a mild sensation of abdominal fullness associated with his ascites. Physical examinations showed abdominal bloating and shifting dullness and telangiectasia on the lunulas of his nails (Fig. 1). He had no cardiac murmurs or any other abnormal findings, including neuropathy. Computed tomography showed perinephric fluid collection and ascites (Fig. 2). Blood tests showed monoclonal gammopathy and a high erythropoietin (EPO) concentration (Table 1). He had been diagnosed with polycythemia vera at a previous clinic, for which he had regularly undergone phlebotomy. Thus, his hemoglobin concentration was normal. A bone marrow examination revealed almost normal findings,

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with only slight hyperplasia. Plasma cells comprised 3.1% of the bone marrow cells (Table 2). An immunofixation test revealed M protein, IgG-κ type (Table 1). In addition to ascites, he also had telangiectasia, erythrocytosis, monoclonal gammopathy, and perinephric fluid collection. Taken together, these findings suggested the diagnosis of TEMPI syndrome.

We accordingly consulted Dr. Sykes, who first described and reported TEMPI syndrome. We are now planning to administer plasma cell treatment, such as a bortezomib-based regimen or daratumumab monotherapy.

Discussion

To our knowledge, only 15 cases of TEMPI syndrome have been reported. TEMPI syndrome was first described by Sykes et al. in 2011 as a plasma cell dyscrasia characterized by telangiectasia, erythrocytosis with high EPO concentrations, monoclonal gammopathy, perinephric fluid collections, and intra-pulmonary shunting (1). Zhang et al. reviewed the 15 reported cases (2). The age distribution of TEMPI syndrome is from 35 to 65 years old. Of the 15 patients, 6 were men, and 9 were women. The manifestations of TEMPI syndrome progress slowly over the years. Not all of the characteristic features are essential for the diagnosis. However, high EPO concentrations, which aid in distinguishing this syndrome from other plasma cell disorders, are required to make the diagnosis. Monoclonal gammopathy and telangiectasia were each present in 12 of the 15 reported cases, as was perinephric fluid collection, whereas intra-pulmonary shunting was found in only 9 cases (2). The causes and pathophysiology of these manifestations have not yet been determined. Eight of the 15 reported patients with TEMPI syndrome had IgG-κ type monoclonal gammopathy predominantly (2). In almost all reported cases, the M protein concentrations did not exceed 3.0 g/dL of M protein; however, in 1 patient, the IgG concentration was 3.6 g/dL (3). The percentage of plasma cells in bone marrow was consistent with monoclonal gammopathy of undetermined significance (<10%) in most of the reported cases; however, 2 patients had >10% bone marrow plasma cells. M protein and abnormal plasma cells are thought to play an important role in TEMPI syndrome, as treatment that targets plasma cells, such as bortezomib-based regimens, daratumumab monotherapy, and autologous hematopoietic stem cell transplantation (ASCT), has achieved dramatic clinical responses. In our patient, the percentage of plasma cells in the bone marrow, M protein concentration, and IgG type were consistent with TEMPI syndrome.

As erythrocytosis and high serum EPO concentrations are distinctive features of TEMPI syndrome, it is sometimes misdiagnosed as polycythemia vera. In fact, our patient had been diagnosed with polycythemia vera at a previous institution. However, there are some features that distinguish TEMPI syndrome from other causes of erythrocytosis, such as polycythemia vera. In primary erythrocytosis, the serum EPO concentrations are usually very low, in contrast to TEMPI syndrome. In addition, the JAK2 mutation is present

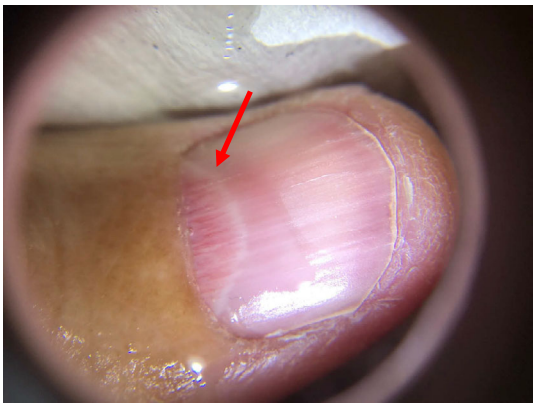

Figure 1. Photograph showing telangiectasia on the lunula of the patient's left thumb (red arrow).

