Secondary Erythermalgia Associated with an Autoimmune Disorder of Undetermined Significance

Abstract
A 50-year-old female patient is described with an acquired, persisting and yet incurable erythermalgia featured by symmetric burning pain and red congestion of the extremities secondary to cutaneous vasculitis. A weakly positive antinuclear antibody titer and high titers of antibodies against gastric parietal mucosa cells pointed to an underlying but unclassifiable autoimmune disorder. It is concluded that histopathology of lesional skin contributes to the differential diagnosis of primary and secondary erythermalgia.

Introduction
Erythromelalgia and erythermalgia are two distinct clinical syndromes of burning painful and red congested extremities [1–3]. The curable variant erythromelalgia is causally related to thrombocythemia and results from platelet-mediated arteriolar inflammation and thrombosis. Aspirin completely alleviates all symptoms by irreversible inhibition of platelet cyclooxygenase activity and aggregation [4–7].

The incurable variant of primary erythermalgia is a rare congenital disorder which spontaneously arises in childhood or adolescence as bilateral symmetrically burning extremities in the absence of detectable disease [8, 9]. The histopathology in primary erythermalgia is nonspecific and may show only slight perivascular infiltration with lymphocytes [9].

Secondary erythermalgia usually arises at the adult age either in association with cutaneous vasculitis or with the use of drugs. Secondary erythermalgia in these conditions responds to treatment of the underlying disorder or discontinuation of the incriminated drug [1, 8, 10, 11].

There also appears to be a persisting and incurable form of erythermalgia arising at the adult age [12]. However, the histopathology of incurable erythermalgia at the adult age has never been investigated. We have had the opportunity to study an adult woman who developed incurable erythermalgia in the setting of an unclassifiable autoimmune disorder. Evidence is presented that the specific clinical manifestations and the histopathological findings contribute to the differential diagnosis of primary and secondary erythermalgia.

Case Report
Since 1984, a 50-year-old woman has suffered from a unilateral painful erythema on the left heel, progressively extending to the foot, ankles and lower leg. In 1986, an erythema of the right foot, ankle and lower leg was noted. The condition progressed to bilateral burning distress and red swelling of both feet, ankles and lower legs. Since
Discussion

Fig. 2. Blood vessels with slightly swollen endothelial cells and nuclear hypertrophy in the periosteum of long bone in a patient with advanced rheumatoid arthritis. (A) Hematoxylin and eosin staining. (B) Immunohistochemistry for CD3 (brown) and CD8 (red) in the same patient. The presence of CD8-positive T lymphocytes in the bone marrow suggests that the immune response to bone may be involved in the pathogenesis of rheumatoid arthritis.
legs became a symmetric feature. At this stage, the symp-
toms superficially resembled the features of primary ery-
thermalgia [9]. As in primary erythermalgia, the lesions had 
a bilateral distribution, there was aggravation by exercise 
elevation of the ambient temperature worsened the 
symptoms. Also, the slight relief by cold, rest and elevation 
of the affected extremities and the resistance to treatment fit 
with the diagnosis of primary erythermalgia. However, par-
ticular symptoms are against the diagnosis of primary ery-
thermalgia and are more in agreement with a secondary 
variant: the complaints and signs started as a unilateral pro-
cess and spread subsequently to both feet and hands, 
whereas in primary erythermalgia the discomfort always 
starts bilaterally as a symmetric process. In contrast to a 
typical fluctuating course with frank exacerbations and 
symptom-free periods in primary erythermalgia, the symp-
toms in our patient became a constant and chronic clinical 
feature without any fluctuations. Moreover in our patient 
symptoms started at adult age unlike primary erythermal-
gia. Histopathology of erythermalgic skin showed peri-
vascular inflammatory infiltrates of lymphocytes and plasma 
cells consistent with (peri)vasculitis, being different from 

fibromuscular proliferation and thrombotic occlusions in 

erythermalgia [7].

This pattern is similar to the histopathology of reporte 
cases in erythermalgia secondary to vasculitis, systemic 

lupus erythematosus in particular [10, 11]. Laboratory test-
ing in our patient revealed a high antinuclear antibody titre 
and antibodies against gastric parietal mucosa cells which 
suggests a coexisting, but not yet clearly defined, autoim-
nune disorder. It is not clear whether the autoimmunity in 
our patient establishes a significant pathogenetic factor or 
even a link.

In this respect, it should be noted that antinuclear anti-
bodies can be found in 10–37% of the healthy elderly an-
parietal cell antibodies are seen in up to 16% of the norma-

population [14, 15]. In another case of severe adult-onset 
erythermalgia, no autoantibodies were detectable [12]. Per-
sisting (secondary) erythermalgia arising at the adult age i.

evry rare, and treatment is difficult. Histopathological 

examination of lesional skin contributes to the differentia 
diagnosis of primary and secondary erythermalgia.

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