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Case-based insights into managing TNF receptor-associated periodic syndrome in low-resource-limited settings

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Abstract

We report the case of a 22-year-old male presenting with a three- and half-year history of recurrent febrile episodes associated with rash, periorbital swelling, and inflammatory joint pain. The patient underwent extensive evaluations and multiple therapeutic trials, including treatments for leprosy, autoimmune pancreatitis, and adult-onset Still's disease, all of which were ineffective. Eventually, a periodic fever syndrome was suspected, and he was diagnosed with probable TRAPS based on clinical criteria, despite the absence of a TNFRSF1A mutation. This case highlights the diagnostic complexity of periodic fever syndromes in resource-limited settings and emphasizes the importance of individualized treatment approaches, such as the successful use of etanercept in the absence of IL-1 inhibitors.

Keywords: TRAPS; Auto inflammatory disorder; Anti-TNF.

Introduction

Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) is a rare auto-inflammatory disorder first described in 1982, characterized by recurrent episodes of fever and systemic inflammation due to mutations in the TNFRSF1A gene [1]. TRAPS is one of the periodic fever syndromes, with patients typically presenting with prolonged febrile episodes, often lasting longer than a week, accompanied by symptoms such as migratory rash, abdominal pain, arthralgia, and myalgia [2]. Unlike infectious or autoimmune conditions, TRAPS arises from inappropriate activation of the innate immune system, leading to chronic inflammation. The pathogenesis of TRAPS involves impaired shedding of the TNF receptor from the cell surface, resulting in increased inflammatory responses [3]. Left untreated, TRAPS can lead to severe complications such as amyloidosis, a condition that can cause significant organ damage, especially in the kidneys [4]. The rarity and nonspecific symptoms of TRAPS make diagnosis challenging, often requiring genetic testing to confirm the presence of TNFRSF1A mutations. In this case report, we discuss a patient with recurrent fever and systemic symptoms, ultimately diagnosed with TRAPS. This case highlights the importance of early recognition and appropriate management to prevent disease progression and long-term complications.

Case report

A 22-year-old male student presented with recurrent episodes of high-grade fever persisting over the last three and half years. Each febrile episode lasted 4-5 days, peaking at 105°F, and was partially relieved by paracetamol. Accompanying the fever, a rash appeared 2-3 days after its onset, initially maculopapular (Figures 1,2) on the trunk and later progressing to plaque-like lesions involving the limbs. The rash was mildly to moderately painful, non-itchy, and resolved with the fever. Additionally, he experienced periorbital swelling (Figure 3) during each episode. The patient reported inflammatory joint pain involving the shoulders, elbows, wrists, knees, ankles, and muscles in a symmetrical pattern, with associated inflammatory low back pain. There was no history of scaly rashes, painful red eyes, bowel or bladder issues, oral or genital ulcers, nodular swellings, or a family history of similar illness. Over this period, he experienced un-

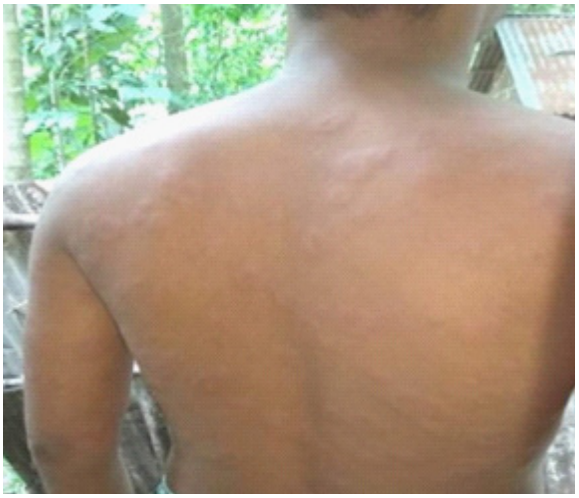
intentional weight loss of 18 kg. The intervals between episodes were symptom-free and lasted 8-10 days. In May 2022, the patient was diagnosed and treated for lepromatous leprosy based on a skin biopsy suggesting indeterminate leprosy; however, there was no clinical improvement after six months. In March 2023, a diagnosis of IgG4-related autoimmune pancreatitis was considered, based on weight loss, imaging, and laboratory findings. He was treated with prednisolone (starting at 40 mg/day and tapered to 15 mg over three months), but symptoms recurred upon discontinuation. Methotrexate (10 mg/week) was tried for three months for a presumed diagnosis of adult-onset Still's disease, but this provided no relief. In November 2023, he was admitted to the Rheumatology Department at BSMMU for further evaluation. At the time of admission, he was asymptomatic as he was between febrile episodes. Examination during the symptom-free interval revealed no abnormalities. Laboratory investigations showed persistently elevated ESR, CRP, and ferritin levels. Tests for RA, anti-CCP, ANA, anti-dsDNA, and the ENA profile were negative. Additional findings included:

