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Erythromelalgia- a clinical sign never to be missed

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Abstract: Erythromelalgia is a rare clinical condition due to post ganglionic sympathetic dysfunction. Diagnosis of this disorder and differentiating it from other common burning pain syndromes like Raynaud's phenomenon and small fibre neuropathy is often difficult. We report a patient who presented with redness, pain and burning sensation of hands, who was managed successfully with aspirin.
Keywords: Thrombocythemia, Erythromelalgia, SCN9A gene, Aspirin

INTRODUCTION:

Erythromelalgia is a rare disease affecting mainly the peripheral extremities, manifested by pain and burning sensation of hands and feet.[1] The term was coined by Silas Weir Mitchell in 1878 and is derived from 3 Greek words 'erythros' (red), 'melos' (extremity), and 'algos' (pain). Primary (idiopathic) and secondary (associated with an underlying disease) forms have been described. The present report is about a middle aged man presented with thrombocythemic erythromelalgia, a rare form of autonomic dysfunction which was treated effectively by antiplatelet agent.

CASE HISTORY:

A 58yrs old gentleman was evaluated for pain and burning sensation of bilateral hands especially at the finger tips of 2 yrs duration. He is a manual labourer and persistent pain interfered with his day today activities. Pain and burning sensation increases on exposure to heat and during activities and reduced on dipping the hands in the cold water. No convincing evidence of any other medical illness in the past or any significant family history was obtained. Patient had several hospital admissions without much relief. Examination revealed moderate built with normal vitals and normal joints. Local examination of bilateral hands revealed slight bluish discoloration with mottling appearance [Figure 1.].

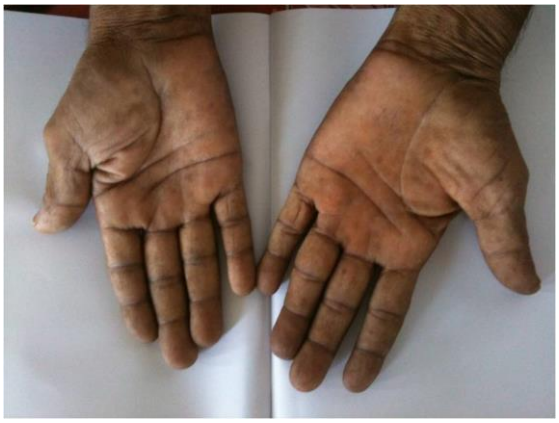

Fig-1:Bluish discolouration with mottling appearance in affected limbs.

Systemic examinations were otherwise within normal limits. On routine lab investigations revealed normal parameters except for an elevated platelet count: 6.3 lac/cumm. His previous records showed platelet count 9.4lac/cumm. Repeated blood examination confirmed the presence of thrombocythemia. Peripheral smear showed normocytic normochromic anaemia, neutrophilic leucocytosis, thrombocytosis [Figure 2.]

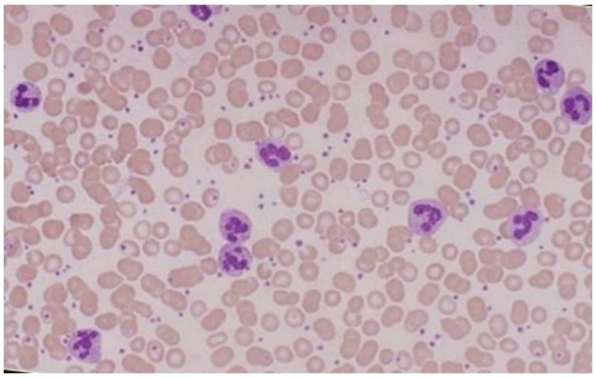

Fig-2: Peripheral smear showing thrombocytosis

Nerve conduction study was normal, rheumatoid factor was positive initially but on repeated examination after a few weeks it became negative, X-ray chest did not reveal any evidence of cervical rib. HIV test was negative, MRI cervical spine showed mild disc bulges without any neural element compression [Figure 3.].

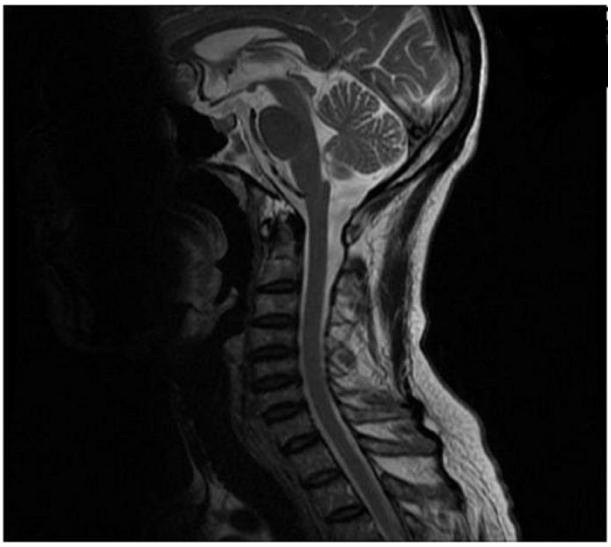

Fig-3: MRI cervical spine showing mild disc bulges without any neural element compression

Protein electrophoresis showed normal composition of albumin and globulin fractions. No monoclonal band was seen. ANA was negative. Initial clinical diagnosis was Raynaud's phenomenon and the patient was started on Nifedepine which worsened the pain. We reviewed the diagnosis and, on retrospective questioning he reported worsening of pain when hand is immersed in hot water. In view of thrombocythemia and pain the diagnosis of erythromelalgia was considered and the patient was started on Aspirin 325 mg BID. With one dosage of Aspirin the patient improved markedly. He became completely symptoms free within few days. He is being continued with Aspirin 50mg BD with no recurrence of symptoms.

