An Infant with TAFRO Syndrome: Case Report and Review of the Literature

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Abstract

A rare lymphoproliferative disorder involving thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O), so called TAFRO syndrome, was first reported in 2010.1 Considered a variant of idiopathic multicentric Castleman's disease, the recent discovery and rarity of this syndrome poses significant challenges to diagnosis and management. In this case report, we review the youngest patient to be reported in the literature with TAFRO syndrome. We highlight the patient's diagnosis, management, and follow-up in the context of current recommendations for treatment and management of TAFRO syndrome.

An Infant with TAFRO Syndrome: Case Report and Review of the Literature

(Case Report of TAFRO Syndrome in an Infant)

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Abbreviations:

CD = Castleman's disease

CRP = C-reactive protein

ESR = erythrocyte sedimentation rate

HHV = human herpes virus

IL = interleukin

TAFRO = thrombocytopenia, anemia, fever, reticulin fibrosis, organomegaly

VEGF = vascular endothelial growth factor

Abstract

A rare lymphoproliferative disorder involving thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O), so called TAFRO syndrome, was first reported in 2010.[1]Considered a variant of idiopathic multicentric Castleman's disease, the recent discovery and rarity of this syndrome poses significant challenges to diagnosis and management. In this case report, we review the youngest patient to be reported in the literature with TAFRO syndrome. We highlight the patient's diagnosis, management, and follow-up in the context of current recommendations for treatment and management of TAFRO syndrome.

Word count: 88

Introduction

Castleman's Disease and TAFRO Syndrome

Castleman's disease (CD) is a rare lymphoproliferative disorder first described in the 1950s by Dr. Benjamin Castleman based on a single patient who presented with a hyperplastic mediastinal lymph node with regressive germinal centers.[2] Castleman's disease is divided into two broad clinical presentation categories, including unicentric CD, the most common form, and multicentric, or systemic, CD.[2] Multicentric CD is further delineated into HHV-8 multicentric CD and non-HHV-8 multicentric CD (idiopathic CD). While unicentric CD may be treated with surgical excision alone, multicentric CD is more aggressive and typically requires chemoimmunotherapy.[2]

A variant of idiopathic multicentric CD, TAFRO syndrome, was first described in 2010.[1] TAFRO encompasses distinct clinical characteristics: thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O). Exclusion of alternate diagnoses including POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes), IgG4-related disease, systemic lupus erythematosus, Sjogren's syndrome, vasculitis syndrome, and infectious causes is of great importance given their clinical overlap with TAFRO.[3] Thus, TAFRO syndrome is approached as a diagnosis of exclusion based on particular criteria.[5,6] As more cases of TAFRO syndrome are reported, formal diagnostic criteria for TAFRO syndrome have been created.[5,6]

Diagnostic Criteria

The 2017 international consensus on diagnostic criteria of TAFRO syndrome requires the presence of both major criteria and at least two minor criteria, one of which includes a laboratory criterion.[6] The major diagnostic criteria include histopathologic features of idiopathic multicentric CD spectrum, including regression of germinal centers or plasmacytosis in addition to lymphadenopathy ($\geq$ 1 cm in diameter) in at least two lymph node regions.[6] Minor laboratory criteria include elevated CRP (>10 mg/L) or ESR (>15 mm/h), anemia (Hgb <12.5 for males of Hgb <11.5 for females), thrombocytopenia (<150K) or thrombocytosis (>400K), hypoalbuminemia (<3.5 g/L), renal dysfunction (eGFR <60 mL/min/1.73 m2) or proteinuria (total protein 150 mg/24 h or 10 mg/100 mL), and polyclonal hypergammaglobulinemia (total g globulin or immunoglobulin G 1.7 g/L).[6] Clinical criteria include constitutional symptoms (night sweats, fever >38

C, weight loss, fatigue), hepatosplenomegaly, fluid accumulation (edema, anasarca, ascites, pleural effusion), eruptive cherry hemangiomatosis or violaceous papules, and lymphocytic interstitial pneumonitis.[6]There are a variety of exclusion criteria to rule out TAFRO mimickers.[6]

Treatment

The Castleman's Disease Collaborative Network (CDCN) provides treatment guidelines for TAFRO syndrome.[4] Like other forms of multicentric CD, TAFRO syndrome can be treated with chemoimmunotherapy. Typical agents include steroids, immunosuppression, rituximab, and anti-IL-6 agents siltuximab and tocilizumab.[1]Hypercytokinemia is suggested as a major driving force of TAFRO's multisystemic features,[1] but the precise pathophysiology remains to be fully elucidated and as such, targeted therapies continue to be limited.

Therapeutic approaches for TAFRO syndrome vary based on clinical severity.[4] For non-severe disease, siltuximab with or without steroids has the most robust supporting evidence (grade 1).[4] When siltuximab is unavailable, treatment options for non-severe disease include tocilizumab +/- steroids and rituximab +/- steroids.[4] However, in severe disease, steroids are standard in addition to an anti-IL-6 agent.[4]Whether partial or complete response is achieved, continuation of siltuximab or tocilizumab +/- steroids is recommended to maintain disease control.[4] In patients with inadequate response, transitioning to alternate immunomodulatory agents or combination chemotherapy comprises the remainder of consensus treatment recommendations.[4]

Here we review the presentation, evaluation, and management of an infant who was ultimately diagnosed with TAFRO syndrome.

