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Case Report
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Tumour Necrosis Factor Receptor Associated Periodic Fever Syndrome (TRAPS): A Diagnostic Challenge

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Abstract

This report describes a case of late-onset TNF-Receptor Associated Periodic Fever Syndrome (TRAPS). We aim to describe the rare case of an 80-year-old Man, who had multiple Hospital admissions for prolonged episodes of fever with no clear cause found despite extensive investigation. Subsequent genetic testing revealed mutation in TNFRSF1A (TNF receptor superfamily member 1A) gene. This patient noticeably did not have a family history of prolonged / repeat episodes of fever or any of the other symptoms expected in TRAPS. He had raised inflammatory markers and showed a satisfactory response to intravenous antibiotic therapy on every occasion, which gave a false sense of security to the treating team, falling into the "trap of TRAPS," which might be an appropriate metaphor for that argument. This is explained by the fact that infections are known to cause flare-ups in patients with TRAPS, although a definitive source of infection was not found on several occasions in our patient despite testing. This led to a diagnostic dilemma and ultimately a significant delay in diagnosis of the underlying condition. Treatment was started with Steroids [short-term] and Anakinra (Interleukin-1 inhibitor) [long-term], to which the patient showed an excellent response. This is one of the very few occasions where TRAPS is diagnosed at such a late age.

Abbreviations

TRAPS: Tumour necrosis factor Receptor Associated Periodic fever Syndrome; CAPS: Cryopyrin-Associated Periodic Syndrome; IL: Interleukin; TNF: Tumour Necrosis Factor; TNFRSF1A: TNF Receptor Superfamily Member 1A; CT: Computed Tomography; HIV: Human Immunodeficiency Virus

Introduction

TRAPS is a rare genetic condition following autosomal dominant inheritance, where the gene coding for Tumour Necrosis Factor Recepetor-1 (TNFR-1) is affected. This leads to immune dysregulation [1] and systemic inflammation most commonly affecting skin, joints, eyes, muscles, Kidneys, and gastrointestinal tract. A family history of recurrent fever is seen in some cases and the clinical course is usually chronic with relapses and remissions. Flares are known to be caused by stress, infections, trauma, hormonal disturbance, and menstruation. Different genotypes / sequences lead to a varying level of penetrance, age of onset, clinical course / severity and ultimately, response to treatment. Management generally involves immunosuppression with Steroids and biological agents. Inadequate control may result in known systemic complications like Amyloidosis.

Case Presentation

Initial admission

An elderly gentleman in his 80s initially presented to the Hospital with fever and fatigue. Medical history of relevance includes a previous localised adenocarcinoma of the rectum for which was treated with papillon radiotherapy and TEMS (Trans anal Endoscopic Microsurgery). Initial set of investigations including an infection screen involving Chest X ray, Urine / Blood cultures were all negative. Blood tests however showed raised white cell counts, neutrophils and C-reactive protein. Imaging was done in the form of CT-Thorax, Abdomen and Pelvis to rule out intra-abdominal abscess and progression / relapse of Rectal Adenocarcinoma. This was diagnosed as a case of PUO

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(Pyrexia of Unknown Origin). He was started on IV antibiotic therapy (empirical) with Piperacillin and Tazobactam, to which he showed a good response with clinical improvement and down-trending of infection markers. He was eventually discharged with follow-up, after 2 weeks of inpatient stay.

Subsequent admissions

The patient had nine subsequent admissions to the Hospital over the course of next two years with prolonged and recurrent episodes of fever associated with fatigue. His blood tests showed raised inflammatory response and was treated with intravenous antibiotics therapy (Amoxicillin / clavulanic acid or Piperacillin / tazobactam) in each of these admissions. The patient was treated for Community-Acquired Pneumonia (CAP), COVID (Corona Viral disease) and gastroenteritis on various occasions. These are thought to be the triggers for flare of TRAPS in the respective admissions, with no identifiable triggers in the rest of the admissions. Notably, the patient was unable to provide a significant family history suggestive of TRAPS.

