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BRIEF REPORT OPEN ACCESS

Efficacy of High-Dose Intravenous Anakinra in Pediatric TAFRO Syndrome: Report of Two Cases and Literature Review

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ABSTRACT

TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly) syndrome is a rare, life-threatening inflammatory condition linked to infections, neoplasms, and idiopathic multicentric Castleman disease. Interlukin (IL)-6 inhibitors are the primary treatment, but refractory cases require alternatives. This study reports the first two pediatric TAFRO cases successfully treated with anakinra, an IL-1 receptor antagonist. Both patients had severe, rapidly progressing disease with multiorgan involvement. Anakinra, combined with corticosteroids, led to significant improvement and remission. We provide a literature review of pediatric TAFRO, confirming its rarity and the partial efficacy of IL-6 inhibitors in many cases.

1 | Introduction

TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly) syndrome is a serious inflammatory condition with multiorgan involvement with sudden fever, hematologic involvement (thrombocytopenia, megakaryocytosis, and reticulin fibrosis in the bone marrow), and anasarca. TAFRO can complicate infections, neoplasms, connective tissue disorders, and, classically, idiopathic multicentric Castleman disease (iMCD) [1]. The latter, iMCD-TAFRO, is the most well-known form and requires the fulfilment of specific diagnostic criteria [2–4]. Most cases have been successfully treated with interleukin (IL)-6 inhibitors; however, refractory cases requiring alternative treatments have been documented [1, 5–7]. IL-1 inhibitors are not considered a first-line treatment for TAFRO, although there are some reports of efficacy in adult patients, as the sole biological agent in combination with corticosteroids or in conjunction with other immunomodulatory drugs [7–9].

Abbreviations: Anti-SSA, anti-Sjögren's syndrome-related antigen A; Anti-SSB, anti-Sjögren's syndrome-related antigen B; CT, computed tomography; IL-1, interlukin-1; IL-6, interleukin-6; iMDC, idiopathic multicentric Castleman disease; IV, intravenous; MAS, macrophage activation syndrome; MRI, magnetic resonance imaging; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly; TNFRI, tumor necrosis factor receptor 1.

Summary

- TAFRO syndrome is a rare and life-threatening inflammatory condition.
- Anakinra is an effective treatment option in pediatric TAFRO.

2 | Case Report

The first patient (P1), a 14-year-old boy, 70 kg, was admitted to our Institute with persistent fever, nausea, headache, asthenia peri-malleolar oedema, hepatosplenomegaly, and lymphadenopathies, occurring 1 month after appendectomy. Blood tests revealed persistently increased inflammatory markers, leukopenia, anemia, and thrombocytopenia. Radiology revealed multicentric lymphadenopathy associated with pleural and peritoneal effusion. Given the poor response to antibiotics and the worsening clinical conditions, examination of ascitic fluid, bone marrow, and cerebrospinal fluid (CSF) was performed, showing no tumoral cells. Due to worsening anasarca and rising inflammatory markers, parenteral methylprednisolone (140 mg/day, 2 mg/kg/day) was started, without improvement. Pleural and peritoneal drainage was performed, and the patient progressed to prerenal acute renal failure, requiring hemodialysis. Renal biopsy confirmed acute tubular necrosis secondary to hypo-vascularization. Given clinical worsening, intravenous (IV) anakinra 200 mg/day was added to ongoing treatment, after approval for off-label use and parental consent. In the following days, fever resolved, poly-serositis improved (pleural and peritoneal drains were removed after 12 and 22 days, hemodialysis was stopped after 4 weeks), and acute phase reactants normalized within 10 days of treatment. Lymph node biopsy was consistent with Castleman disease (Table 1 and Figure S1A). Of note, after central catheter removal, the patient experienced sudden dyspnea and seizures, requiring treatment with heparin and levetiracetam. A brain magnetic resonance imaging (MRI) showed signs of extensive leptomeningeal inflammation with normal CSF tests. This finding, together with thrombocytopenia, anasarca, and leptomeningitis, was consistent with the diagnosis of TAFRO syndrome. Despite tapering corticosteroids, anakinra led to gradual resolution of symptoms and was switched to subcutaneous after 4 weeks from start (Figure 1A). Of note, plasmatic IL-6 levels, measured before corticosteroids, were normal.

The patient was discharged after 3 months in good condition; steroidal treatment was progressively tapered and withdrawn after 7 months. After 9 months, anakinra was tapered to 100 mg/day subcutaneous for 6 months, then progressively reduced to 100 mg weekly. Heparin was administered for 5 weeks, then replaced with fondaparinux for 5 months; levetiracetam was withdrawn after 12 months.

