

## Case Presentation

### Recurrent migratory angioedema as cutaneous manifestation in a familiar case of TRAPS: dramatic response to Anakinra

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## ABSTRACT

**Background:** Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is a hereditary autoinflammatory syndrome characterized by recurrent episodes of fever and localized inflammation. Clinical presentation can be very variable in terms of duration of fever attacks, periodicity, and accompanying manifestations. One of the most characteristic symptoms is the occurrence of migrating skin rash with myalgia that is sustained by monocytic inflammation.

**Observations:** We herein present the case of a family suffering from TRAPS who had been misdiagnosed for a long period of time and whose main symptom was migrating angioedema. Skin biopsy from one of the patients documented a monocytic panniculitis. All the living patients responded dramatically to anakinra treatment.

**Conclusions:** The classic symptom of migratory angioedema with myalgia in TRAPS can be produced by monocytic panniculitis. This manifestation is so characteristic of TRAPS that its occurrence, even in the absence of other manifestations, should prompt genetic analysis. Our patient's condition responded promptly to anakinra treatment.

## INTRODUCTION

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is a hereditary autoinflammatory syndrome characterized by recurrent episodes of fever and localized inflammation. The clinical presentation can be variable, in terms of duration of fever attacks, periodicity, and accompanying manifestations, such as abdominal pain, myalgia, migratory erythematous skin eruption, and periorbital edema [1,2]. TRAPS is caused by mutations in the TNFRSF1A gene [2-6]. With the identification of the genetic defect, knowledge of clinical presentation of TRAPS is now broadening from the classical clinical spectrum to patients with oligo-symptomatic or atypical manifestations [2,4,7,8]. We herein present the case of a family with a known disease-causing mutation for TRAPS. The main problem from which they suffered, migratory angioedema, is now thought to be very characteristic of TRAPS.

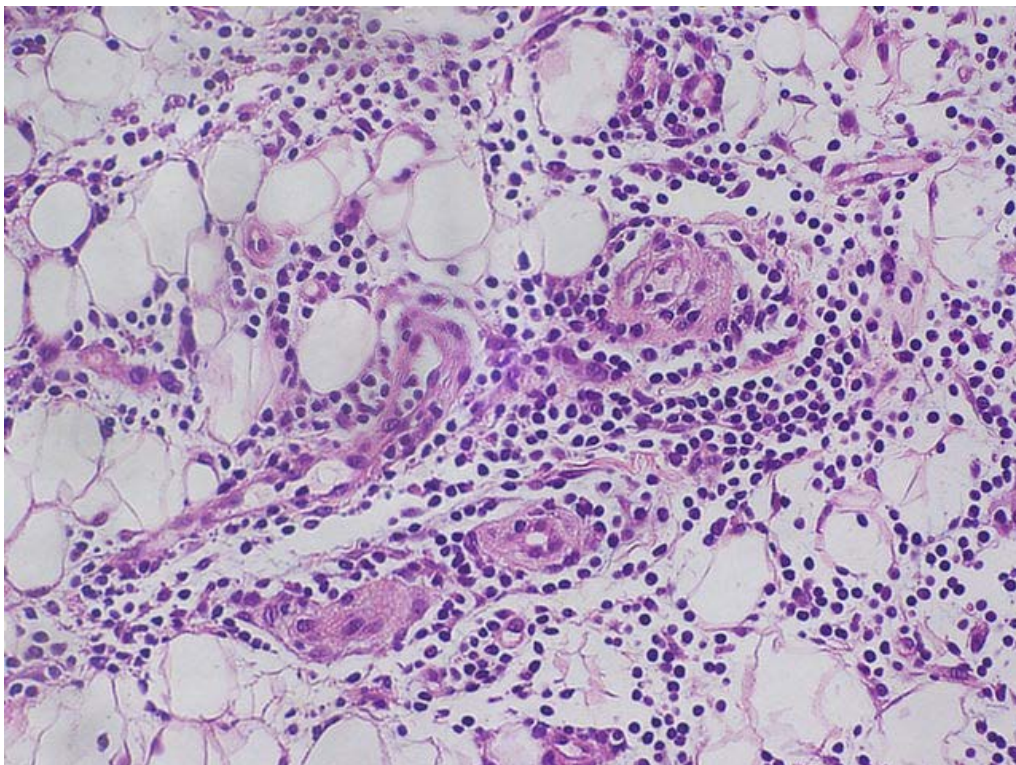
## CASE REPORT

A young man born in 1987 came to our attention for immunological investigation at the age of 21 years. His past clinical history was characterized from the age of 9 years by recurrent swelling and erythema involving the limbs and trunk, with a

