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ORIGINAL ARTICLE

The experience of diagnosis and treatment for TAFRO syndrome

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Abstract
Early identification, diagnosis and treatment of TAFRO syndrome are very importants. We retrospectively analysed 6 patients with TAFRO syndrome. Their clinical manifestations, treatment methods, survival and other aspects were summarized. All patients were pathologically diagnosed with Castleman's disease, with fever, an inflammatory storm state and varying degrees of anasarca. All patients received steroid therapy; four of them also received chemotherapy, and 1 received rituximab. Of the 3 patients with severe disease, only 1 patient who received the recommended dose of glucocorticoids survived. Early administration of glucocorticoids can improve the prognosis, especially in patients with severe disease, and adequate glucocorticoids are important.

Keywords Castleman · TAFRO syndrome · Clinical manifestations · Diagnosis

Introduction

TAFRO syndrome is a systemic inflammatory disease characterized by thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction and organ enlargement [1]. TAFRO syndrome was first reported by Japanese scholars in 2010 and considered a special subtype of multicentric Castleman disease (MCD) and clearly proposed in 2012 [2]. The pathogenesis is thought to be related to a strong cytokine storm, mainly involving interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) [3]. The incidence of this disease is extremely rare, and clinicians do not have sufficient knowledge of this disease. It is difficult to diagnose the disease in time and treat patients as early as possible. This study summarized the clinical characteristics, diagnosis and treatment information of 6 patients with TAFRO syndrome diagnosed in the First Affiliated Hospital of Zhengzhou University to provide a reference for follow-up studies of this disease.

Methods

Patients and diagnostic criteria

From October 2016 to October 2022, six patients with TAFRO syndrome confirmed through clinical, laboratory and pathological examinations and from the First Affiliated Hospital of Zhengzhou University were recruited in this study. The patients' data were obtained from the medical records and via telephone interviews, and the data included general information, clinical complaints and symptoms, results of pathological tests, clinical laboratory tests, imaging performed and follow-up information. The follow-up period was until October 1, 2022. The diagnostic criteria of TAFRO syndrome required all three major categories and at least two of four minor categories [4].

The major categories are as follows: (A) anasarca, including pleural effusion, ascites and general oedema; (B) thrombocytopenia, including platelet count ≤ 100,000/μL, without myelosuppressive treatment; (C) systemic inflammation, defined as fever of unknown aetiology above 37.5 °C and/or a serum C-reactive protein concentration ≥ 2 mg/dL. The minor categories included Castleman disease-like features

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on lymph node biopsy, reticulin myelofibrosis and/or an increased number of megakaryocytes in bone marrow, mild organomegaly and progressive renal insufficiency. Moreover, malignancies, autoimmune disorders, infectious disorders, POEMS syndrome, hepatic cirrhosis and thrombotic thrombocytopenic purpura should be excluded [5, 6].

Classification of disease severity

The patients were scored according to the degree of oedema, thrombocytopenia, systemic inflammatory reaction and renal insufficiency, and the degree of disease inflammation was evaluated according to the score, specifically as follows: (A) oedema (≤ 3), pleural effusion on imaging, ascites on imaging and pitting oedema on physical examination, 1 point each; (B) thrombocytopenia (≤ 3), 1 point for lowest platelet counts < 100,000/μL, 2 points for the lowest platelet counts < 50,000/μL and 3 points for the lowest platelet counts < 10,000/μL; (C) fever or inflammation (≤ 3), 1 point for fever ≥ 37.5 °C but < 38.0 °C or for CRP ≥ 2 mg/dL but < 10 mg/dL, 2 points for fever ≥ 38.0 °C but < 39.0 °C or for CRP ≥ 10 mg/dL but < 20 mg/dL and 3 points for fever ≥ 39.0°C or for CRP ≥ 20 mg/dL; and (D) renal insufficiency (≤ 3), 1 point for GFR < 60 mL/min/1.73 m^2, 2 points for GFR < 30 mL/min/1.73 m^2 and 3 points for GFR < 15 mL/min/1.73 m^2 or in need of haemodialysis. Zero to four points for grade 1 is mild, 5–6 points for grade 2 moderate, 7–8 points for grade 3 slightly severe, 9–10 points for grade 4 severe and 11–12 points for grade 5 very severe [4, 7].