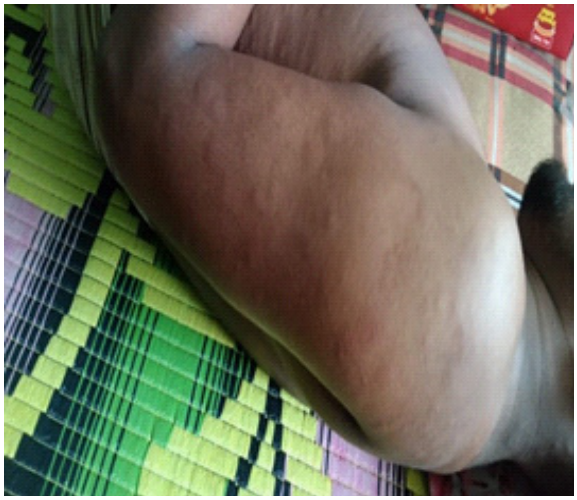
IgG4 level: Elevated at 253 mg/dL (normal range: 2-121 mg/dL).

PET-CT: Showed a bulky pancreas with diffuse increased FDG uptake, along with hepatosplenomegaly.

MT test: chest X-ray, and abdominal ultrasound: Normal.

Given the constellation of symptoms—recurrent fever, myalgia, periorbital edema, migratory rash, and lack of family history-a periodic fever syndrome, most likely TNF Receptor-Associated Periodic Syndrome (TRAPS), was suspected. Although certain features, such as the duration of episodes being less than 7 days, were atypical for TRAPS, the diagnosis was considered based on clinical criteria per PRINTO guidelines. Genetic testing was advised. The genetic test showed no TNFRSF1A mutation (required for TRAPS diagnosis); instead, a PIK3CD gene mutation was identified. Colchicine (0.6 mg twice daily) was initiated but proved ineffective after one and half months. Given the unavailability of IL-1 inhibitors in Bangladesh, etanercept, a TNF inhibitor, was prescribed. The patient was initially treated with etanercept at a dose of 50 mg weekly for the first three months, during which he showed significant clinical improvement. This was followed by a reduction to 25 mg weekly for another three months as his inflammatory markers, including ESR and CRP, normalized, and his symptoms further improved. Subsequently, the dosing interval was extended to 25 mg every two weeks for two months. Currently, the patient is maintained on a monthly dose of 25 mg, with excellent disease control and sustained remission.





Figures 1 and 2: Rashes during attack.

Figure 3: Periorbital edema during attack.

Figure 4: During maintenance treatment.

Discussion

This challenging diagnostic case involves a 22-year-old male with a three- and half-year history of recurrent febrile episodes and systemic inflammation. His clinical features overlapped with several autoinflammatory and autoimmune syndromes, complicating the diagnostic process. Ultimately, a thorough evaluation, including the exclusion of closely related conditions, led to the identification of a PIK3CD gene mutation-a rare finding consistent with Activated PI3K Delta Syndrome (APDS).