proximal- to- distal migratory pattern that occurred at irregular intervals (Figure 1). Each episode lasted for 5-15 days, depending on the site of appearance, and resolved spontaneously. The patient never reported fever during the episodes. Although the patient had a normal quality of life between the episodes, he was strongly disturbed in his daily activities during the acute phase of these manifestations. At his first outpatient visit, our patient exhibited warm and tender angioedema on the left arm . The patient was afebrile. Routine labwork showed normal blood cell counts and normal renal and liver function; CRP and ESR were slightly elevated. Immunological evaluation (T and B cell subset counts, C3, C4, CH50, C1qINH, anti nuclear antibodies, immunoglobulin serum levels including IgD and IgE) was normal. Over time the edema spontaneously disappeared within 15 days. Biopsy of the involved skin area showed minimal hyperkeratosis of the epidermis with a slight inflammatory infiltrate in the superficial dermis. In the deep dermis, within an island of adipose tissue, there was a marked inflammatory infiltrate, with predominance of monocytes, giving the aspect of a panniculitis. Inflammatory cells were in a perivascular distribution, but no signs of vasculitis were present (Figure 2).



**Figure 1.** The typical clinical manifestation affecting the trunk of one of the patients: macular erythema is present, which is very tender and infiltrated on palpation



**Figure 2.** Biopsy from the patient showing a marked inflammatory infiltrate within an island of adipose tissue, with predominance of monocytes

Patient's family history revealed that his mother and his mother's sister suffered from similar clinical manifestations since their childhood. Additional clinical features, such as recurrent episodes of fever and of abdominal pain were present in both females. Our patient's aunt was treated for a brief period of time with hydroxychloroquine (200 mg daily), with good results, but the drug was discontinued for ocular side effects and never reintroduced. Medical records of their deceased father were reviewed. In the mid sixties, when he was 45 years old, he was hospitalized for recurrent fever attacks, myalgia, and angioedema. Laboratory testing showed elevated ESR and CRP and proteinuria. A skin biopsy showed edema in the deep layer of dermis with infiltration of lymphocytes and plasma cells. A muscle biopsy showed some atrophic fibers, infiltrating histiocytes, lymphocytes, and plasmacells in the perimysium. A presumptive diagnosis of dermatomyositis was made and he was treated with immunosuppressive therapy. He died of complications during an influenza epidemic. The two women recalled that their father was also frequently suffering from recurrent episodes of abdominal pain from his childhood.

Based on our patient's clinical features and his family history, an autoinflammatory syndrome was suspected. Sequence analysis of the genes known to cause autoinflammatory syndromes, revealed a C to T substitution of the TNFRSF1A gene, leading to a T50M, thus a definite diagnosis of TRAPS was made. The same mutation was found in his mother and her sister, allowing a diagnosis of TRAPS in these affected family members as well. Given the risk of renal involvement in TRAPS, Serum amyloid A (SAA) levels were assessed in all three family members and found to be elevated (more than 1000 mg/L) in all, although none of our three patients have proteinuria, so far.

During follow up our patient exhibited worsening of symptoms over time with multiple sites becoming concurrently involved and interfering significantly with his quality of life. Interestingly, even though our patient denied fever when specifically asked, assessment of body temperature during an outpatient visit revealed an elevated temperature of 39°C. Based on our experience of the efficacy of anakinra in TRAPS patients, we decided to administer this drug at a dosage 2 mg/kg/day, subcutaneously. After the first injection, the patient's pain resolved and within three days the skin manifestations and fever completely vanished. SAA decreased to normal levels and our patient has had no additional angioedema episodes. Our patient now feels well and has a normal quality of life. Anakinra treatment was then started in his mother and her sister, with good response. Their autoinflammatory episodes also vanished and both patients perceived great improvement in their general condition. SAA decreased to normal levels in the two women also. Our patient's mother experienced a local uncomfortable injection site reaction but decided to continue the treatment, given the great benefit she was experiencing.