Results

Clinical characteristics and manifestations

A total of 6 patients met the diagnostic criteria for TAFRO syndrome. All patients were male. Their average age was 50.5 years (39–58 years). Two patients were previously diagnosed with Castleman's disease, and the other patients had TAFRO syndrome as the first symptom. The subsequent pathology was consistent with a Castleman's diagnosis, including plasmacytoid variant, hyaline vascular variant and mixed. The clinical manifestations of the patients were varied. Almost all patients had fever and multiple lymphadenopathies. Some patients experienced chest tightness, oedema and bleeding (Table 1).

Auxiliary examination

All patients had different degrees of systemic oedema, thrombocytopenia and systemic inflammation. The main diagnostic criteria for TAFRO syndrome were met. Specific information is shown in Table 2. All patients had hypoalbuminemia (albumin < 30 g/L). Three patients underwent monoclonal protein related tests, but no monoclonal phenomenon was found. Two of the six patients had elevated alkaline phosphatase, with the highest values being 310 and 319 U/L, respectively. The remaining patients had normal alkaline phosphatase levels. Patients 1 and 2 had haematuria proteinuria at the same time, patient 6 had haematuria, and the rest of the patients had

Table 1 Characteristics and manifestation of TAFRO patients

Patient	Age (y)	ECOG PS	Whether CD was diagnosed before	Type of CD	Complaints and symptoms
1	58	4	No	Mixed	Fever and multiple lymphadenopathies
2	52	4	Yes	PC	Fever and haemoptysis
3	51	2	Yes	HV	Chest tightness
4	58	2	No	Mixed	Fever
5	39	3	No	Mixed	Fever
6	45	4	No	HV	Oedema of both lower limbs

Table 2 Severity Score of TAFRO patients

Patient	Anasarca	Thrombocytopenia ($\times 10^9$/L)	Fever (°C)	CRP (mg/dL)	eGFR (ml/min/1.73m^2)	Total score
1	Pleural effusion + ascites + pitting oedema	45	37.8	26.9	8.5	9
2	Pleural effusion + ascites	3	38.1	32.8	12.9	9
3	Pleural effusion + ascites	34	37.6	4.2	58.0	6
4	Pleural effusion + ascites + pitting oedema	89	37.8	21.8	49.1	6
5	Pleural effusion + ascites + pitting oedema	12	37.6	26.9	37.9	7
6	Pleural effusion + ascites + pitting oedema	40	38.7	6.2	14.5	10

