Erythromelalgia: Diagnosis and Classification

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Erythromelalgia is not a commonly recognized or diagnosed condition that affects the lower extremities. The first reported case was in 1878, when Mitchell suggested the term "erythromelalgia." This condition is characterized by a burning sensation with erythema of the involved extremity. When the extremity is lowered, or heat is applied, the pain is intensified. The application of cold or elevation of the extremity will have the opposite effect of decreasing the pain. Erythromelalgia is classified as primary or idiopathic if there is no accompanying disease process. Secondary erythromelalgia is associated commonly with myeloproliferative syndrome-related thrombocythemia, and is mostly evident in adult onset of the condition. Treatment for adults with erythromelagia includes a single daily dose of aspirin, but children who have no associated underlying disorder find little to no relief with acetylsalicylic acid. (The Journal of Foot & Ankle Surgery 38(3):238–241, 1999)

Key words: erythermalgia, erythromelalgia, extremity pain, polycythemia vera

History

The first reported case of this disorder was in 1878, when Mitchell suggested the term *erythromelalgia*. The word has its derivation from the three Greek words: *erythros* (red), *melos* (extremities), and *algos* (pain) (1, 2). There was not much documentation of this disorder until it was classified in 1938 by Smith and Allen, who divided it into two types: idiopathic and secondary (3). The idiopathic type is also known as the primary type, whereas the secondary type is associated with some other underlying disease. Primary erythromelalgia is present when there is no associated disease of the nervous, vascular, or hematologic systems (4). Smith and Allen also recommended that the name of the condition be changed to erythermalgia, to stress the increase in the heat of the extremity, and this term has been used in some of the literature on this subject (1, 2).

Incidence

Erythromelalgia is a very rare condition to be diagnosed in the general public. Even in pain clinics, it is usually found in only about 3 out of 5,000 patients (1). The majority of cases of erythromelalgia are seen with myeloproliferative diseases, but a defined prevalence in this group is varied (1). The most common myeloproliferative disorder seen with erythromelalgia is usually polycythemia vera (1) which occurs in approximately 59% of these patients. Essential thrombocythemia is also seen with erythromelalgia in about 38% of the patients.

Clinical Presentation

Brown was the first to assign five basic criteria for erythromelalgia: there is burning pain of the feet or hands; standing, exercising, or exposure to heat intensifies the pain; cooling or elevating the limb will relieve the pain; the affected extremity is erythematous and warm compared to unaffected limbs; and the condition is refractory to therapy (5). Erythromelalgia is characterized by swollen, erythematous, severely painful extremities. The pain commonly affects the feet, but it can also affect the hands. When the extremity is lowered, or heat is applied, the pain is intensified. The attacks seem to be related to walking, standing, exercising, sleeping under the covers, wearing shoes or gloves, or placing the extremity near heaters (4). The attacks are also more prevalent in the summer months because of the increase in temperature (4). A study performed at the Mayo Clinic determined the critical point to be usually between 32° and 36°C (4). The application of cold or elevation of the extremity will have the opposite effect of decreasing the pain (1). These symptoms are present without any arterial occlusion being noted (1). The condition may rarely extend to the knees (1). Erythromelalgia is a disease in which there are exacerbations and remissions.

Classification

Classically, patients who prescribe with the disorder but have no underlying disease are diagnosed as having

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primary or *idiopathic erythromelalgia*. The term *secondary erythromelalgia* is reserved for patients who have some myeloproliferative disorder. When erythromelalgia was first investigated, it was believed that there was no underlying disease; therefore, it was designated as primary or idiopathic, no matter if the patient was an adult or child (6). This led to disagreement in the medical community, with some stating that erythromelalgia present in adults is always accompanied with myeloproliferative syndrome-related thrombocythemia (6). Kurzrock and Cohen proposed that the nomenclature be clarified by designating erythromelalgia as either adult-onset and early-onset (6). Then they recommended the adult form be classified into idiopathic and secondary to thrombocytosis versus other systemic disorders (6).

Primary erythromelalgia is commonly diagnosed in middle-aged patients (1). It has been seen in patients ranging from children through patients in their eighties (1). The ratio of male to female is 2:1 (1).

Early-Onset Erythromelalgia

Because of the confusion in terminology with the use of primary or idiopathic erythromelalgia, erythromelalgia that appears in children will be referred to as early-onset erythromelalgia in this article. Early-onset erythromelalgia is commonly identified in childhood or teenage years, with the average age being 10 (6). It is more common in females, with a ratio of 1:2.5 (males: females) (6).

The lower extremities are most often affected in early-onset erythromelalgia, as they are in adult-onset erythromelalgia, but it is bilateral and symmetrical in almost all cases (4). The affected areas of the lower extremities include the ankles, feet, and lower legs (6).

There has been no identified associated disease process in early-onset erythromelalgia (6). Several authors have identified hypertension in two children, and one patient had nephritis (6). The patient who had nephritis also had several relatives with erythromelalgia and renal disease (6). There has been no evidence that relates any correlation with the two disease processes.