## DISCUSSION

TRAPS is a dominantly inherited disease characterized by prolonged episodes of fever and inflammation caused by mutations in the TNFRSF1A gene [3]. The clinical spectrum is very broad in terms of periodicity and duration of fever attacks and number/intensity of the associated symptoms [1-11]. The identification of the genetic cause responsible for TRAPS has greatly increased the possibility to better characterize this disease and to diagnose oligosymptomatic patients who otherwise may have remained misdiagnosed.

TRAPS attacks are characterized by elevation of the levels of acute phase reactants, including serum amyloid A (SAA). Renal AA amyloidosis represents the most serious long-term complication of TRAPS. Therefore a delay in the diagnosis could expose the patients to this dreadful complication. It is generally accepted that cysteine mutations lead to a higher risk of amyloidosis. Nonetheless, based on published case reports, it is estimated that risk of amyloidosis occurs in 13% of patients carrying the T50M mutation [4,7]. In our three living patients, levels of SAA were very high, but no signs of amyloidosis were present. On the other hand the family ancestor presented with proteinuria when hospitalized for fever and myalgia, leading us to speculate he was most probably suffering from TRAPS attacks that went undiagnosed for almost forty years and his disease was likely complicated by renal amyloidosis.

In our family, the leading symptom that drove the patients to seek medical aid was the presence of the typical episodes of migrating angioedema and myalgia. Fever was not constantly associated with these manifestations. Our patient did not report fever during inflammatory attacks, although at one visit he was febrile. It may well be, in our opinion, that patients with TRAPS get very used to fever and it may not be perceived as unusual. Nonetheless all three patients confirmed significant benefit in terms of general wellbeing after therapy with anakinra was started, confirming the high impact a state of chronic inflammation may have on such patients.

Although the underlying cause of skin eruption and myalgia in TRAPS patients is still debated, it has been well demonstrated that this manifestation, which is so typical for TRAPS, is caused by a monocytic fasciitis [11,12]. We found it very interesting that even though the biopsy from our patient comprised only skin and dermis, it showed that monocytes were the predominant inflammatory cells. Interestingly, the full thickness biopsy of our patient's grandfather showed the presence of inflammatory cells progressively increasing from superficial dermis to deeper tissues, although these cells were not characterized as

monocytes. These observations support, in our opinion, the hypothesis that this typical manifestation in TRAPS patients is determined by recurrent episodes of panniculitis and fasciitis.

It is also intriguing that this manifestation was well controlled in one of our patients by the use of hydroxychloroquine. Even though we don't have a specific explanation for such an effect, it's interesting to note that hydroxychloroquine can interfere with IL-1 release by monocytes and interfere with production of TNF- $\alpha$  [13,14].

In conclusion we hereby present a family with a well-known TRAPS mutation, whose principal manifestations were the migrating pain and angioedema. We confirmed that, even though fever can be the main symptom in children, adult patients may tolerate it, so this is not perceived as a clinical clue [10]. Nonetheless we have shown great improvement in quality of life and general well-being in patients whose symptoms were well-controlled. Moreover our patients support evidence that the episodes of migrating pain and skin eruption are provoked by inflammation of the deep connective tissue. Finally we confirmed our previous experience that anakinra is a valid therapeutic option in patients with TRAPS [15].

Because the genetic base of TRAPS has only recently been recognized, we strongly agree with other authors that the spectrum of TRAPS clinical manifestations is still broadening and it is premature to establish clinical criteria for this disorder. Nonetheless the angioedema is so characteristic of TRAPS that its presence should prompt genetic testing even in the absence of other symptoms. We now have very effective drugs with which we can improve the general quality of life in these patients and reduce the risk of serious complications such as amyloidosis. Therefore every effort should be made to avoid any delay in the TRAPS diagnosis.

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