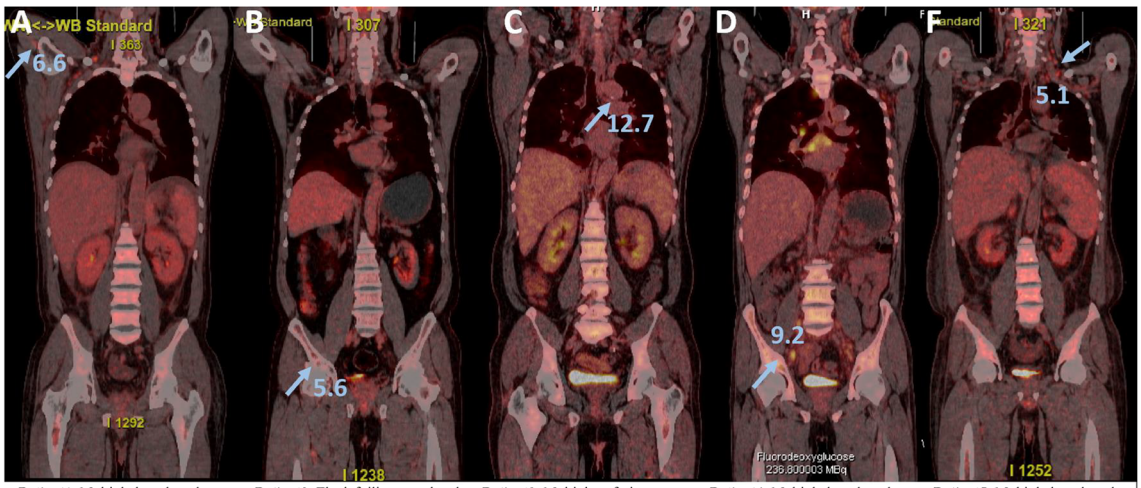
no abnormalities. Three patients had mild anaemia, and one patient had moderate anaemia. IL-6 levels were measured in 2 patients, and both patients had significantly elevated levels. All patients presented with multiple systemic lymphadenopathies, pleural effusion and abdominal effusion, accompanied by different degrees of pitting oedemas. Some patients underwent serous puncture catheterization, and the effusion test results tended to be considered exudate. PET-CT was performed in 5 patients, and the location of the enlarged lymph nodes and SUVmax values are shown in Fig. 1. Patient 6 had only normal CT and showed multiple lymphadenopathy (multiple lymph node enlargement in mediastinum, bilateral axilla, interhepatogastric, perigastric, hepatic portal, retroperitoneum, mesenteric lymph nodes, bilateral iliac vessels and so on). All 5 patients who underwent PET-CT performed needle biopsy on the site with the highest SUV value. PET-CT reported spleen enlargement in patient1, patient 4 and patient 5, and spleen enlargement in patient 6 through ultrasound examination. Patients 4 and 6 had liver enlargement. Patient 2 and patient 3 had no hepatosplenomegaly on impact examination. The 5 patients who were performed PET-CT showed diffuse metabolic activity in the central and peripheral bone marrow. Bone scintigraphy was performed in 1 patient, which showed multiple hyperactive bone metabolism throughout the body. One patient underwent bone marrow aspiration, and the results showed active bone marrow hyperplasia. According to the score, 3 patients in our study were classified as severe, and the other 3 patients were classified as moderate to slightly severe.

Treatment and survival

Six patients were treated with glucocorticoids, and only one patient received pulse glucocorticoid doses at the TAFRO Syndrome Study Group [4, 7] recommended levels (1 mg/kg per daily dose of prednisolone for 2 weeks, followed by tapering or pulse therapy using 500–1000 mg daily dose of methylprednisolone for 3 days). The use of glucocorticoids in 5 patients was not completely as recommended by the TAFRO Syndrome Study Group (the use time was not reached). Three patients had severe disease, and only 1 patient who met the TAFRO Syndrome Study Group recommendations for glucocorticoid use survived. Four patients received chemotherapy, and 1 patient was treated with rituximab, as shown in Table 3.

Discussion

Castleman disease (CD), also known as giant lymph node hyperplasia or angiolymphatic follicular tissue hyperplasia, is a group of rare heterogeneous lymphoma tissue proliferative diseases. In May 2018, it was included in the First Rare Diseases Catalogue of China. CD is classified into monocentric (UCD) and multicentric (MCD) types according to the extent of involvement and into hyaline, plasmacytic and mixed types according to histopathological features [8]. In 2010, Japanese scholars first reported 3 patients with fever, systemic oedema, thrombocytopenia,



Patient1: Multiple lymph node enlargement in both neck, superior diaphragm, mediastinum, bilateral axilla, abdominal cavity, retroperitoneum, bilateral iliac blood vessels, and groin.
SUVmax is about 6.6.

Patient2: The left iliac vessel and left groin with multiple swollen lymph nodes were more metabolically active.
SUVmax is about 5.6.

Patient3: Multiple soft tissue masses and nodules in the anterior mediastinum were metabolically active, and the enlarged lymph nodes above and below the left clavicle and mediastinum were metabolically active.
SUVmax is about 12.7.

Patient4: Multiple lymph node enlargement in the head and neck, intermuscularis of both upper arms, mediastinum, hilum of both lungs, bilateral internal milk lymphatic chain, bilateral axilla, supraprenic, abdominal cavity, iliac vascular lymph nodes, etc.
SUVmax is about 9.2.

Patient5: Multiple lymph node enlargement in bilateral posterior ear, bilateral subcutaneous neck, bilateral parotid gland, bilateral neck, mediastinum, bilateral axilla, abdominal cavity and retroperitoneal region, and inguinal region.
SUVmax is about 5.1.

