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Unusual and treatable cause of erythromelalgia: Acute small fiber neuropathy with vasculitis

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Abstract

A 25-year-old patient presented with progressive distal limb pain associated with redness and increased temperature, suggesting the diagnosis of erythromelalgia. Initial clinical and laboratory screening found no treatable cause. An unsuccessful pain management lead to the consideration of more exams, including small fiber assessment through Quantitative Sensory Testing and a skin biopsy, that showed evidence of small fiber neuropathy and vasculitis respectively. The patient was then treated with corticosteroid that completely reverted all symptoms.

The case highlights that in patients with acute presentation of erythromelalgia, it's important to be aware of its association with small fiber sensory neuropathy and vasculitis, because it can guide appropriate diagnostic workup and treatment.

Keywords

Erythromelalgia; acute small fiber sensory neuropathy; leukocytoclastic vasculitis.

Introduction

Acute Erythromelalgia (AE) is a rare condition clinically characterized by burning pain, redness and increased temperature affecting upper and lower limbs distally. Symptoms may last a few minutes to days, may be precipitated by exercise, alcohol consumption or warmth and can be relieved by cooling.

It can basically occur as primary or secondary phenomenon, comprehending genetic and multiple secondary etiologies. Autosomal dominant gain-of-function SCNA9 variants cause enhanced excitability,

and consequent dysfunction of the encoded mutant. Nav1.7 channel in the inherited form [3,4], whilst the secondary forms are associated to diverse mechanisms, including thrombocythemia, diabetes, collagen vascular disease, drugs, intoxication and in some reports with vasculitis. Pain management can be very difficult and appropriate control may only be obtained if a treatable etiology is found [1].

Small Fiber Sensory Neuropathy (SFSN) is a well known condition that causes distal pain and sensory disturbance, classically following a length dependent progression. Classically associated with impaired glucose metabolism and Sjogren disease it has a chronic and non-incapacitating course.However, a subset of patients, present with and acute form, frequently debilitating and poorly responsive to pain killers. This form seems to have an autoimmune pathomechanism, corroborated by nerve biopsies showing vasculitis and corticosteroid response.

Case Report

A 25-year-old woman presented with 3 months of severe pain in both hands and feet. Symptoms started at the sole of her feet, in short attacks. After a few weeks, attacks got longer, involved her hands and were accompanied then by redness and sensation of increased temperature. There were no other major complaints. On her past medical history, she reported a thimectomy due to a positive anti acetylcholine receptor Myasthenia Gravis, that was otherwise well controlled with pyridostigmine.

On examination, she was tearful, anxious and tachycardic. Her feet were swollen, red and hot. Neurological examination was unremarkable, apart from diminished pinprick and light touch sensation in both feet. Vibration sense, motor function and deep tendon reflexes were normal.

Laboratory screening was normal, including CBC, blood glucose, thyroid function, vitamin B12, folate, C-reactive protein, serum protein electrophoresis, anti-nuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, cryoglobulins, complement C3 and C4, lupic anticoagulation factor assay, anti SSA, anti SSB and screening for hepatitis B, C, syphilis, HIV and Lyme disease. CSF analysis, brain and spine MRI and nerve conduction studies were all normal. Quantitative sensory testing (QST) showed elevated thermal thresholds for warm sensation (49°C; normal interval: 32°C to 41,8°C), and reduced thresholds for cold-induced pain (2°C; normal interval: 26,9°C to 32°C) suggesting a small fiber involvement.

The neuropathic pain could not be relieved, despite of multiple pain killer trials. At some point, she spent more than 16 hours a day with the feet on cold water to soften the pain. This habit led to cutaneous infection, including the addition of pustular vesicles in her basal erythematous swollen feet (Figure 1A), demanding hospitalization for IV antimicrobial treatment.

Approximately 45 days since the beginning of symptoms and 15 days after the infection subsided, a skin biopsy was performed, confirming the diagnosis of leukocytoclastic vasculitis (Figures 1B and 1C). Oral prednisone 1 mg/kg/day for 1 week reverted, completely, all symptoms.