Four years after disease onset, while receiving anakinra 100 mg weekly, the patient experienced a disease flare, characterized by fever, abdominal pain, and arthralgia, treated with an increase of the dosage of anakinra to 200 mg/day. The patient has been in remission for 2.5 years on anakinra 100 mg/day.

The second case (P2), an 8-year-old female patient, 50 kg, was transferred to our Institute due to a persistent inflammatory condition lasting 3 weeks, despite antibiotics and IV methylprednisolone (1 mg/kg/day). In the initial phase, the clinical presentation was predominantly gastrointestinal, with diarrhea, abdominal pain, and nausea. Helicobacter pylori infection was found, and the patient received antibiotics. Bone marrow aspiration and colonoscopy were normal, echocardiography showed minimal pericardial effusion, and abdominal computed tomography (CT) scan revealed peritoneal effusion, mild splenomegaly, and lymphadenopathies. The patient tested positive for antinuclear, anti-Sjögren's syndrome-related antigen A (SSA)/Ro, and anti-SSB/La antibodies, with normal parotid ultrasound. Notably, the patient never reported symptoms suggestive of Sjögren's syndrome. One day after admission, she presented with respiratory distress, fever, worsening anasarca, and behavioral changes. Blood tests revealed elevated inflammatory markers, hypoalbuminemia, thrombocytopenia, coagulation abnormalities, neutrophilic leucocytosis, and renal insufficiency. She required albumin infusions and paracentesis. A brain MRI showed a millimetric ischemic lesion in the right frontobasal region. Total body MRI revealed hepatosplenomegaly, symmetric lymphadenopathies, and signs of bone marrow reconversion in the spine, pelvis, and bones. Bone marrow biopsy revealed dyserythropoiesis, megakaryocytes hyperplasia, and inflammatory infiltrate; lymph node biopsy confirmed Castleman disease (Figure S1B–D); salivary gland biopsy showed a nonspecific inflammatory lymphoplasmacytic infiltrate (Figure S2). Given the clinical picture suggestive of TAFRO syndrome, anakinra (8 mg/kg/day) was added to IV methylprednisolone at 8 mg/kg/day. Plasmatic cytokine levels could only be measured the day after starting treatment with anakinra, while the patient was still in the active disease phase. IL-6 levels were normal, while tumor necrosis factor receptor 1 (TNFRI) and IL-18 levels were elevated (Table 1). Additionally, IL-1RA was also elevated, but likely related to the ongoing treatment with anakinra. Improvement was noted after 7 days: fever resolved, renal and liver function improved (peritoneal drainage removed after 7 days), and inflammatory markers normalized in 10 days (Figure 1B and Table 1). The patient was discharged after 1 month, on treatment with anakinra (4 mg/kg/day, switched to subcutaneous after 1 month from start), oral prednisone (0.5 mg/kg/day), and low dose aspirin. Steroid treatment was tapered and withdrawn after 3 months. Five months after discharge the patient remains asymptomatic on anakinra 2 mg/kg/day subcutaneously.

3 | Literature Review of Pediatric TAFRO Cases

To our knowledge, there are only 13 reported cases of pediatric-onset TAFRO. Anakinra had been used only in one case with a concurrent diagnosis of Epstein–Barr virus-associated secondary hemophagocytic lymphohistiocytosis (*Material* in Supporting Information and Table S1) [10–19].

4 | Discussion

TAFRO syndrome should be considered in hematologic as well as immuno-rheumatologic and emergency settings due

TABLE 1 | Demographic, clinical, and biochemical characteristics of the described patients.

	Patient 1 (P1)	Patient 2 (P2)
Age at onset (years)	14	8
Sex	Male	Female
Ethnicity	Caucasian	North African
Family history	Uninformative	Uninformative
Past medical history	Congenital factor VII deficiency Tonsillectomy in infancy EBV and CMV infections	Uninformative
Antibiotics	Yes (metronidazole and clarithromycin, piperacillin-tazobactam, meropenem, tigecycline and gentamicin)	Yes (amoxicillin–clavulanic acid, piperacillin–tazobactam, metronidazole, ceftriaxone, and vancomycin)
Hepatomegaly	Yes	Yes
Splenomegaly	Yes	Yes
Renal failure	Yes	Yes
Renal biopsy	Yes	No
Hemodialysis, duration	Yes, 3 weeks	No
Bone marrow biopsy	Yes	Yes
Lymph node biopsy	Yes	Yes
Salivary gland biopsy	No	Yes
Autoantibodies		
ANA	Negative	1:320 (speckled)
ENA	Negative	Anti SS-A/Ro, anti-SS-B/La
Anti-dsDNA	Negative	Negative
Anticardiolipin	Positive IgG, Negative IgM	Negative
Lupus anticoagulant	Negative	Negative
Anti-beta2 glycoprotein	Negative	Negative
Pharyngeal and nasal swab	Negative	Negative
Quantiferon	Negative	Negative
Celiac disease screening	Negative	Negative
ADAMTS13 activity	Normal	Normal
HHV-8 DNA	Negative	Negative
EBV DNA	Negative	Negative
CMV DNA	Negative	Negative
IgA (mg/dL, nv 70–400)	52	76
IgG (mg/dL, nv 700–1600)	526	648
IgM (mg/dL, nv 40–230)	104	35
IgG1 (mg/dL, nv 370–1150)	419	454
IgG2 (mg/dL, nv 72–480)	160	103
IgG3 (mg/dL, nv 13–149)	28,3	14,8
IgG4 (mg/dL, nv 3–210)	4,7	1,3
IL-6 (plasma, pg/mL)[a]	<1.64 (ELISA; nv 0–10)	21 (ELLA; nv 0–22.6)
IL-18 (plasma, pg/mL)	Not available	509 (ELLA; nv 108–359)
TNFRI (plasma, pg/mL)	Not available	5487 (ELLA; nv 586–1038)