Fig. 1 PET-CT of 5 patients showing the location of the enlarged lymph nodes and SUVmax values

Table 3 Treatment information for TAFRO patients

Patient	Severity of disease	Chemotherapy and other treatments	Use of glucocorticoid	Dialysis	Prognosis
1	Severe	VRD	Dexamethasone 20 mg for 5 days	Permanent dialysis	Dead
2	Severe	Rituximab + methylprednisolone	Methylprednisolone 500 mg for 5 days	eGFR recovered after 7 days of dialysis	Surviving
3	Moderate	TCP	Prednisone 100 mg for 5 days	No	Surviving
4	Moderate	CVP	Prednisone 100 mg for 5 days	No	Surviving
5	Slightly Severe	VCRP	Prednisone 60 mg for 3 days	No	Surviving
6	Severe	Methylprednisolone	Methylprednisolone 160 mg for 3 days	permanent dialysis	Dead

VRD bortezomib, lenalidomide, dexamethasone. *TCP* thalidomide, cyclophosphamide, prednisone. *CVP* cyclophosphamide, vincristine, prednisone. *VCRP* bortezomib , cyclophosphamide, lenalidomide and prednisone

lymph node enlargement and bone marrow reticular fibrosis. Lymph node biopsies were performed, and all patients showed clear vascular-type CD. The concept of TAFRO syndrome was clearly proposed in 2012 [9, 10]. TAFRO syndrome is extremely rare and has a low incidence [9], and few cases have been reported in the literature. We summarized the clinical manifestations, examination and treatment of 6 cases of TAFRO syndrome to facilitate clinicians to better understand the disease with early identification and reasonable treatment.

At present, the aetiology and pathogenesis of the disease are still being explored. Possible mechanisms reported in the literature include (a) intense cytokine storms, including involvement of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF); [2] abnormal immune function; and [3] infectious factors: bacterial or other viral (HHV-8 expected) infections may be a driving factor for the onset of TAFRO syndrome [10, 11]. IL-6 was measured in 2 of the 6 patients in our study, with levels of 4692.65 pg/ml in 1 patient and 29.46 pg/ml in the other, which may be related to the time of detection. VEGF was measured in patient 1 and patient 2, and the results were 350.5 pg/ml and 21.8 pg/ml, respectively. The time of detection both was the fourth day of the outbreak of TAFRO syndrome. The level of VEGF in patient 1 decreased to normal within 1 week with remission of TAFRO syndrome (113.0 pg/ml). Patient 2 continued to have a normal VEGF assay. We think that IL-6 is elevated in patients with TAFRO and high level of VEGF may be associated with a worse prognosis. At the 2022 Castleman Disease Collaborative Network (CDCN) meeting, the team of Professor David Fajgenbaum from the University of Pennsylvania conducted transcriptomic sequencing of 11 iMCD-TAFRO samples. The results showed that the expression of the PLA2GS2A and CCL23 genes in TAFRO samples was significantly higher than that in sentinel lymph node samples. It also showed abundant expression of genes involved in the coagulation cascade [12].

TAFRO syndrome patients have diverse clinical manifestations accompanied by multiple organ injury. Two patients were previously diagnosed with CD and developed TAFRO syndrome [13]. One patient had fever, anuria and haemoptysis within 2 days of chemotherapy intermission. Another patient was diagnosed with CD without treatment and subsequently developed symptoms of chest tightness. The result of auxiliary examination was consistent with the diagnosis of TAFRO. The immune systems of TAFRO patients were overactivated. All patients in our study had fever of varying degrees accompanied by CRP elevation. All 6 patients had different degrees of thrombocytopenia, which might be caused by abnormal bone marrow increases and immune abnormalities. All patients developed serosal effusion due to multiple organ injury, cytokine storm and hypoalbuminemia. Three patients developed renal failure with eGFR < 30 ml/min/1.73 m^2, which may be related to IL-6 inducing excessive production of VEGF, leading to glomerular endothelial injury. In 2020, Japanese researchers reported a case series study of 7 patients with TAFRO syndrome who underwent renal biopsy [14]. The pathological findings of renal aspiration showed thrombotic microangiopathy (TMA) and membranous hyperplastic glomerulonephritis (MPGN). The patients with relatively early renal biopsy tended to have TMA, while those with late renal biopsy tended to have MPGN, suggesting that MPGN lesions in TAFRO syndrome result from chronic TMA lesions [15]. Due to thrombocytopenia, a bone marrow biopsy was performed in only one patient during the onset and showed active bone marrow metabolism without reticulin fibrosis. Nuclear medicine imaging of 3 patients showed active diffuse metabolism in central and peripheral bone marrow. In conclusion, the possibility of TAFRO should be considered when CD patients develop symptoms such as oliguria, noninfectious fever, oedema, or thrombocytopenia inconsistent with the intensity of the patient's chemotherapy. Moreover, in patients with enlarged lymph nodes who have not had a biopsy, the medical team should be alert to these symptoms. Early diagnosis is the key to improving the prognosis of patients.

