TAFRO syndrome: a case report

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November 10, 2021

Abstract

A man diagnosed as TAFRO syndrome was successfully responded to a novel immunosuppressive regimen containing methylprednisolone and mycophenolate mofetil. Blood cells firstly recovered, followed by the general situation and complete recover 1 month later, highlighting the danger of TAFRO syndrome and the importance of immunosuppressive agents in reversing pathological course

TAFRO syndrome: a case report

Short Title: an extremely severe case of TAFRO syndrome

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Fundings: This work was supported by Grants from the Second Affiliated Hospital of Xi'an Jiaotong University–Scientific Research Fund (2020YJ(ZYTS)158).

Disclosure of Conflicts of Interest: None

Patient Consent Statement: The informed consent to report individual case and a written informed consent for patient information and images to be published were both provided by the patient.

Introduction

Castleman disease (CD) is a rare lymphoproliferative disease firstly defined in 1954[1]. It could be divided into two major forms, unicentric CD (UCD) and multicentric CD (MCD). MCD may cause multiple lymph nodes enlargement and organs dysfunction[2]. Approximately 50% of patients with MCD who are negative for HIV and HHV8 comprise a subgroup that has been termed as idiopathic MCD (iMCD)[3]. As a special subtype of iMCD, TAFRO syndrome was very rare to be reported, which characterized by thrombocytopenia [T], anasarca [A], fever [F], Renal failure[R], and organomegaly [O]. The rarity of TAFRO syndrome has

greatly limited the ability to perform systematic studies providing solid evidence of therapeutic strategies. Till now, some of the investigators have tried to synthesize a treatment algorithm for the clinicians[4]. Here we report a severely ill patient who was diagnosed as TAFRO syndrome and successfully responded to combined immunosuppressive regimens including thalidomide, methylprednisolone and mycophenolate mofetil. This report will provide valuable experience for patients suffered from this disease who cannot afford those expensive agents.

Case examination and treatment

A 36 years old man without special past history, was admitted due to fever, chest tightness and shortness of breath on 16 November, 2018. After admission, systemic laboratory and imaging examinations were performed and he was successively treated with antibiotics and supportive treatment. On day 3, since the patient had severe thrombocytopenia, needle inguinal lymph node biopsy was performed. The results were shown in **Figure 1A** . On day 8, continuous renal replacement therapy (CRRT) was performed to release swelling. All these strategies did not effective and the patient started to show a decrease of limb muscle strength to grade 3 with normal muscle tension. On day 13, PET-CT showed a multiple enlargement of lymph nodes, indicating hematological malignancy. At the same time, the platelet counts (PLT) remain under 20×10^{9}/L, with a getting worse liver function and general condition. On day 18, a second needle lymph node biopsy was performed. **Table 1** showed some important laboratory examination results. Until then, the patient was diagnosed as TAFRO syndrome.

On day 18, prednisone hydroxide (30 mg/d) was added. PLT gradually increased and pleural effusions were also reduced. On day 22, thalidomide (50 mg/d) was also added. PLT gradually increased to 40×10^{9}/L and the enlarged superficial lymph nodes were also diminished. On day 29, thalidomide was terminated because of the severe systemic allergic rash. Instead, experimental chemotherapy COP regimen was given. On day 30, patient started fever again, accompanied by an obvious abdominal distension then antibiotics were added again to control the potential infection. At this time his advanced intelligence started retardate. Cranial MRI showed there might be bilateral subfrontal cortex ischemia, and limbs electromyogram showed moderate to severe lesion of motor branches of peripheral nerves in extremities. Therefore, prednisone hydroxide (30 mg/d) was changed to methylprednisolone (40 mg/d) on day 30 because of its minimal side effect. On day 34, the patient started to show paroxysmal bradycardia during sleep with heart rate dropped to 40 beats per minute. Then methylprednisolone dose was increased to 80 mg/d and γ-Globulin (20 g/d) and mycophenolate mofetil (1500 mg/d) were also added. On day 36, the patient showed convulsion and seizure like features. Electroencephalogram showed a mild abnormality. After consulting neurologist, phenobarbital (200 mg/d) and lamotrigine (25 mg/d) was added to control seizure. Other supportive treatments were also persistently performed.