Therapy for early-onset erythromelalgia has not been very successful. Many patients diagnosed with this disorder in their early years commonly have symptoms through their adult lives (6). Several patients treated conservatively by avoiding heat and exercise have shown spontaneous remissions, but this is not the normal course of the disease (6). Strozik observed the greatest relief of pain in his patients came with the use of tricyclic antidepressants (7). One common therapy for early-onset erythromelalgia is cooling of the extremities. Some patients resort to immersing their feet in buckets of ice to relieve the pain (6). This type of therapy has many complications such as maceration, immersion foot, hypothermia, and ulceration. The inability to walk due to gangrene is the ultimate complication (6). There have been reported cases of septicemia with peripheral gangrene requiring bilateral amputations (6). Treatment is usually ineffective, but some investigators have suggested the use of nitroprusside as being effective (6).

Adult-Onset Erythromelalgia

Adult-onset erythromelalgia is divided into two distinct categories. The first is the idiopathic or primary form, which is not associated with any other disease process. The second type is referred to as secondary erythromelalgia because it is associated with a myeloproliferative disease, which commonly manifests itself before the diagnosis of erythromelalgia is made. Secondary erythromelalgia is the most documented and researched type (6). It has been postulated that the etiology of the secondary type is also different from the primary or idiopathic form.

Primary Erythromelalgia

Patients who present with the idiopathic form of adult-onset erythromelalgia are commonly in the age range of 30–80, and there is a male to female ratio of 2:1 (4, 6). The presentation is similar to early-onset erythromelalgia with bilateral involvement of the extremities, lower extremities most commonly affected, and alleviation of symptoms with the use of aspirin (6). It is also possible that the onset of the myeloproliferative disorder will follow, therefore changing the diagnosis of idiopathic erythromelalgia to secondary erythromelalgia (6).

Secondary Erythromelalgia

Secondary erythromelalgia is commonly associated with a myeloproliferative disorder such as polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, myelofibrosis, or chronic myelogenous leukemia (6). About 59% of the patients present with polycythemia vera. About 41% of the patients present with essential thrombocythemia (6). It has also been reported with hypertension, diabetes mellitus, rheumatoid arthritis, gout, systemic lupus erythematosus, multiple sclerosis, astrocytoma of the brain, vasculitis, and pernicious anemia (6).

The majority of the patients (85%) develop the symptoms of secondary erythromelalgia well before the onset of the myeloproliferative disorder. The average time between the diagnosis of erythromelalgia and the diagnosis of a myeloproliferative disorder is 2 1/2 years (1). The occurrence of erythromelalgia in patients with myeloproliferative disorders ranges from 3% to 65%, depending on the source (8). About 10% of the patients presenting with the

symptoms of erythromelalgia are diagnosed with a myeloproliferative disorder at the same time (6, 8). In only 5% of the cases, erythromelalgia follows the diagnosis of the myeloproliferative disease (6). Most of the patients who develop this form of erythromelalgia are men, and the ratio of men to women is 3:2, with the average age of onset being in the late 6th decade (6). To date, no children have been reported to have this form of erythromelalgia (6).

In secondary erythromelalgia, the lower extremities are commonly affected, as in early-onset erythromelalgia, with the plantar aspect of the forefoot and the toes being frequently affected (6). Secondary erythromelalgia is asymmetric, whereas early-onset erythromelalgia is symmetrical (6). The usual presentation is an itching, prickly sensation that will also lead to severe throbbing, burning pain (6). Physical examination reveals increased skin temperature, edema, and erythema of the extremity. The vasculature is intact, with palpable pulses of the dorsalis pedis and posterior tibial arteries (6). The pain can be induced by increasing the skin temperature, or by placing the limb in dependency (6, 8). Cooling or elevating the extremity will lead to reduction of the pain of the extremity (6, 8).

Therapy

Therapy for secondary erythromelalgia consists of one dose of 500-mg acetylsalicylic acid (6). A study by Smith and Allen revealed that a single dose of 650 mg of aspirin relieved the symptoms in some patients for up to 4 days (3). There are still some patients who present with the classic erythromelalgia symptoms and are resistant to this therapy.

According to Uno and Parker, the most effective therapy for this condition is keeping the extremities at an icy cold temperature (9). Some patients do respond to 25 mg of indomethacin, but this will only last for 24 hours (8). One case substituted piroxicam for aspirin due to an aspirin allergy, what seemed to resolve the symptoms for this patient (10). Other antiplatelet medications have shown no appreciable effect on symptoms relief. There have been some investigators who have seen results with adrenergic β-blockers for reducing the attacks (11). One case dealt with a 32-year-old woman who had been dealing with the pain of erythromelalgia for many years, and was resistant to much of the treatment. She had exhausted all forms of therapy, which then left the only option of neurectomy of the nerves of the foot (12). The patient underwent crushing of the left posterior tibial and superficial peroneal nerves at the ankle, and then 6 months later, neurectomy of the posterior tibial, saphenous, sural, superficial, and deep peroneal nerves was performed (12). It seems the most effective therapy is heat and the avoidance of exercise (6). This will lessen the severity of attacks and reduce the frequency. Some researchers recommend the use of capsaicin cream to be applied to the extremities for a period of at least 3 months before starting other therapy. When this is initiated, the patient must be advised that sometimes this will make the pain increase for several days, and it will then subside.