This patient's initial symptoms-recurrent fever, migratory rash, periorbital swelling, and inflammatory joint and muscle pain-pointed towards an autoinflammatory condition. The early consideration of leprosy and IgG4-related disease reflects the broad differential diagnoses necessitated by overlapping clinical features. However, the lack of sustained response to treatment for these conditions, alongside symptom recurrence and progressive weight loss, necessitated further investigation. The pivotal diagnostic features included persistently elevated inflammatory markers ESR, CRP, ferritin, and imaging evidence of a bulky pancreas accompanied by hepatosplenomegaly. These findings initially reinforced the consideration of IgG4-related disease, particularly given the elevated IgG4 levels. However, the absence of response to corticosteroids and methotrexate led to reevaluation. The suspicion of TNF Receptor-Associated Periodic Syndrome (TRAPS) based on PRINTO criteria, despite some atypical features such as shorter febrile episodes, prompted genetic testing. The identification of a PIK3CD gene mutation raises the possibility of APDS, a rare primary immunodeficiency caused by hyperactivation of the PI3K delta signaling pathway. This genetic mutation is associated with recurrent infections, autoimmunity, lymphoproliferation, and, less commonly, autoinflammatory syndromes, which aligned with the patient's presentation though the patient doesn't have any history suggestive of recurrent infection. The impact of anti-TNF (tumor necrosis factor) therapies on Tumor Necrosis Factor Receptor-Associated Periodic Syndromes (TRAPS) is a significant area of discussion in autoinflammatory disease management. TRAPS is a rare hereditary autoinflammatory condition caused by mutations in the TNFRSF1A gene, which encodes the TNF receptor. This results in dysregulated inflammation and periodic fever episodes. Anti-TNF therapies, such as infliximab, etanercept, and adalimumab, target TNF to modulate the inflammatory response.

Anti-TNF agents like infliximab and adalimumab, which are monoclonal antibodies against TNF, have not shown consistent efficacy and, in some cases, have led to paradoxical worsening of inflammation [2]. This may be due to the formation of immune complexes or the failure to adequately clear TNF receptor aggregates that are dysfunctional in TRAPS [5]. This variable response has led clinicians to explore alternative therapies, particularly IL-1 inhibitors like anakinra and canakinumab, which have demonstrated greater efficacy in many patients with TRAPS [3]. Etanercept, a soluble TNF receptor fusion protein, has been particularly effective in some cases by binding and neutralizing TNF, thus reducing inflammation and particularly in cases where IL-1 inhibition is ineffective or not well tolerated. The soluble receptor-based therapy (etanercept) might work better in this context because it mimics natural receptor activity without inducing receptor cross-linking, unlike monoclonal anti-bodies [6]. Limited clinical data suggest that etanercept may offer symptom relief in mild to moderate TRAPS cases. However, its long-term benefits remain uncertain. Studies have shown that etanercept can decrease the frequency and severity of febrile attacks and help prevent long-term complications like amyloidosis [1]. The choice of therapy should be individualized, based on patient response and tolerance to treatment [4] IL-1 inhibitors (e.g., anakinra, canakinumab) have shown greater efficacy and are increasingly preferred due to the central role of IL-1 in TRAPS pathogenesis [7]. IL-1 blockade has emerged as a more effective strategy for managing TRAPS, as it targets a broader inflammatory pathway associated with the disease. For severe cases, therapies targeting IL-6 (tocilizumab) or broader immunosuppressants may be explored [8].

While anti-TNF therapies can provide relief for some TRAPS patients, their efficacy and safety profile are inconsistent due to the unique pathophysiology of the disease. Etanercept shows promise in select cases, but monoclonal antibodies often exacerbate symptoms. IL-1 inhibitors are now the cornerstone of TRAPS treatment, highlighting the importance of precision medicine in managing autoinflammatory diseases.

Conclusion

In resource-limited settings, the use of anti-TNF therapies must be approached with caution due to their inconsistent efficacy and potential for adverse effects. Etanercept may offer a viable option for mild to moderate cases where IL-1 inhibitors are inaccessible. However, optimizing TRAPS management requires precision medicine approaches, leveraging local resources and expertise to tailor therapy to individual patient needs. Advancing awareness and accessibility of IL-1 inhibitors could significantly improve outcomes for TRAPS patients globally, particularly in underserved regions.

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