



Published in final edited form as:

Am J Med Sci. 2008 April ; 335(4): 320–322. doi:10.1097/MAJ.0b013e31812f65e7.

A Patient With Adult Erythralgia: Evidence Suggesting an Autoimmune Etiology

AUTUMN L. JACKSON, MD and JOHN A. OATES, MD

Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

We report the case of a woman with a combination of erythralgia, idiopathic thrombocytopenic purpura, and vitamin B-12 deficiency with positive parietal cell antibodies. The patient was treated with intravenous administration of immunoglobulins together with small doses of prednisone, which resulted in an improvement in her platelet counts, rise in her vitamin B12 levels, and resolution of her painful discolored digits. These findings suggest an underlying autoimmune component to the development of erythralgia.

KEY INDEXING TERMS

Erythralgia; Intravenous immunoglobulins; Idiopathic thrombocytopenic purpura; Vitamin B-12 deficiency

Erythralgia is a rare condition comprising a triad of symptoms including red, hot, painful distal extremities in the setting of a trigger, such as exercise or warmth. Although both involve discoloration of the digits, erythralgia differs from Raynaud's phenomenon in that the trigger is warmth, not cold; in fact, the patient's pain with erythralgia is relieved with cooling of the extremities. The diagnosis of erythralgia is dependent on the presence of 5 criteria: (1) burning extremity pain, (2) pain aggravated by warming, (3) pain relieved with cooling, (4) erythema of affected skin, and (5) increased temperature of the affected skin.¹ This clinical entity does not have a uniform pathogenesis, and several classifications dividing it into a number of subsets have been proposed. Primary erythralgia consists of an inherited form associated with mutations in sodium channel Na_v1.7 that usually presents in children and adolescents, as well as an adult form that is sporadic, without the evidence of heritability and more often considered as "idiopathic." The term "secondary erythralgia" has been applied to painful discoloration of extremities associated with known myeloproliferative disorders that have thrombocytosis, with vasculitis, and with certain drugs.^{2,3} The secondary forms reported in the literature, particularly those associated with myeloproliferative disorders, often do not meet the 5 criteria for erythralgia, and many if not most of these probably represent painful thrombotic microvascular ischemia rather than erythralgia.

We present an adult patient with primary erythralgia that is associated with 2 autoimmune diseases.

Evaluation and Treatment of the Patient

The patient is a 64-year-old woman with a medical history significant for hypertension who presented with painful burning in both feet precipitated by warmth. Her symptoms began as bilateral swelling of the feet with discoloration ranging from red to purple. Her feet then began to burn, a problem that spread to both hands as well. With the most severe episodes of burning and redness of her feet, she also had acute elevations in her blood pressure.

Venous duplex ultrasound revealed no obstruction to vascular circulation. Rheumatoid factor levels and antinuclear antibody titers were negative. She was found to have a decrease in her platelet counts to 118,000/ μ L, which was thought to be consistent with idiopathic thrombocytopenic purpura (ITP). She had no evidence of myeloproliferative disease or thrombotic thrombocytopenic purpura. Additionally, she was found to have vitamin B-12 levels of 127 pg/mL and positive parietal cell antibodies with no evidence of anemia.

Initially, oral methylprednisolone at 4 mg/day brought some relief to the patient, but major morbidity from the problem persisted. She then was intravenously administered with immunoglobulin (IVIg) infusions at 400 mg/kg for 3 consecutive days. When she was seen in clinic 2 months later, her platelet count had recovered to 388,000, with marked improvement in the burning and discoloration of her extremities. After receiving her first IVIg infusion, the patient also had a spontaneous rise in her vitamin B12 levels to 2000 pg/mL without supplemental B12 administration.

Eventually, the purple discoloration did return 3 months after her first IVIg infusion, with a less pronounced severity in the discoloration and pain than before the IVIg infusion. Hence, she received a second IVIg infusion at a higher dose of 500 mg/kg daily for 3 days. On the third day of infusion, she developed a severe persistent headache that lasted for 5 days during which she developed an acute increase in her blood pressure to 198/119 accompanied by chest tightness. She was hospitalized and treated for hypertensive urgency with resolution of her pressure to 122/80. Angiography revealed no coronary artery disease.

Seven months after this second series of IVIg infusions, the erythralgia is in remission. She is free of pain, able to tolerate the warmth, and notes that the discoloration of her extremities has cleared. Prednisone had been tapered and then discontinued. Examination reveals only a light pink uniform erythema of the fingers and toes that was not considered by her or the examiner to be abnormal. Slight mottled purple discoloration was evident on the metatarsal soles. Platelet count is normal (261,000/ μ L), as is the level of vitamin B12 (745 pg/mL) (Table 1). Antiparietal cell antibody is still detectable.