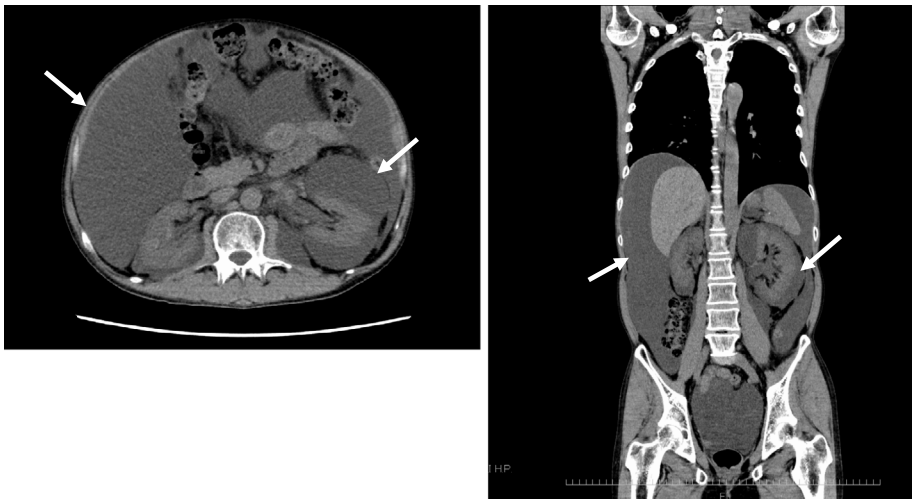

Figure 2. Computed tomography images showing perinephric fluid collection and ascites (white arrows).

Table 1. Laboratory Result.

<Hematology>		<Immunofixation test>	
White blood cell	5,800 /u	IgG-κ type M Protein	(+)
Red blood cell	573 ×10⁴/uL	<Coagulation>	
Hemoglobin	12.6 g/dL	PT%	79.3 %
Hematocrit	43.4 %	PT-INR	1.14
Platelate	24.5 ×10⁴/uL	APTT	30.4 sec
<Chemistry/Serology>		<Immunology>	
Total protein	7.1 g/dL	ANA	<40
Albumin	3.2 g/dL	SS-A antibody	(-)
Lactate dehydrogenase	145 IU/L	Jo-1 antibody	(-)
alkaline phosphatase	153 IU/L	Mitochondoria antiboy	(-)
aspartate aminotransferase	10 IU/L	MPO-ANCA	(-)
alanine aminotransferase	8 IU/L	PR3-ANCA	(-)
γ-GTP	8 IU/L	C3	90 mg/dL
Cholinesterase	204 IU/L	C4	15.1 mg/dL
Total-biliribin	0.7 IU/L	CH50	38 mg/dL
Blood urea nitorogen	20.5 mg/dL	IgG	2,465 mg/dL
Creatinine	1.48 mg/dL	IgA	86 mg/dL
Na	131 mEq/L	IgM	47 mg/dL
K	4.1 mEq/L	IgE	62 IU/L
Cl	102 mEq/L	IgG4	29 mg/dL
Glu	124 mg/dL	<Infection>	
β2-Microglobulin	2.8 mg/dL	HBs-antigen	(-)
Bence Jones-Protein	(-)	HBs-antibody	(-)
ESR	1 mm/h	HBc-antibody	(-)
VEGF	236 pg/mL	HCV-antibody	(-)
Erythropoietin	4,468.3 mIU/mL	HIV-1/2 antibody	(-)
M2BPGi	1.17	<ascites analysis>	
IgG-κ	81.5 mg/dL	White blood cell	66 /ul
IgG-λ	12.8 mg/dL	Mononuclear cell	95.5 %
κ/λ	6.37	Polynuclear cell	4.5 %
C-reactive protein	0.34 mg/dL	Culture	(-)
<Protein Fraction>			
Albumin	52.6 %		
α1	3.0 %		
α2	6.7 %		
β	8.0 %		
γ	29.7 %		
A/G ratio	1.1		

MPO-ANCA: myeloperoxidaze anti neutrophil cytoplasmic antibodies, PR3-ANCA: proteinase anti neutrophil cytoplasmic antibodies

Table 2. Bone Marrow Examination Result.

