TNF-receptor associated Periodic Fever Syndrome and Response to Interleukin 1 Antagonist Therapy

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations in the gene encoding the Tumor Necrosis Factor (TNF) Receptor Super Family1A (TNFRSF1A) on chromosome 12p13. TRAPS is characterized by recurrent attacks of fever, abdominal pain, migratory rash, and myalgia. Despite several hypotheses explaining the pathogenesis of TRAPS, the exact etiology remains obscure.

We report a female child who presented with clinical manifestations suggestive of macrophages activating syndrome (MAS) in addition to features of TRAPS syndrome. Next-generation sequencing was used to assess the genomic DNA of the patient and heterozygous c.362G>A p.(Arg121Gln) a variant in the TNFRSF1A gene (chr.12); an autosomal dominant inheritance was identified. After being treated for MAS manifestations, the patient was initiated on anti-inflammatory drugs including TNF-receptor antagonist with partial clinical response. However, the patient had a significant clinical response to interleukin 1β (IL-1β) therapy and normalization of the inflammatory markers. Our findings suggest that IL-1β antagonist is a more effective alternative treatment for TRAPS complicated with MAS.

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TRAPS is a rare autosomal dominant disease characterized by recurrent attacks of prolonged fever associated with abdominal pain, myalgia, migratory erythematous skin rashes and eye manifestations[1]. TRAPS was first described in 1982 in a large pedigree of three families of Irish-Scottish descent as Familial Hibernian Fever (FHF) with distinct clinical entity[2].

In the following years, genome-wide searches and linkage analysis in the affected families identified FHF susceptibility gene on chromosome 12p13. The chromosome region includes several candidate genes: CD4, LAG-3, CD27, C1R, C1S and TNFRSF1A. Thereafter, FHF was re-named as TRAPS after discovering mutations in the gene encoding the TNF Receptor Super Family 1A (TNFRSF1A) on chromosome 12p13[3].

In the largest reported case series on patients with TRAPS, genetic variants revealed variable clinical manifestations at presentation. The most common TNFRSF1A variant was R92Q (34%), followed by T50M (10%). The median age at presentation was 4.3 years but 9.1% of patients present above 30 years of age. The most common features associated with the pathogenic variants were: fever, limb pain, abdominal pain, rash and eye manifestations[4].

The aim of this report is to present a child with macrophages activating syndrome (MAS) followed by the appearance of clinical phenotype of TRAPS syndrome.

THE CASE

A two-years-and-8-months old female presented with a history of intermittent fever for 3 weeks, with a temperature reaching up to 39 °C, mainly at night and were associated with chills and perspiration. Associated with the fever was pain in the ankles and knees which were progressive, and more prominent at the time of fever. The joints pain progressively increased and the child was eventually unable to bear weight.

The patient had a history of generalized abdominal pain, which was associated with episodes of vomiting. Poor appetite was

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reported but no loss of weight. Furthermore, the child's mother reported painful skin rash in the form of red patches and dark bluish spots which was noticed in the lower limbs.

Her past medical history revealed recurrent episodes of prolonged fever, abdominal pain, and joint pain since the age of one year. She was usually treated with antibiotics with no significant improvement.

The child was born to parents of second-degree consanguinity. She has 7 siblings who were well and healthy.

On examination, the child was febrile (39 °C). She looked irritable with remarkable periorbital puffiness. Neck examination revealed small palpable lymph nodes. These were firm and non-tender in the submandibular and cervical regions. Cardiovascular and chest examination was normal, the abdomen was soft with a palpable spleen of 3 cm below the costal margin. Her musculoskeletal examination revealed swelling and tenderness in both ankles and knees, more prominent on the right side. Quadriceps muscles were also tender with some restriction in the range of hips movements. The skin rash showed bruises and ecchymosis which were mostly located along the shins, see figure 1.

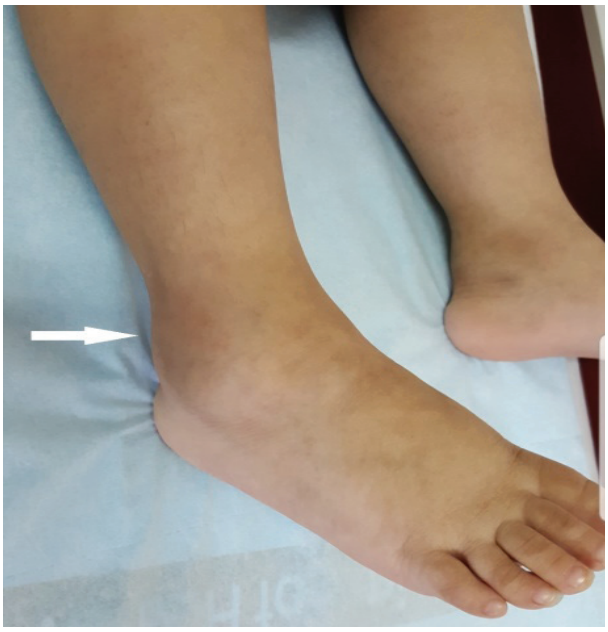

Figure 1: Right Ankle Swelling with Faint Erythematous Rash Closer to Lateral Malleolus. Tiny Dark Spots and Small Ecchymotic Patch Close to Medial Malleoli in Left Foot

Laboratory investigations showed a hemoglobin (Hb) level of 8.4g/dL and platelet count of 496 10^9/l. White blood cells (WBCs) were at 16.8 10^9/l (Neutrophils: 84.7%; Lymphocytes: 10.4%; Monocytes: 4.1%). The peripheral smear showed no abnormal cells.

