Small Fiber Neuropathy Underlies Erythromelalgia

BY JANE SALODOF MACNEIL
Southwest Bureau

PARK CITY, UTAH — Small fiber neuropathy plays an important role in erythromelalgia, a rare and mysterious skin condition characterized by red, hot, and painful extremities, Dr. Mark D.P. Davis said at a clinical dermatology seminar sponsored by Medicis.

Thermoregulatory sweat testing and other neurologic evaluations of 32 erythromelalgia patients showed that people with the syndrome do not sweat in all or part of their bodies, he reported.

Dr. Davis, dermatology professor at the Mayo Clinic in Rochester, Minn., illustrated his talk with diagrams of various patterns of impaired sweating, from the new study. These included regional and distal, multifocal, global, and distal areas where the patients did not sweat.

"Sweat glands are innervated by small nerves," he explained. "If they are dysfunctional, you may not sweat normally."

Recent papers documenting SCN9A mutations in an inherited form of erythromelalgia confirmed the neuropathic basis of the condition (J. Med. Genet. 2004;41:171-4 and J. Invest. Dermatol. 2005;124:1333-8). "Neurologists are now saying this is the prototype of a painful neuropathy," he said.

Dr. Davis described nerves and the skin as "an underinvestigated area of dermatology that needs to be investigated" and suggested that the combination "may explain some of our unexplained conditions."

The prevalence of neuropathy and vasculopathy in erythromelalgia suggests that "in other flushing conditions it is conceivable that the same thing is going on," he said. He cited leprosy and brachioradial pruritus as infectious and itching skin disorders, respectively, that involve both nerves and skin.

The first description of erythromelalgia was published in 1878, Dr. Davis said. In 2000, he and his colleagues presented a natural history of the disorder based on 168 patients seen between 1970 and 1994 at the Mayo Clinic (Arch. Dermatol. 2000;136:330-6). None had other diagnoses to explain their symptoms. The patients' average age was 56 years, with a wide range of 5-91 years and average follow-up of 9 years. The majority, 72%, were female.

Two-thirds of the patients presented with abnormalities in the affected limb. These included redness (49%), acrocyanosis (10%), ulcers (6%), and reticular skin pattern (5%).

Half the patients were unable to walk long distances or stand for long periods. About 14% were unable to keep a job and 13% were unable to drive. Functional impairment was so debilitating that 3% required a wheelchair and 2% were bed-bound.

'Sweat glands are innervated by small nerves. If they are dysfunctional, you may not sweat normally.'

DR. DAVIS

The investigators obtained Short-Form 36 Health Survey questionnaires from 98 patients. They scored poorly on all eight domains in the survey. The worst scores were for physical health and physical functioning.

All told, the patients had tried 84 different treatments with varying degrees of success. Nothing worked consistently, and the underlying cause of the condition remained elusive.

Dr. Davis cited several theories: excessive vasodilation causing high blood flow, increased local metabolism leading to hypoxia and tissue damage, and a platelet disorder with microvascular aspects.

In 2003, he and his colleagues offered a fourth, suggesting that erythromelalgia is associated with neuropathy and vasculopathy and possibly increased local cellular metabolism. They based their findings on 67 patients evaluated from 1999 through 2001 (Arch. Dermatol. 2003;139:1337-43).

Dr. Davis said that most patients in this study had neuropathy: Seventy-eight percent had small fiber neuropathy and 36% had abnormal electromyography studies. Among 57 patients for whom autonomic reflex screening was done, 49 (86%) had abnormalities. The most common abnormality was reduced or abnormal sweat production in sudomotor studies. ■

Changes Proposed for Hydroxyurea Labels

The Food and Drug Administration is reviewing proposed label changes for Hydrea and Droxia (hydroxyurea capsules) that warn of cutaneous vasculitic toxicities.

Bristol-Myers Squibb has notified health care professionals about revisions to the Warnings and Adverse Reactions sections of the prescribing information to include information about vasculitic ulcerations and gangrene that have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. The vasculitic toxicities were reported most often in patients who had received, or were currently receiving, interferon therapy.