On day 45, the patient's general condition gradually improved. Both imaging and laboratory examinations showed steadily improvement, as shown in **Figure 1B.** The clinical course and laboratory parameters changes were shown in **Figure 1C** . On day 64, he was discharged from the hospital.

After a follow up of 36 months, the patient is still alive with a normal blood routine test result, liver function and normal muscle strength of his lower limbs, suggesting the durable curative effect of our treatment strategy.

Discussion

In this case, the patient showed intermittent fever, anemia, thrombocytopenia, intensive edema, elevated liver enzymes, renal dysfunction, hypoproteinemia, paralysis of lower extremity and even arrhythmia and seizure during the course, highlighting the complex manifestations of iMCD. To note, some of the patients diagnosed as iMCD showed more aggressive clinical course and have worse outcome. They have been proved to have TAFRO syndrome (Thrombocytopenia, Anasarca, Fever, Reticulin Fibrosis, and Organomegaly). Now it has been proved to be a novel subtype of iMCD according to the histopathological similarity of lymph node lesions. And the five-year survival rate is worse in TAFRO subtype than the others. In our case, the patient fitted Thrombocytopenia, Anasarca, Fever, Renal failure and Organomegaly, which was finally

diagnosed as TAFRO syndrome.

Till now, its etiology and pathogenesis remain unclear. It has been speculated that two factors play key roles in it. First is overproduction of IL-6 from germinal center B cells[5]which can cause lymph node enlargement, plasmacytic infiltration, hepatosplenomegaly, and reactive bone marrow plasmacytosis with polyclonal hypergammaglobulinemia[6,7]. As reported, we also observed a dramatically decreased IL-6 level after remission (from 18.7 pg/ml to normal). Another factor is autoimmune diseases which will aggravate the condition[8]. In our case, autoimmune related examination such as autoantibodies, antineutrophil antibodies and rheumatism series indexes were all negative.

For iMCD/TAFRO syndrome treatment, a consensus, evidence-based treatment guidelines were established in 2018[9]. The monoclonal antibody targeting the interleukin-6 signaling pathway (siltuximab/tocilizumab) with or without corticosteroids is the preferred first-line therapy for these patients with a response rate of single anti–IL-6 mAb 66% (88/144)[10]. Rituximab is also a first-line alternative to anti–IL-6 mAb therapy for patients who do not have marked cytokine-driven symptomatology[11]. In this case, we did not choose tocilizumab or rituximab because of financial reasons.

As a universal and powerful immunosuppressor, corticosteroids are also widely used in iMCD by suppressing the hypercytokinemia in a high dose, which may greatly increase the incidence rate of bacterial infection and sepsis. Furthermore, it has been proved that cessation of therapy or steroid tapering will inevitably cause disease relapse. Therefore, in this case, high dose methylprednisolone was used to initially control the disease, and thalidomide and mycophenolate mofetil were also added in initial disease control, with intermittent gamma globulin transfusion. During the maintenance setting, methylprednisolone dose was gradually reduced.

Mycophenolate mofetil is a novel immunosuppressive agent widely used in immune thrombocytopenia and stem cell transplantation[12]. It is considered relatively safe even overdose with a rare incidence rate of seizure[13]. Though it is not recommended for iMCD treatment, it did show potent efficacy in combination with cyclosporin in a 50-year-old male patient who was finally diagnosed as retroperitoneal hyaline-vascular CD[14]. In our case, the patient also responded well after adding mycophenolate mofetil. Of course, it could not completely due to mycophenolate mofetil since he might have responded to the earlier agents such as high dose steroids. Three days after adding mycophenolate mofetil, the patient showed convulsion and seizure like features. The possible reason might be the progression of the disease since he gradually showed a decrease of limb muscle strength and advanced mental retardation before taking mycophenolate mofetil.