Liver function tests and renal function tests including electrolytes were normal. Blood, stool, and urine cultures revealed no growth. Inflammatory markers were: CRP was 134 mg/L (N: 0-3) and ESR was 126 mmhr (N: <20). Ferritin was 1639 mcg/L (N: 7-282). The coagulation profile was normal. Lipid profile showed an elevated triglyceride level of 2.9 mmol /L (0.2-1.8) and normal cholesterol. Viral serology for CMV, EBV, hepatitis profile and HIV were all negative. Urine analysis was normal, however, the protein-creatinine ratio (PCR): 111 mg/mmol (N:< 22)

ECG was normal. The echocardiogram of the heart reported no structural or functional abnormalities. Plain radiographs of the knees and ankles demonstrated soft tissue swelling. The chest radiograph was normal. A tuberculin skin test was normal. Ultrasonography of the abdomen revealed an enlarged liver and spleen. Ophthalmology screening was normal. Bone marrow (BM) aspiration with bilateral trephine biopsies showed 90% cellularity, normal megakaryocytes and active erythropoiesis. Histiocytes with hemophagocytic activity were observed. No abnormal collection of cells were seen, see figure 2.

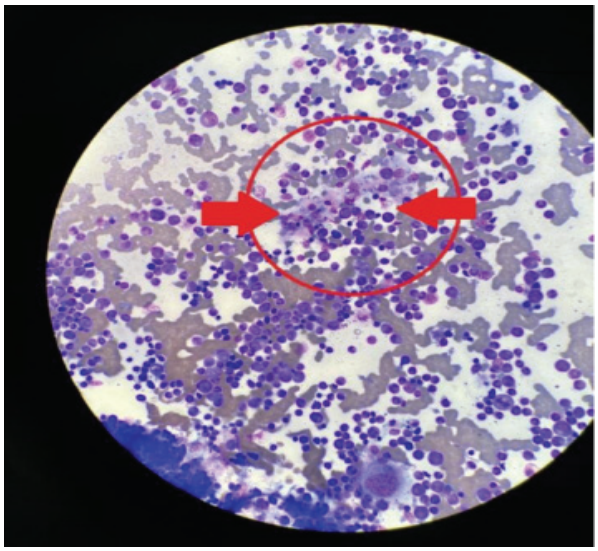

Figure 2: Bone Marrow Aspirate Revealed Active Erythropoiesis, Normal Megakaryocyte, and Clusters of Histocytes with Hemophagocytosis (Circle with Arrows). (Wright & Giemsa Stain), (40 X oil)

Serology workup was positive for antinuclear antibody (ANA) (1/80) with a speckled pattern and a positive anti-histone antibody. The rheumatoid factors, Ds DNA antibody, anti streptolysin antibody (ASO) titer and antineutrophil cytoplasmic antibody (ANCA) were negative. Complements (C3 & C4) assays were normal. The serum amyloid level was 958 mg/l (N: up to 6.4 mg/l). The suspicion of macrophage activating syndrome (MAS) was highlighted based on findings of high ferritin, high lipids, and the presence of activated macrophages in the BM aspiration. Therefore, the underlying etiologies of MAS were investigated.

Genetic workup was negative for primary HLH. Genetic screening for metabolic diseases and oncology causes were negative. Because of the presence of skin rash and arthritis, the possibility of an unspecified rheumatic disease which is complicated by MAS was raised. Pulsed methylprednisolone (10 mg/kg/day) for 3 days was initiated followed by oral prednisolone (1-2 mg/kg/day). The cyclosporine was started but the child could not tolerate it. The fever subsided and the synovitis considerably improved after one week.

The patient was started on Etanercept (an Anti-TNF agent) with an oral steroid and naproxen. Initially, she showed clinical improvement. However, she had several relapses marked by fever and active synovitis. Recurrent urinary tract infection was treated with antibiotics.

The genetic study detected a heterozygous variant in the TNFRSF1A gene of TRAPS syndrome (mentioned below). Therefore, Etanercept was changed to interleukin 1 antagonist (Anti IL1) along with steroid therapy. The patient was started on monthly subcutaneous injections of anti-interleukine-1β (Anti IL1-β), Canakinumab (CAM) (3 mg/kg/dose). The patient showed remarkable clinical improvement and no arthritis episodes or rash reported. Repeated serology markers for ANA and Anti-Histone antibody were negative, and the PCR decreased to 11.4 mg/mmol (0-22). However, serum amyloid level could not be repeated as it was done in an overseas laboratory. The patient remained clinically stable on monthly injections of Canakinumab, and prednisolone 0.7 mg/kg/day for more than one year.