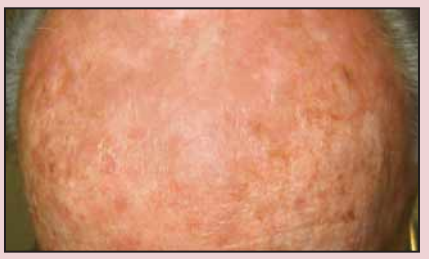
Significant tumor response to Hydrea has been demonstrated in melanoma, resistant chronic myelocytic leukemia; and recurrent, metastatic, or inoperable carcinoma of the ovary. Used concomitantly with irradiation therapy, the drug is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

Droxia is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises. Hydroxyurea should be discontinued in these patients if cutaneous vasculitic ulcerations develop. Changes have also been added to the Precautions section of prescribing information to warn physicians that elderly patients may be more sensitive to the effects of Hydrea.

For more information, or to report serious adverse events suspected to be associated with Hydrea or Droxia, contact the company by calling 800-321-1335 or contact the FDA's MedWatch Reporting System by calling 800-332-1088.

—Kerri Wachter

DERM DX



An 88-year-old white man with a history of nonmelanoma skin cancer presented for a skin cancer surveillance visit with complaints of a 3-year history of a pruritic scalp. Triamcinolone cream had failed to resolve the problem.

An examination revealed a large, shiny, erythematous patch that was not indurated. There was no scale. Barely palpable papules were scattered throughout the lesion. What's your diagnosis?

VANCOUVER, B.C. — A biopsy from the scalp of this 88-year-old patient revealed a deep and diffuse lymphoid infiltrate extending into fat.

The histopathology of this lesion resembled a follicle from a lymph node, and it contained a germinal center, a mantle zone, and a surrounding marginal zone.

"Of note, there was a grenz zone, a sparing of the papillary dermis, which is characteristic of B-cell lymphoma," commented Jenny Murase, M.D., a dermatology resident at the University of California, Irvine, who presented the case at the annual meeting of the Pacific Dermatologic Association.

Immunohistochemical stains were performed, with CD20 and CD79 marking nodular aggregates. "These are present in malignant B cells," she said.

CD3, CD7, and CD43 marked smaller background lymphocytes, which are T-cell markers.

Also relevant was positive CD-30 (Ki-1) staining, consistent with a diagnosis of follicular B-cell lymphoma, recently renamed follicle center cell lymphoma by the World Health Organization.

"Interestingly, CD10 staining was negative, although it is usually positive in follicle center lymphoma," Dr. Murase said.

The patient's positive *BCL-2* gene findings helped to clinch the diagnosis.

Dr. Murase explained several features that can aid in differentiating progressive transformation of germinal centers from lymphoma.

"Germinal centers have significant mitoses as compared to neoplasms," she said. In addition, tingible body macrophages contain "ingested nuclear debris, which represents lymphocytes that have been selected to be destroyed in reactive follicles.

"This selection process will not occur in neoplasms," she said.

Follicular B-cell lymphoma, or follicle center cell lymphoma, represents about 30% of cases of non-Hodgkin's lymphoma. Its incidence has been rising by 3%-5% per year for 20 years.

The median age at diagnosis is 60-65 years.

An indolent clinical course is common. Median survival is 5-10 years, and the survival rate is 75%.

"This tumor is very radiosensitive," Dr. Murase said.

Recent studies have suggested that rituximab (Rituxan) and fludarabine (Fludara) have a greater chemotherapeutic effect on this cancer than commonly used multidrug combinations.

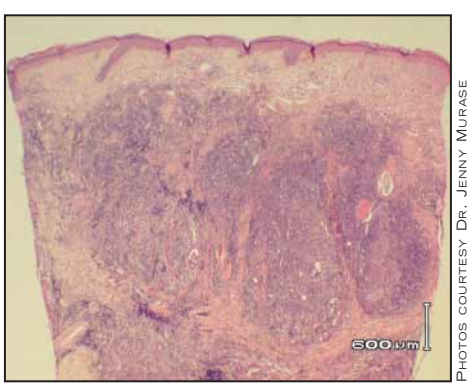
Dr. Murase's patient had a normal blood chemistry panel and CT scan. However, a PET scan revealed activity in the lower left anterior cervical region and bilateral pulmonary hila involvement. A bone marrow biopsy showed extensive disease, and the patient was staged as IVA.

He received a 6-week course of 375 mg of infused rituximab which he tolerated well and which led to a resolution of his pruritus. He remains alive with his disease.

Dr. Murase said the case demonstrates the need to biopsy and work up a patient who is not responding to traditional therapy for a seemingly simple problem.

Moreover, "I feel this case demonstrates that very subtle skin findings can have potentially serious implications. In this case, a patient's pruritic scalp led us to his bone marrow involvement," she said.

—Betsy Bates



PHOTOS COURTESY DR. JENNY MURASE