Case Presentation

A previously healthy 11-month-old female presented with fever, oliguria, diarrhea, and fatigue. On admission, physical exam was notable for cervical lymphadenopathy, anasarca, and splenomegaly. Laboratory workup revealed anemia Hgb 8.6 g/dL (10.5-13.5 g/dL), elevated C-reactive protein 159.0 mg/L (<10 mg/L), hyperkalemia 5.6 mmol/L (3.4-5.0 mmol/L), hypocalcemia – ionized whole blood calcium 0.9 mmol/L (1.14-1.32 mmol/L), hypoalbuminemia 1.7 g/dL (2.5-5.0 g/dL), proteinuria 30 mg/dL (negative), and thrombocytopenia 24 K/cc mm (250-600 K/cc mm). Fluid status was managed by albumin infusions, calcium replacement, and loop diuretics. The patient underwent a CT scan of the chest, abdomen, and pelvis with contrast demonstrating anasarca, ascites, and diffuse lymphadenopathy.

The patient's initial cytokine panel was significant for elevation in soluble interleukin 2 (sIL-2) 61,490.0 pg/mL (175.3-858.2 pg/mL), interleukin 6 (IL-6) 6.3 pg/mL (<2.0 pg/mL), interleukin 10 (IL-10) 30.9 pg/mL (</= 2.8 pg/mL), and vascular endothelial growth factor (VEGF) 178 pg/mL (9-86 pg/mL). A bone marrow evaluation was negative for malignancy ,but demonstrated increased myelofibrosis and megakaryocytic hyperplasia with atypical morphology (Figure 1).

Treatment was initiated with methylprednisolone IV 1 mg/kg twice daily, however, two days later, the patient experienced progressive electrolyte abnormalities and fluid retention, including a pleural effusion. Following sedation for lymph node biopsy, her respiratory status declined requiring intubation and chest tube placement. Steroids were continued and tocilizumab was administered; her respiratory status improved and she was extubated to a high-flow nasal cannula within 24 hours. Given persistent anasarca and electrolyte derangements, tacrolimus was initiated. Finally, with pleural effusion resolution, her chest tube was removed.. Despite these interventions, elevated IL-6 levels and thrombocytopenia persisted. Additionally, the patient developed hypertension requiring amlodipine and labetalol. The lymph node biopsy demonstrated Castleman-like changes, including vascular proliferation and occasional atretic follicles (Figure 1). Following exclusion of other disease entities, the patient was deemed to meet criteria for TAFRO syndrome. Weekly tocilizumab was initiated for three more doses with plan to transition to every 3 week dosing thereafter. Finally, laboratory and clinical parameters showed resolution or improvement and the patient was discharged after a six-week stay. As an outpatient, she continued a steroid taper as well as daily tacrolimus

and tocilizumab as described. Additionally, she required multiple anti-hypertensives post-discharge.

Nearly six months after her initial presentation, the patient underwent repeat imaging which demonstrated resolution of anasarca, splenomegaly, and lymphadenopathy. Steroids were also weaned successfully six months after presentation with tacrolimus discontinuation shortly thereafter. Anti-hypertensives were discontinued with completion of steroid taper. The patient continued to have stable cytokine levels (Figure 2). At the time of this manuscript publication, the patient is twenty-one months since diagnosis and is continuing on every three-week tocilizumab with stable interleukin and VEGF levels. She is clinically well and thriving.

Discussion

The limited number of cases of TAFRO syndrome published to date in any age bracket remains scant. To our knowledge, this is the first report of TAFRO syndrome in an infant. The unusual combination of features and rarity of this entity posed a significant diagnostic challenge, but once identified, the patient was able to receive appropriate therapy with dramatic improvement. Drawing attention to this rare diagnosis, which is likely to have increased recognition in the future, is of critical importance. Continuing to raise awareness and suspicion of TAFRO syndrome will foster early diagnosis and more standardized treatment moving forward.

Word Count: 1,087 (excludes Abstract)

Ethics Statement

The parent of the child presented in this paper provided informed consent for publication including use of history, laboratory values, imaging, and other studies. The consent for publication of this case was submitted and reviewed by the Oregon Health & Science University Institutional Review Board (IRB) prior to publication and waived from full IRB review.

Conflict of Interest

No authors have any financial disclosures relevant to this topic.

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their story for the benefit of the medical community and future children yet to be

diagnosed with this rare syndrome.

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Figure Legend

Figure 1. A reticulin stain, 100x, performed on the bone marrow core biopsy highlights a diffuse increase in reticulin fibers with extensive intersections, indicating mild-to-moderate marrow fibrosis (A). H&E stained section, 100x, of the bone marrow core biopsy demonstrate increased megakaryocytes, some of which are distributed in loose clusters. The megakaryocytes show atypical morphologic features, including hyperlobulated nuclei, hyperchromatic nuclei, and abnormally large size (B). H&E stained section, 100x, of the right inguinal lymph node demonstrate atretic follicles surrounded by concentric layers of mantle zone lymphocytes (blue arrow). The interfollicular zones are expanded with vascular proliferation and are lymphocyte depleted. A prominent plasma cell expansion is not present. HHV8 infected cells were not identified by an HHV8 immunohistochemical stain (C).

Figure 2. The graph outlines the trend in clinically relevant cytokines including soluble interleukin 2 (sIL-2), interleukin 6 (IL-6), interleukin 10 (IL 10), and vascular endothelial growth factor (VEGF). Treatment included steroids starting with IV methylprednisolone 2 mg/kg/day twice daily (black arrow) followed by oral prednisone 2 mg/kg/day twice daily (red arrow), and a taper with oral prednisone (light blue). Tocilizumab administered on day three of admission followed by weekly during weeks four, five, and six. Thereafter, tocilizumab is being given once every three weeks.