<Bone marrow asipiration>			
Myeloblast	0.6 %	Proerythroblast	0.1 %
Promyeloblast	0.1 %	Basophilic erythroblast	0.3 %
Myelocyte	3.8 %	Polychromatic erythroblast	21.2 %
Metamyelocyte	0.6 %	Oprthchromatic erythroblast	0.1 %
Stab	2.2 %	Lympocyte	25.6 %
Seg	33.9 %	Plasma cell	3.1 %
Baso	0.3 %	Reticulum cell	1.0 %
Monocyto	5.6 %	M/E	1.97

in almost patients with forms of primary erythrocytosis. While a number of researchers have theorized why serum EPO concentrations are high in TEMPI syndrome, no hard conclusions have been drawn. Our patient's extremely high serum EPO concentration suggested TEMPI syndrome rather than a primary erythrocytosis, such as polycythemia vera.

Perinephric fluid collection, another component of TEMPI syndrome, was present in 12 of the 15 reviewed patients. The pathophysiology of this condition has not yet been determined. Viglietti et al. suggested that perinephric fluid collection may be associated with malformation of the renal lymphatic tissue (4). M protein may be related to perinephric fluid collection via an as-yet-unknown mechanism, as bortezomib treatment has been reported to result in regression of this condition. Our patient had both perinephric fluid collection and ascites. In addition, one of the previously reported patients had ascites, the mechanism of which was not determined (4).

Intra-pulmonary right-to-left shunting associated with moderate to severe hypoxia has been reported in all patient with TEMPI syndrome. All reported circulatory shunt indexes in patients with TEMPI syndrome were >10% according to technetium-99 m macroaggregated albumin scanning or the 100% oxygen method. Some patients with TEMPI syndrome have required wheelchairs and continuous supplemental oxygen because of their progressive hypoxia (5, 6). However, some patients with TEMPI syndrome have not had right-to-left shunting at their first presentation (7, 8), possibly because the characteristic manifestations progress slowly over several years.

Telangiectasia, which is typically most prominently on the face, neck, upper extremities, and trunk, is another feature of TEMPI syndrome, having been present in 12 of the 15 reported patients (2). The exact mechanism is unclear. It has been suggested that hypoxia due to right-to-left shunting may cause an increased blood flow beneath the skin surface and dilation of capillaries. Our patient had telangiectasia in his lunular and nail fold capillaries.

There are currently no standard diagnostic criteria for TEMPI syndrome. The diagnosis requires the identification of a plasma cell clone and erythrocytosis in conjunction with the characteristic findings, together with the exclusion of other plasma cell disorders, such as multiple myeloma, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder and skin changes), and amyloid light-chain (AL) amyloidosis. We ruled out multiple myeloma on the basis of the bone marrow plasma cell percentage. We also ruled out POEMS syndrome because our patient did not have polyneuropathy; however, he had M protein, skin changes, a slightly increased serum vascular endothelial growth factor, and ascites. In the review of TEMPI syndrome, none of the previously reported patients had high serum vascular endothelial growth factor concentrations. TEMPI syndrome and POEMS syndrome may have overlapping mechanisms concerning the involvement of plasma cells. AL amyloidosis and TEMPI syndrome are similar plasma cell disorders. However, there are several distinctive features. First, the subtype of light chain is predominantly to κ-type in TEMPI syndrome, unlike in AL amyloidosis, where the subtype is predominantly λ-type. Erythrocytosis and high serum EPO concentrations can also be used to differentiate these two conditions because these two abnormalities are present in all patients with TEMPI syndrome.

The review cited above (2) revealed that treatment targeting plasma cells, such as bortezomib-based regimens, ASCT, and daratumumab monotherapy can achieve dramatic responses in patients with TEMPI syndrome. Bortezomib-based regimens are recommended as the first choice of treatment, rather than ASCT. If the disease is refractory to a bortezomib-based regimen, the second option is ASCT; however, this carries potential complications, such as infection and autoimmune hemolytic anemia. Daratumumab monotherapy was recently reported to be effective in two patients with disease that had relapsed or was refractory to both bortezomib and ASCT. These findings indicate that TEMPI syndrome can be reversed with appropriate treatment.

In conclusion, we herein report a patient with telangiectasia, erythrocytosis and monoclonal gammopathy, perinephric fluid collection, and ascites, which taken together are suggestive of TEMPI syndrome. Because this syndrome responds well to plasma cell treatment, it is important to diagnose it early and treat it appropriately.

The authors state that they have no Conflict of Interest (COI).

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