Next-generation sequencing (NextSeq, Illumina) of the genomic DNA extracted from circulating white blood cells was performed. A disease exome-based NGS panel for 8 genes (ELANE, LPIN2, MEFV, MVK, NLRP3, NLRP12, PSTPIP1, and TNFRSF1A) was analyzed.

Molecular genetic testing revealed a heterozygous c.362G>A p. (Arg121Gln) a variant in the TNFRSF1A gene (chr.12).

Upon testing the parents, the same variant was detected in heterozygosity in the father.

DISCUSSION

It is proposed that TNFR1 trafficking defect with deregulated intracellular transcriptional activators and increased production of cytokines (including IL-1β) appear to be the cause of the disease[5]. The latter mechanism may explain the poor clinical response to TNF- antagonists in patients suffering from TRAPS. This also explains the significant increase in the secretion of the pro-inflammatory cytokines interleukin-1 beta (IL-1β), IL-1 receptor, IL-6, IL-8, and IL-12[6]. In addition, a blockade of IL-1β treatment was effective in an open trial that included twenty patients regardless of the underlying mutation[7].

One hundred and seventy missense sequence variants in the TNFRSF1A gene have been identified as causes of TRAPS. Most of these mutations are found in exons and introns 2, 3, 4, and 6, as well as mutations in exons and introns 1, 5, 7, 8, and 10. Forty-three missense variants have been validated as pathogenic and 56 as likely pathogenic variants[8,9].

The active variant sequence in the TNFRSF1A gene is located mainly in the extracellular domain encoded by exon 2-6, it consists of 4 cysteine-rich domains (CRDs) which are the main factor in homotrimerization (CRD1) and ligand binding (CRD2 and CRD3). However, the nonsense variants of the same gene are located either in the transmembrane or death domains and this is what makes it a missense domain. Mutations located in the CRDs region of the TNF-receptor are highly penetrant and associated with the most severe clinical phenotypes[10].

Other than the pathogenic structural variants in TNFR1, there are a few known low-penetrance variants, most notably p.Arg121Glu (c.362G>A) (alternate nomenclature R121Q, also known as R92Q) and p.Pro75Leu (P75L, also known as P46L). These variants can be found in multiple sclerosis, Behcet disease, and a syndrome of periodic fever, aphthous stomatitis, pharyngitis, adenitis, together termed as (PFAPA syndrome)[11-13].

Macrophage activating syndrome (MAS) has been considered as a disorder related to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH). Hemophagocytosis is defined as engulfment of blood cells, including red blood cells, white blood cells, or platelets by macrophages. The pathophysiology behind MAS is related to the defect in lymphocyte cytolytic activity which promotes apoptosis in the activated macrophages in the presence of any infection or inflammation. As a result, a defect in cytolytic activity may lead to overstimulation of the immune system and intensification of a pro-inflammatory cytokine cascade[14,15].

Macrophage activating syndrome has been previously reported as the initial presentation in one case with TRAPS syndrome[16]. However, anti-nuclear antibody and anti-histone antibody were not reported in previous literature on TRAPS syndrome.

Most patients with R92Q variant of TRAPS syndrome are treated with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids; up to 20% of those patients may require biological therapy. Moreover, R92Q variant was found in many patients with autoinflammatory symptoms, hence it is still considered as a low-penetrance mutation rather than a polymorphism[11,12,17].

The use of IL1 receptors antagonist for patients with TRAPS was successful, both in acute and long-term management. Anakinra is the first recombinant homolog of IL-1 receptor used in these patients, it works by inhibiting the binding process of IL-1- alpha and IL-1- beta to its receptors. It is an effective drug but unfavorable for use due to the need for daily subcutaneous administration in children[7]. However, long-lasting anti-IL1 drugs targeting IL-1-beta, such as Canakinumab (CAM) have better tolerability since it is administered subcutaneously every 4 to 6 weeks. CAM, is a high-affinity human monoclonal anti-interleukin-1β antibody that was efficient in treating TRAPS manifestations in a second phase trial study. CAM induced rapid disease control in 19 out of 20 patients with active TRAPS and sustained improvement on long-term treatment[18].

Since the patient's clinical condition stabilized on anti-IL1 therapy and a low dose of oral steroid, we found that the use of anti-IL1 is a promising treatment for TRAPS syndrome associated with MAS.

CONCLUSION

A child with a clinical phenotype of TRAPS syndrome and heterozygous TNFRSF1A mutation. The clinical condition was complicated with MAS syndrome. The patient showed a remarkable response to Anti-IL1b treatment. Further research into the use of IL1b-antagonist therapy to treat this condition is recommended.

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