Abbreviations: ANA, antinuclear antibodies; anti-dsDNA, antidouble-stranded DNA antibodies; CMV, citomegalovirus; EBV, Epstein–Barr virus; ENA, antiextractable nuclear antigens antibodies; HHV-8, human herpesvirus 8; Ig, immunoglobulin; IL-6, interleukin 6; nv, normal value.

[a]Variations in the reference values for IL-6 levels are due to differences between laboratories.

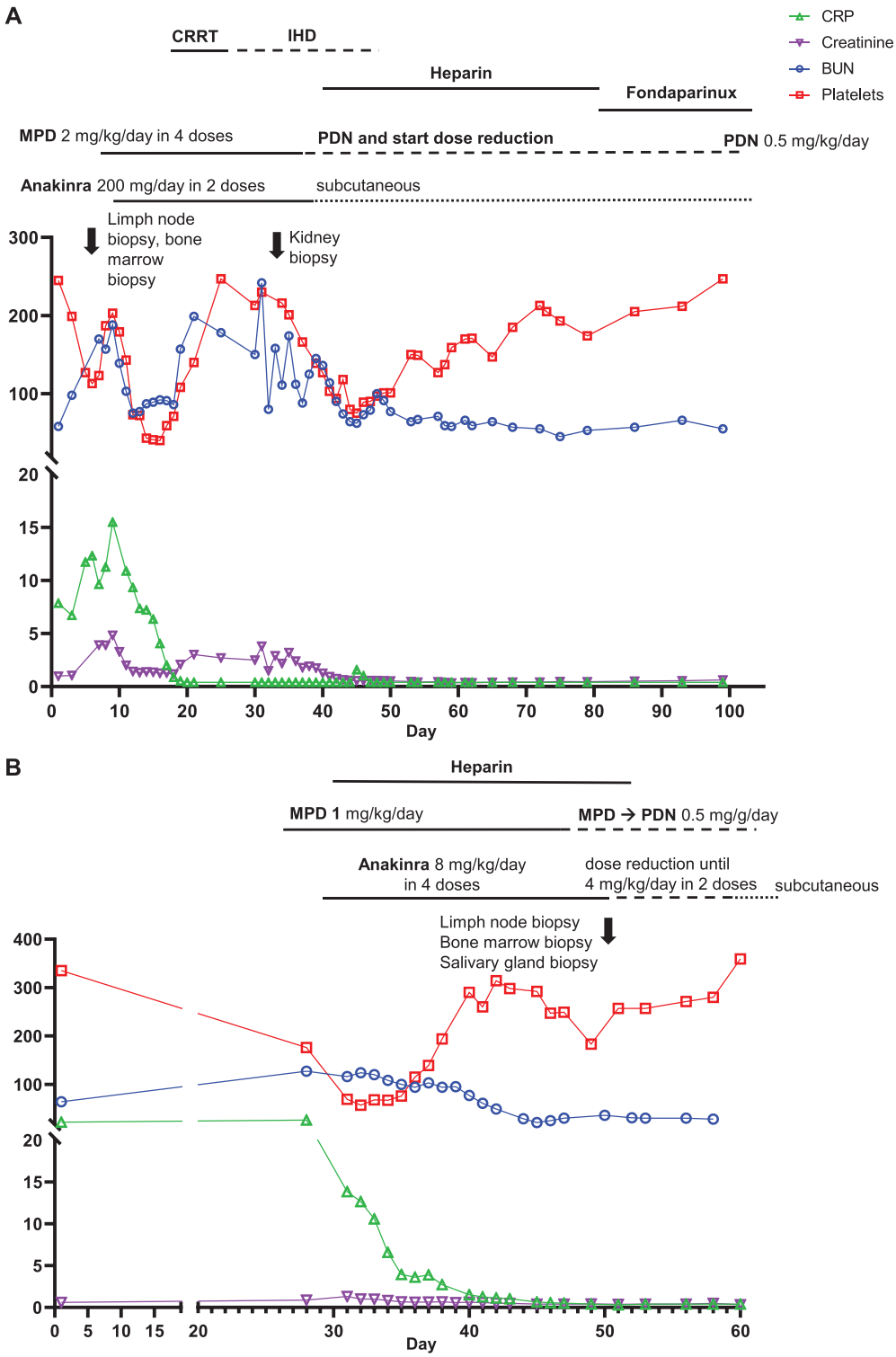

FIGURE 1 | Laboratory parameters and therapy performed in patient 1 (A) and patient 2 (B) during the admission. BUN: blood urea nitrogen; CCRT: continuous renal replacement therapy; CRP: C-reactive protein; IHD: intermittent hemodialysis; MPD: methylprednisolone; PDN: prednisone.

to its severity and clinical overlap with sepsis, autoimmune lymphoproliferative syndrome, macrophage activation syndrome (MAS), and systemic lupus erythematosus [1].

The two patients described in this report presented with symptoms consistent with iMCD-TAFRO syndrome, with patient 1 fulfilling the 2015 Masaki criteria and patient 2 the revised 2019 criteria [2]; moreover, lymph node histology was compatible with MCD in both patients [3].

Interestingly, our first patient experienced acute TAFRO during adolescence following an appendectomy, like one of the previously described cases [19]. The second patient tested positive for anti-SSA and anti-SSB antibodies and had a salivary

gland biopsy showing inflammatory lymphocytic infiltrate, although she has never shown symptoms indicative of Sjögren's syndrome or met the clinical criteria for it [20]. Additionally, a recent association between the positivity for anti-SS antibodies has been described in iMCD-TAFRO, distinguishing them from isolated iMCD cases without TAFRO-related symptoms [21].

The most frequently described therapy for TAFRO syndrome associated with iMCD was IL-6 blockade, also in pediatric cases. Most reported cases were diagnosed and treated in China and Japan, where IL1-blockers were not widely used, especially in the past. Notably, our patients had severe disease without elevated IL-6 levels, which are only documented in a subset of TAFRO patients [22]. Moreover, TAFRO patients usually do not exhibit some typical laboratory findings usually observed in IL-6-driven inflammation, such as hypergammaglobulinemia and thrombocytosis, suggesting the possibility of a different cytokine hierarchy in this condition. Together with this report, four patients with iMCD-associated TAFRO syndrome (two adults and two pediatric) were