Histology

Microscopic examination has revealed narrowing of the lumen of arterioles in the skin, but no effect on the capillaries, nerves, or venules (6, 8). There is considerable swelling of the endothelial cells of the arterioles with proliferation of the smooth muscle cells in the arterioles. Narrowing of the arteriolar lumen appears to occur by proliferation of smooth muscle cells, splitting the internal elastic membrane, and giving rise to the appearance of fibromuscular intimal proliferation (8). Often the arterioles are occluded by thrombi, made up of platelet aggregates that become completely fibrosed when peripheral necrosis had occurred (8).

Etiology

The cause of secondary erythromelalgia is believed to be the hyperaggregability of the platelets, which leads to the blockage of the arterioles (6). Skin biopsy findings and alleviation of the symptoms with aspirin therapy supports this theory. The aspirin is a known antiplatelet inhibitor that has been shown to relieve the symptoms very rapidly. One study compared the effects of aspirin against indomethacin. The results of this study were that the aspirin relieved the symptoms for days, opposed to only relieving the pain for less than 24 hours with the use of indomethacin. This is expected since acetylsalicylic acid irreversibly inhibits platelet cyclooxygenase, but the indomethacin reversibly inhibits the cyclooxygenase (8). This same study also compared the effects of a variety of drugs, including analgesics, anticoagulants, and antiplatelet drugs (dasoxiben, ticlopidine, and dipyridamole). All of the antiplatelet drugs also have no effect on the cyclooxygenase-inhibiting activity (8). These data have demonstrated the role of cyclooxygenase-related platelet activation in the pathogenesis of secondary erythromelalgia (8). Skin biopsy samples have shown consistently inflammation, muscle cell proliferation, and thrombosis in the arterioles (8). The proliferation of the smooth muscle that causes the intimal thickening is initiated by the platelet-derived growth factor that is released from the activated platelets (6). The ultimate complication of the intimal thickening is total occlusion of the vessel leading to acrocyanosis and gangrene.

Blood Tests

Blood tests are usually unremarkable in this condition. Patients usually have normal erythrocyte sedimentation rates, protein electrophoresis, lupus erythematosus test that is negative, normal PT, PTT, fibrin split products, and normal blood counts. When a myeloproliferative disease develops the blood counts will show evidence of this. For example, a leukocytosis, thrombocytosis, and elevated hemoglobin may develop in polycythemia vera (6). For a patient who has thrombocytosis, it is believed that the control of the platelet counts is very important. When the platelet counts reach $400-550 \times 10'6L$ there can be a relapse of the erythromelalgia, but this is not true for all patients (6). Elevated leukocyte alkaline phosphatase, leukocytosis, and a high hematocrit may be a sign of a myeloproliferative disorder (8). Patients who present with blood counts outside of normal limits will often need biopsy and aspirate of bone marrow. X-rays are almost always normal, but occasionally arterial calcification and osteoporosis are demonstrated (6).

Differential Diagnosis

The differential diagnosis includes reflex sympathetic dystrophy, recovery phase of frostbite, hyperperfusion phase of Raynaud's, peripheral vascular disease, and cellulitis. Reflex sympathetic dystrophy (RSD) can be differentiated from erythromelalgia by a correlation with recent trauma. The skin temperature is sometimes cool, but may be warm and erythematous. RSD is usually characterized by burning pain, tenderness, and hyperesthesias. In these conditions, heat or dependency does usually not exacerbate the pain, and the pulses are not palpable.

Conclusion

Erythromelalgia is a condition that is identified by pain, erythema, and warmth of the extremities. The symptoms are exacerbated by heating, exercise, or lowering the extremity; the pain is relieved by elevating or cooling the extremity. There are two separate forms of the condition. The first is early-onset erythromelalgia and the second type is adult-onset erythromelalgia, which is further divided into idiopathic erythromelalgia and secondary erythromelalgia. The early-onset erythromelalgia is found in children, and there has been no associated disease process identified. Early-onset erythromelalgia is also very difficult to treat, with no response noted with administration of aspirin or other forms of therapy. Idiopathic erythromelalgia and secondary erythromelalgia that are found in adults are easily relieved by small doses of aspirin. Secondary erythromelalgia is asymmetrical and is usually associated with polycythemia vera or essential thrombocythemia. The etiology seems to point to intravascular platelet activation and aggregation with plugging of arterioles in the forms associated with myeloproliferative disorders. The etiology of idiopathic erythromelalgia and, early-onset erythromelalgia is still not understood.

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