DISCUSSION:

In this case the clinical symptoms, presence of thrombocythemia and improvement on Aspirin suggest the clinical diagnosis of erythromelalgia. Erythromelalgia also known as Michell's disease, was first described by Sir Silas Weir Mitchell in 1878[2]. It is a rare disease which affects the peripheral extremities mostly involving hands and feet. It usually evident in adulthood[2]. But there are many childhood[3] and infantile[4] cases of erythromelalgia reported in the literature. Many classification of Erythromelalgia have been proposed. Recently on basis of clinical, laboratory, and histopathological studies, it has been classified into three distinct types- erythromelalgia in thrombocythemia, primary erythromelalgia, and secondary erythromelalgia[5]. But sometimes thrombocythemic erythromelalgia has been grouped under secondary erythromelalgia[6].

The pathophysiology of erythromelalgia depends on the cause. Primary erythromelalgia is inherited in autosomal dominant manner. The root cause is mutation in the human gene SCN9A, which encodes for alpha subunit of voltage gated sodium channels called Na (v) [7]. These voltage gated sodium channels mainly present on postganglionic sympathetic nervous system and c-fibres of dorsal root ganglion. Normally postganglionic sympathetic system controls the cutaneous vascular tone and response to body cooling.[8] In primary Erythromelalgia, mutated voltage gated sodium channels present in the post ganglionic sympathetic system alters the responses to various stimuli and results in manifestations. The nociceptors and warm receptors in human skin are innervated by c fibres.[9] In primary erythromelalgia mutated voltage gated sodium channels present in c-fibres causes hyper excitability of c-fibres which results in manifestations of erythromelalgia.

Secondary erythromelalgia is due to underlying systemic diseases like SLE, myeloproliferative diseases , polycythemia Vera, connective tissue disorders, neuropathies, spinal cord diseases, carcinoma of the colon and thyroid, and astrocytomas[10]. The symptoms of erythromelalgia may precede the onset of a myeloproliferative disease by a median of 2 1/2 years [6]. Thrombocythemic erythromelalgia is due to increased platelet counts resulting in platelet thrombi and hence causes arteriolar occlusion and fibrosis[11]. Manifestations of erythromelalgia is a triad of redness, pain and burning sensation of peripheral extremities[12]. The symptoms aggravate on exposure to heat and hanging the affected extremities downward. Exposure to cold and elevation of affected limbs can decrease the symptoms[2].The cases of erythromelalgia has to be differentiated from Raynaud's phenomenon, the differentiating points are shown in Figure 4.

Erythromelalgaia	Raynaud's disease
1. Sympathetic dysfunction	Sympathetic overactivity
2.Hyperemic	Hypoperfusion
3.Extremities are red and warm	Blue and cold
4.Symptoms are relieved by cold	Symptoms aggravate on exposure to cold
5.Aggravated by calcium channel blockers like nifedipine	Relieved by calcium channel blockers

Fig- 4: Differences between Raynaud's phenomenon and Erythromelalgia

In rare cases gangrene and ulceration may occur. On clinical examination the affected part appears to be red, dusky and mottled with warmth. The other clinical findings may give a clue regarding the underlying systemic diseases.

Supportive evidences such total blood count and histopathological studies may give a great clue regarding the underlying diseases and helps in classifying the type of disease and in excluding other diagnoses[13]. Infrared thermography can also help in diagnosis of conflicted cases. Thermography of an erythromelalgic patient may reveal increased temperature in the affected area. Hence detecting and visualizing the hyper thermal area can assist in diagnosing the patient, assessing the therapeutic results, and understanding the disease course of erythromelalgia[12].

There is no definitive treatment for erythromelalgia[14]. Aspirin (100 -300mg/day) is the treatment of choice specially in thrombocythemic erythromelalgia as in our case[15]. Aspirin inhibits platelet aggregation hence results in dramatic relief of symptoms [16]. Positive response may also helps in confirming the diagnosis. Other oral medications like sodium channel blockers –lidocaine, mexiletine have been tried with lesser effect[7].Surgical measures like sympathectomy have been experimented in cases which are resistant to all medical measures[17].

Following up the patient is mandatory as in our case for serial tests of blood counts. As we stated earlier erythromelalgia may precedes the onset of myeloproliferative diseases. Hence blood counts have to be monitored for early detection and bone marrow examination in suspected cases.

CONCLUSION

Patients presenting with isolated features of burning sensation and redness of peripheral extremities without much of other clinical findings, the diagnosis of erythromelalgia has to be considered. Raynaud's phenomenon and small fibre neuropathy are other close differentials. Therapeutic trial of Aspirin is very useful in arriving at a clinical diagnosis of erythromelalgia.

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