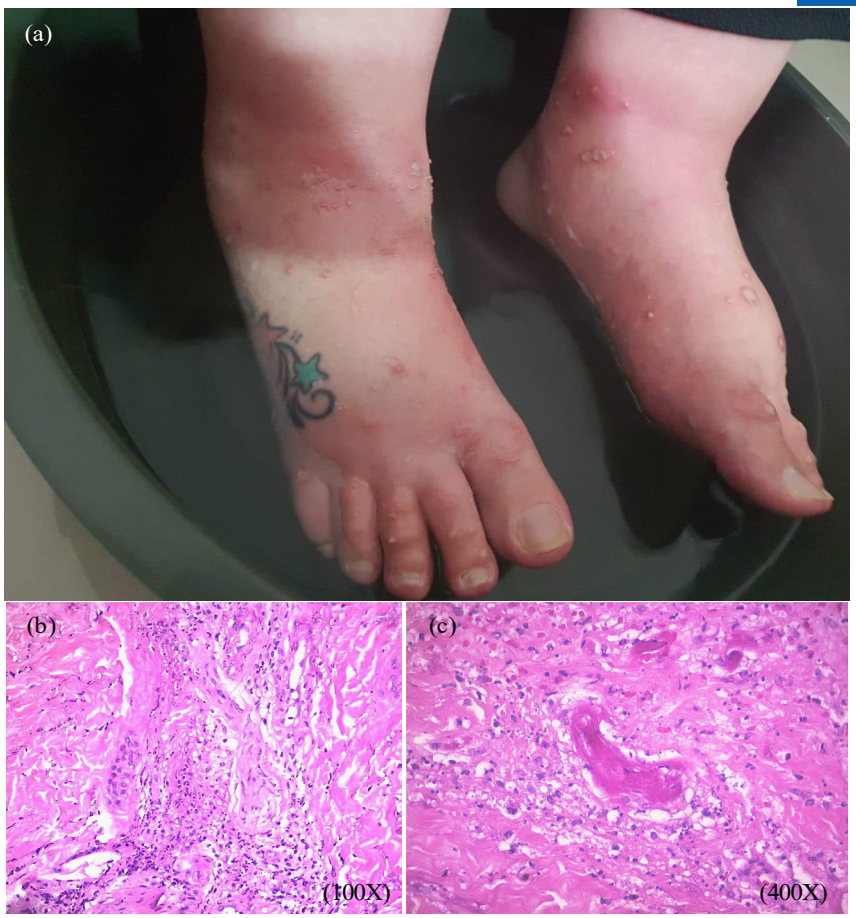

Figure 1: Clinical and hystopathological evidence of inflammation. **(A)** Patient´s feet showing redness and subjacent skin infection. **(B)** Vessels with neutrophil exocytosis – 100x lens. **(C)** A vessel with fibrinoid necrosis, neutrophil exocytosis and erythrocyte leakage – 400x lens.

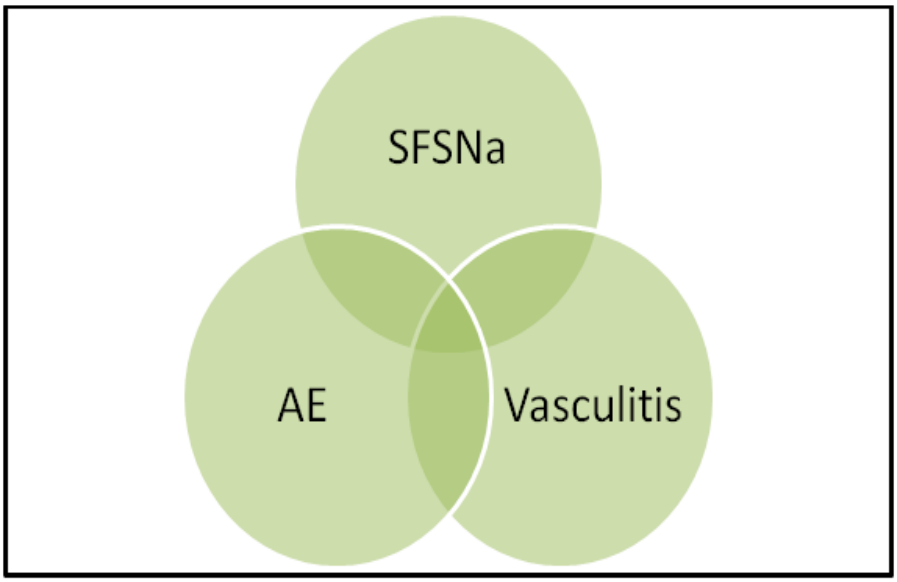

Figure 2: Clinical correlation between AE, SFSNa and vasculitis. The diagram shows the intersection between these conditions, and how inflammation can be the common factor of them all. SFSNa: Acute Small fiber sensory neuropathy. AE: Acute Erythromelalgia.

Discussion

Acute Erythromelalgia (AE) and acute small fiber sensory neuropathy (SFSNa) are rare conditions that can present with acute onset neuropathic pain [2]. These two entities can have several causes, with vasculitis being a possible etiology for them and, more specifically, leukocytoclastic vasculitis has already

been reported in both [1,3,4,5]. Some authors suggested that SFSNa could be an atypical subtype of the Guillain Barré Syndrome (GBS) [6], but the time to reach the peak of symptoms (>4 weeks) and the glucocorticoid response differs from what occurs in GBS patients, suggesting that in SFSNa the cellular response may overlap the humoral inflammation. Additionally, even though skin biopsy is rarely reported, mononuclear inflammatory infiltrates has been consistently found in the nerve biopsy of patients with SFSNa [3]. The diagnosis of this condition is based on clinical presentation and is supported by small fiber assessment techniques, like QST or SUDOSCAM. Corticosteroid is a well described treatment option [2].

The pathomechanism suggested to occur in erythromelalgia is abnormal nociception pathway activation, with small fiber impairment and inflammatory mediators release caused from disruption of local vascular dynamics, possibly related to a non-viable perfusion due to an arteriovenous shunting in the microcirculatory bed [5]. It seems that corticosteroid may play a major role among treatment options, like what happens in SFSNa, with better outcomes if early initiated, before nociceptive remodeling and central sensitization occurs [7].

Taking this in consideration, in our opinion, SFSNa and AE can be understood as different clinical expressions of the same complex inflammatory process and, sometimes, AE can be the clinical picture of a patient with SFSNa. Identifying a vasculitic pattern in a patient with AE and SFSNa reinforces this association (Figure 2).

Even though the leukocytoclastic vasculitis pattern in our patient could be attributed to the prior skin infection or even the cold or drugs exposure, it guided treatment decision with oral costicosteroids. The response to glucocorticoid therapy suggests that inflammation was a major component in this case.

So, even in adults, if all treatable causes are ruled out, skin biopsy should be considered in the diagnostic workup of patients with AE and SFSNa since it can help to confirm the small fiber impairment and inflammation. It is important to be aware of the association with vasculitis and that early consideration of corticosteroid treatment can avoid unnecessary interventions and fasten clinical improvement.

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Declaration of competing interest: The authors declare that they have no competing interests.

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