Discussion

This adult patient presented with a triad of findings including erythralgia, mild idiopathic thrombocytopenia purpura, and vitamin B12 deficiency with positive parietal cell antibodies. This seems to be the first reported case of erythralgia occurring in association with 2 separate autoimmune disorders. Subsequently, major relief of the painful burning and red-purple discoloration of her extremities and recovery of her platelet counts and vitamin B12 levels were seen with the administration of IVIg infusions. The IVIg infusions were superimposed on low doses of methylprednisolone or prednisone that previously had improved her symptoms but did not eliminate them.

Previously, there has been only a nascent understanding of the pathophysiology of the adult sporadic form of erythralgia. A shunt hypothesis proposed that insufficient channeling of blood through nutritional capillaries of the skin causes skin hypoxia. This leads to arteriolar dilatation that causes increased skin temperature and accelerated metabolism further

compromising the skin's nutrition. One trigger for this process was suggested to be prostaglandin deficiency. Therefore, it was proposed that prostaglandin analogs that serve as vasodilators, such as misoprostol, would improve skin oxygenation by redistributing skin perfusion in favor of the capillaries, which would result in higher levels of skin oxygen tension leading to constriction of the vessels supplying blood supply to the skin and reduced skin temperatures. In a double-blinded, crossover, placebocontrolled study, Mørk et al reported that oral misoprostol resulted in reduced symptomatology and arteriovenous shunting in patients with erythermalgia.⁴ The prostacyclin analogue, iloprost, also has been reported to produce clinical improvement in erythermalgia with reduced symptoms and sympathetic dysfunction.⁵

The patient described here is the second reported patient in whom erythermalgia has been associated with ITP. Rey et al described a 66-year-old patient with ITP who developed erythermalgia concurrently with the most severe episodes of thrombocytopenia.⁶ Treatment of that patient with IVIg and prednisolone led to transient remission of both the thrombocytopenia and the erythermalgia. Subsequent splenectomy was followed by sustained relief from the erythermalgia as well as the thrombocytopenia. In addition to that patient's response to immunotherapy, response to plasma exchange has been reported in other patients.⁷

This also is the second report of an association of erythermalgia with antibodies against gastric parietal cells. Drenth et al evaluated a 50-year-old patient with classical erythermalgia and high titers of these antibodies, and in that patient, immunohistochemistry of cutaneous vessels demonstrated subendothelial staining for IgM and complement (C3).⁸

In addition to its association with other autoimmune diseases and response to therapy directed at circulating antibodies, other findings also support the hypothesis that adult erythermalgia could be an autoimmune disease. A pox virus was isolated from patients with epidemic erythermalgia in China; these patients developed antibodies to that virus.⁹ HIV infection has been associated with erythermalgia, as have a number of rheumatic diseases. Further, erythermalgia occurs as a paraneoplastic phenomenon, and many paraneoplastic syndromes are considered to result from antibodies to antigens on neoplastic cells that cross-react with normal cells, including neurons.¹⁰

The inherited form of erythermalgia that presents during childhood and adolescence has been linked to mutations in the neuronal sodium channel, Na_v1.7, that is preferentially expressed in nociceptive dorsal root ganglia and sympathetic ganglion neurons.¹¹ The mutated channel decreases the threshold for impulses in these pain sensing and autonomic neurons. The similarity of the phenotype of inherited erythermalgia to that of the adult form of the disease raises the possibility that an activating autoantibody to this channel or another regulatory protein in the nociceptive dorsal root ganglia and sympathetic ganglion neurons could produce the adult sporadic form of erythermalgia.

In summary, congruent findings engender a hypothesis that the adult form of erythermalgia is an autoimmune disease. Further examination of that hypothesis offers promise for improved strategies for treatment and for understanding the molecular pathophysiology of the disease.

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Table 1

Results of Platelet Counts and Vitamin B12 Levels in Relation to IVIg Therapy

Date	Stage	Platelet Counts (Cells/ μ L)	Vitamin B12 Levels (pg/mL)
December 9, 2006	Presentation	116,000	127
January 9, 2006	First IVIg treatment	136,000	
January 10, 2006		142,000	
January 11, 2006		157,000	
March 6, 2006	Follow-up	388,000	2,000
April 24, 2006	Second IVIg treatment	313,000	1,048
April 25, 2006		303,000	
April 26, 2006		280,000	
December 4, 2006	Follow-up	261,000	745