successfully treated with anakinra. Notably, while the two adult patients received the standard dosage of 100 mg/day subcutaneously [8, 9], the two pediatric patients in this study were given a higher dosage. Patient 1 received approximately 3 mg/kg/day, while patient 2 was administered 8 mg/kg/day due to more severe symptoms upon arrival at our center and the more recent evidence supporting the safety of high-dose IV anakinra in other inflammatory conditions, such as MAS and multisystem inflammatory syndrome in children [23, 24]. The higher dosage of anakinra in patient 2 allowed us to maintain a lower dose of methylprednisolone (Figure 1).

Although the mechanism of action of anakinra (IL-1alpha and IL-1beta inhibitor), in this condition, is not yet fully understood, two hypotheses can be proposed. The first is related to the pathogenic role of IL-1beta, secreted following the activation of the noncanonical NLRP3 inflammasome pathway, potentially triggered by the lipopolysaccharide toxin secreted by gram-negative bacteria. Supporting this hypothesis, TAFRO has been described after a prior gastro-enteric bacterial infection [25–27].

Additionally, IL-1alpha may also play a role, as it is secreted by stressed cells, including endothelial cells, in a paracrine manner and it can sustain the cycle of endothelial permeability in this disease [28], supporting the use of an IL-1 blocker able to inhibit both IL-1alpha and IL-beta, like anakinra.

In conclusion, we report the first two pediatric TAFRO cases successfully treated with the IL-1 receptor antagonist anakinra. It was chosen over anti-IL-6 due to its rapid pharmacokinetics and manageability, particularly in the context of severe liver dysfunction. Larger studies are required to establish the role of anakinra in TAFRO, especially in pediatric patients.

Author Contributions

S. P. drafted the manuscript. J. F. conducted the histological analysis and authored the section on histological findings. S. P., V. N., C. M. C., S. V., R. P., S. R., S. S., V. G. V., R. C., and M. G. managed patient follow-up and contributed to reviewing the manuscript draft. R. C. conceived the idea for the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

R. C., S. V., and R. P. received consultancy and speaker fee from SOBI. M. G. received consultancy and speaker fee from Boheringer, Fresinius-Kabi, Kiniksa, Novartis, and SOBI.

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Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.