Wu CB et al. reported 6 cases of TAFRO syndrome [16], including 5 males and 1 female, with an average age of 41.5

years (27–59 years). The pathological types included plasma cell type in 3 patients, mixed cell type in 2 patients and hyaline vascular type in 1 patient. All patients had fever, systemic oedema (body oedema, pleural and peritoneal effusion, pericardial effusion), organ enlargement (liver, spleen, lymph nodes) and varying degrees of increased creatinine. Two patients had oliguria and needed renal replacement therapy, and 2 patients underwent renal biopsy, which showed renal thrombotic microangiopathy associated with subacute tubulointerstitial nephritis and secondary capillary proliferative glomerulonephritis. The levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were increased in all 6 patients, and the levels of VEGF were increased in 4 patients who received this test. CHOP chemotherapy was used in 2 patients, glucocorticoids were used in 1 patient, and glucocorticoids combined with rituximab or tocilizumab were used in 3 patients. Among them, 1 patient died because of disease progression after 5 years, and the other 5 patients were still stable.

There is no standard treatment for TAFRO syndrome due to its low incidence and unknown cause. Among the 12 patients counted by this study and Wu CB et al., 11 (91.7%) were male, with an average age of 50.5 years and 41.5 years, respectively. Nine patients (75%) were alive. The incidence of TAFRO syndrome is higher in middle-aged men. Timely identification and adequate drug treatment are the key to achieving a good prognosis. The TAFRO study group recommended high-dose steroids, tocilizumab, rituximab, thalidomide combined with cyclophosphamide and prednisone, plasma exchange and cyclosporine A for TAFRO patients [17, 18]. Early use of glucocorticoid pulses is the key to improving patient outcomes. The recommended regimen is as follows: prednisolone 1 mg/kg/day for 2 weeks, followed by tapering, or methyl-prednisolone pulse therapy with 500–1000 mg/day for 3 days if an emergency occurs [4, 19]. Clinical practice showed that 2 patients who did not use glucocorticoids according to the prescribed type and dose did not go into remission and died. The remaining four patients received timely glucocorticoid treatment in the early stages of the disease and achieved remission, even though some patients did not follow the recommended dosage. How long to get better depends on the timing of glucocorticoid application. Anti-IL-6 therapies can effectively improve various symptoms of patients [20]. We also observed that rituximab helped restore patients' kidney function early. The use of cyclosporine A should be avoided in patients with renal insufficiency. Symptomatic treatments such as anti-infection, dialysis treatment and nutritional support are also essential.

The median age of patients in our study was 51.5y (39–58 y). Patients in the Western cohort counted by Maisonobe et al. [21] were younger, with a median age of 32 years. The 2-year overall survival was above 95% in patients of Maisonobe's study. Our study showed that survival was not promising, with 2 out of 6 patients dying. And the cause of death was closely related to the outbreak of TAFRO syndrome. The possible reasons are as follows: [1] The patient is older and the severity score is high. [2] Most of the patients in the study of Maisonobe et al. used tocilizumab or rituximab, but only one patient in our study cohort used rituximab.

In conclusion, the incidence of TAFRO syndrome is very low, and the diagnosis is difficult. We hope to improve the cognition of clinicians through our research, with early diagnosis and reasonable treatment.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by XW, XZ, SQ, CS, XL, XF, LZ, JG and ZL. The first draft of the manuscript was written by XW, XZ and MZ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Due to the anonymized retrospective nature of the data, ethical approval of the study was not necessary.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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