For some patients, chemotherapy regimens can also be tried such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CVAD (cyclophosphamide, vincristine, adriamycin, etoposide)-like regimens. In this case, we also performed a COP regimen but the result showed that it did not help. The possible reason may be the aggressive and severity of the condition.

Thalidomide is a potent immunomodulatory agent, which could inhibit the production of several cytokines, including IL-1, IL-6, IL-12, tumor necrosis factor-a, and VEGF and had been shown treatment activity in iMCD. It is also recommended with or without other agents because of its less toxicity and similar efficacy (69% response)[15,16]. A phase 2 study also proved the effectiveness and safety of an oral thalidomide-cyclophosphamide-prednisone regimen for iMCD patients when tocilizumab or other monoclonal antibodies were not available. During our initial treatment, thalidomide was also adopted in combination with corticosteroids and it did show an increase of platelet count, suggesting it could be a promising choice for these patients.

In conclusion, we reported a case of HIV and HHV-8 negative TAFRO syndrome which was successfully treated with corticosteroids, thalidomide and mycophenolate mofetil, providing another choice for these patients.

Authorship list

Shan Meng: Participated in the whole therapy, summarized clinical data and wrote the articles

Hailing Liu: edited the figures and proofread the manuscript

Wanggang Zhang and Aili He: provided valuable diagnostic information and treatment suggestions

Honghong Sun and Ru Zhang: provided important treatment suggestions

Xiaoli Chen: provided pathological pictures

Yinxia Chen: Participated in the whole therapy and guided the article writing

Acknowledgement

We are also indebted to colleagues from the Department of Hematology, the Second Affiliated Hospital of Xi'an Jiaotong University.

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Table 1. Laboratory finds after admission

Test	value	Normal ranges
white blood cell ($\times 10^{9}$/L)	12.49	4.0-10.0
hemoglobin (g/L)	121	131-172
platelet ($\times 10^{9}$/L)	42	100-300
albumin (g/L)	19.9	35-55
globulin (g/L)	30.2	20-40
serum creatinine (μmol/L)	133.97	57-111
ALT (IU/L)	9	9-50
AST (IU/L)	28	15-40
γ-GT (U/L)	87	10-60
IgG (g/L)	13.9	7-16
IgA (g/L)	1.88	0.7-4.0
IgM (g/L)	0.4	0.4-2.3
CRP (mg/L)	232	0-3.5
PT(s)	11.9	10-14
APTT (s)	30.6	23-35
FIB (mg/dl)	562	185-350
D- dimer (μg/L)	12690	<590
FDP (mg/L)	41.76	<5
IL-6 (pg/ml)	18.7	0-14
EBV-DNA (IU/ml)	negative	$<1\times10^{3}$
CMV-DNA (IU/ml)	negative	$<1\times10^{3}$
ADAMTS13 activity (%)	76.7	68-131
HIV	negative	negative
HHV8 (copy/ml)	negative	$<1\times10^{-3}$
Blood immunofixation electrophoresis	negative	Negative
Urine immunofixation electrophoresis	negative	negative

*ALT: alanine aminotransferase; AST: alanine aminotransferase; γ-GT: γ-glutamyl transpeptidase; CRP: C reactive protein; PT: prothrombin times (s), APTT: activated partial thromboplastin time (s); FIB: fibrinogen; FDP: fibrinogen degradation product; IL-6: interleukin-6; HIV: human immunodeficiency virus; HHV8: human herpes virus 8.

Figure legend

Figure 1. Pathological results and image manifestation during the course. (a) pathological results of lymph nodes. H-E staining and immunohistochemical staining from inguinal lymph node. It showed multiple plamsa cells infiltration in the lymph medullary cord. While the complete structure of lymph node sinus and diffused angiogenesis were not typical because of the limitations of fine-needle aspiration biopsy. (b) chest and abdominal CT image changes during the clinical course. (c) the whole clinical course. PLT,

platelet; CRRT, continuous renal replacement therapy; COP chemotherapy, cyclophosphamide, vinorelbine and prednisone hydroxide.