As per Specialist advice, an extensive set of investigations to rule out the causes of PUO (Pyrexia of unknown origin) was performed, including rare / atypical infections (Legionellosis, Tuberculosis, Brucellosis, Bacterial endocarditis), Viral infections (Hepatitis B/C, HIV), Vasculitis and Haematological causes (Myeloma, Lymphoma and Haemolytic syndromes). PET (Positron emission tomography) scan done showed an area of increased uptake in the Stomach, but subsequent assessment with a Gastroscopy and Biopsy did not reveal any feature of a malignant lesion. By this time, the patient had 7 sets of Blood cultures, which were negative for bacterial growth. As the initial set of investigations failed to identify a cause for repeat episodes of fever, genetic testing was eventually performed which identified a mutation inTNFRSF1A (TNF Receptor Superfamily Member 1A) gene at residue 88 of the mature protein (Ser88 pro) [2]. This was only seen in 8% of the alleles, indicating a de-novo somatic mutation and "somatic mosaicism", a phenomenon well described in patients with CAPS (Cryopyrin-associated periodic syndrome), although it has also been reported in patients with TRAPS [3]. A diagnosis of TRAPS was eventually made, and the patient was started on maintenance therapy with Oral Steroids at 7.5 mg/day, which was increased to 15 mg/day during flare-ups. He was subsequently started on Anakinra (IL-1 inhibitor) for long-term management of TRAPS [4]. Preliminary tests done to rule out the complication of systemic amyloidosis like Urine albumin / creatinine ratio, serum electrophoresis, serum free light chains, serum immunoglobulins and urine Bence-Jones proteins were satisfactory.

Outcome/Follow-up

The patient showed excellent response to Oral Steroids (Prednisolone) and injections of Anakinra with reduced frequency of relapse and reported general overall improvement in his well-being. He is under regular follow-up by the Rheumatology team.

Discussion and Conclusion

TRAPS (Tumour necrosis factor receptor associated periodic fever syndrome) is a rare genetic disorder (prevalence of 1:1,000,000 worldwide) with an autosomal dominant inheritance, which can often run in families, although de-novo variants (like in the case above) have also been described (frequency unknown). Molecular mechanisms underlying the pathogenesis of this condition is not completely understood although certain factors like oxidative stress, proteasomal degradation, defective autophagy are implicated [1]. Immune dysfunction leading to prolonged episodes of fever lasting a few weeks, and occurs every 4-6 weeks, along with multi-system involvement. Other common symptoms include pain (due to inflammation), arthralgia, myalgia, chest pain, abdominal pain, rash, conjunctivitis. Some factors known to trigger flare-ups include Stress, infection, hormonal disturbance, although no triggers may be found in a few cases. Age of onset is variable from early childhood to adulthood (very rarely in the elderly), depending on the pathogenic variant [5-7]. Diagnosis is by clinical examination and genetic testing [8]. The one described in this case (Ser88 pro) is commonly known as "S59P" mutation [2], which is thought to cause constitutive activation of TNF-R1 / IL-1Rpathway, inhibition of apoptosis and persistent NF-kB activation in response to IL-β1 stimulation. TRAPS is known to be the one of the entities in all the periodic fever syndromes to have a variable presentation dependent on the nature of the mutation, as this affects age of onset, penetrance and severity. Complications include Systemic Amyloidosis commonly affecting various organs like Kidneys (Nephrotic syndrome), Thyroid, Myocardium, Liver and Spleen. Atypical manifestations involving the Gastrointestinal tract (Isolated Colonic amyloidosis) [9,10] have also been described. Diagnosis can often be challenging [11] due to the non-specific nature of presentation and lack of routine availability of genetic testing across healthcare settings. Treatment involves the use of immunosuppressive therapy in the form of Corticosteroids (for short-term management of flare-ups) and biological agents for long-term management. This includes Interleukin-1 (IL-1) inhibitors like Anakinra and Canakinumab. Other agents shown to be of benefit include Tumour Necrosis Factor (TNF) inhibitors like Etanercept [12-14]. These agents are also known to help reduce the frequency of relapse and occurrence of known complications as described above. Routine follow-up with specialist review is advised. The pattern of inheritance also highlights the importance of genetic counseling to affected individuals to help them make informed decisions before planning a family.

Important Learning Points

1. TRAPS is a rare genetic entity seen mostly in Children and young adults, but has occasionally been reported in elderly, as described in this case report.

2. Lack of family history does not preclude the diagnosis of TRAPS as de-novo mutations are seen in a small cohort of patients.

3. Diagnosis can be challenging and is often delayed due to variable/non-specific presentation and unavailability of genetic testing in routine clinical care. It is important to always consider periodic fever syndromes in patients with prolonged and repeat episodes of fever/temperature spikes.

4. It is important to remember that response to antibiotic therapy does not singularly confirm the diagnosis of an infection, especially in those with recurrent episodes.

5. Immunomodulatory therapy has proven benefits and early institution of the same is necessary to reduce the frequency of flare-ups and to prevent known and often debilitating complications like systemic Amyloidosis.

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