# Caution Advised When Diagnosing Behçet's

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EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – A conservative approach is best when it comes to making a diagnosis of Behçet's disease, Dr. Kenneth Calamia said at the meeting.

Although oral and genital ulcers are common in the disease, they also are a common manifestation of many other conditions, and it is important to consider the other possible causes first.

The importance of a Behçet's diagnosis doesn't have anything to do with ulcers – it has to do with the risk or presence of serious manifestations, including vascular disease, central nervous system manifestations, and uveitis, said Dr. Calamia of the department of medicine at the Mayo Clinic in Jacksonville, Fla.

"You don't want to [needlessly] give a patient the baggage of that diagnosis," he said, noting that in patients diagnosed with Behçet's, everything will be attributed to the disease for the rest of their lives.

In the United States and Europe, true Behçet's is quite rare (about 0.3-7.5 cases/100,000 population), compared with places like Turkey and other "Silk Road" areas, which have a very high prevalence (100-370 cases/100,000 population). In those areas, more severe forms are much more prevalent, and the benign mucocutaneous symptoms that comprise most of the cases in the United States are referred to as American Behçet's disease, Dr. Calamia said.

The term "Behçet's syndrome" also can be used to describe the types of cases typically seen in the United States, but in many cases, the diagnosis is actually "complex aphthosis," he said, adding that Behçet's treatment principles can nonetheless be used to help patients with this condition.

Complex aphthosis is a term used by oral dermatologists to help classify types of recurrent aphthous stomatitis. As opposed to simple aphthosis, which is characterized by episodic, short-lived lesions that are few in number, recur three to six times per year, and tend to affect nonkeratinized mucosa, complex aphthosis lesions can be continuous, numerous, large, slow-healing, and debilitating.

Keep in mind that both simple and complex aphthosis can be associated with menstruation, sprue, inflammatory bowel disease, HIV, hematologic disorders (such as cyclic neutropenia, IgA deficiency, myelodysplasia/myeloproliferation), various deficiencies (B vitamins, folate, iron, and zinc), and smoking cessation, Dr. Calamia said, explaining that smoking tends to increase keratinization, which protects against ulcers, and that protection is lost when a patient quits.

In a study conducted by an oral dermatologist several years ago, only 9% of 269 patients with severe complex aphthosis – 16% of whom also had genital ulcers – had a Behçet's diagnosis, he noted.

Some other diagnoses in the cohort included anemia in 25%, gastrointestinal disease in 16%, hematologic disorders in 5%, mucosal disease in 6%, smoking discontinuation in 4%, and drug-related ulcers in 3%.

"[Complex aphthosis] is the diagnosis I prefer in those who have mouth and genital ulcers, but nothing else to support a diagnosis of Behçet's," he said.

Consider the other possible causes of the ulcers, and also consider the differential diagnoses for recurrent aphthous stomatitis, which include recurrent intraoral herpes simplex virus, Wegener's granulomatosis, oral Crohn's disease, pyostomatitis vegetans, erythema multiforme, lichen planus, mucous membrane pemphigoid, and pemphigus vulgaris, he said.

A diffuse, widespread, and chronic presentation, which is not characteristic of recurrent aphthous stomatitis or Behçet's disease, can help differentiate between those conditions and these differential diagnoses, he said.

Dr. Calamia disclosed that he has received research support from Genentech and Celgene, and has served on an advisory board for Centocor. ■

# *Tx Available for Behçet's Mucocutaneous Symptoms*

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – Although no agent has been approved for the treatment of Behçet's disease in the United States, several treatments have been tried in patients with mucocutaneous manifestations of the disease, said Dr. Kenneth Calamia.

Behçet's disease is relatively rare in the United States and Europe, occurring in 0.3 to 7.5 per 100,000 people, but among those affected, mucocutaneous symptoms are common, and in fact are among the hallmarks of the disease. In a study of 164 patients treated from 1985 to 1997 at the Mayo Clinic in Jacksonville, Fla., where Dr. Calamia is associate professor of medicine, 98% had oral ulcers and 80% had genital ulcers. These were the most common manifestations, he said.

According to 2008 EULAR guidelines for the treatment of Behçet's, the decision to treat skin and mucosal involvement should be based on the severity perceived by the physician and patient, and mucocutaneous involvement should be treated according to the dominant or codominant lesions present (Ann. Rheum. Dis. 2008;67:1656-62).

Topical treatments should be used first line for isolated oral and genital ulcers and acnelike lesions; colchicine should be used when the dominant lesion is erythema nodosum; and azathioprine, interferon-alpha, and tumor necrosis factor (TNF)-alpha antagonists can be considered in resistant cases, according to the guidelines.

The list of treatments used for the management of mucocutaneous manifestations includes these and other agents. One of Dr. Calamia's favorite concoctions for oral ulcers is "magic mouthwash," an elixir of half Decadron (betamethasone) syrup or Celestone syrup and half Benadryl topical anesthetic. "This can control ulcerations very well, especially if used early at the first sign of a breakout," he said. The elixir is used before meals and at bedtime, and is swished in the mouth, held as long as possible, and spit out.

According to Dr. Calamia, other treatments that have been used for mucocutaneous manifestations of Behçet's include topical steroids, which work and have a better side effect profile than do systemic treatments; topical tacrolimus, pimecrolimus, and pentoxifylline, which dermatologists particularly like; azathioprine, which works; interferon-alpha, which also works; thalidomide, which works but causes neuropathy, so it is no longer used for this disease; dapsone, which is another favorite of dermatologists; methotrexate, which is used but which he is "not personally impressed with" for mouth ulcers; colchicine, which can be used for this or any of the other manifestations of the disease; and anti-TNF agents, which are clearly of benefit.

In a randomized, placebo-controlled study of etanercept, 40% of 40 patients who received etanercept were ulcer free at 4 weeks, compared with just 5% of those who received placebo. There was a significant reduction in oral ulcers, modular lesions, skin lesions, and arthritis attacks at 4 weeks, he said (J. Rheum. 2005;32:98-105).

"There's no question that anti-TNF drugs do work, but it is probably best to try nonbiologics in these patients, especially for mucocutaneous disease," said Dr. Calamia, who disclosed that he has received research support from Genentech and Celgene and served on an advisory board for Centocor. ■

# IgG4-Related Systemic Aortitis Responds to Rituximab

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO – Rituximab is showing promise as an effective treatment for IgG4-related aortitis, a condition which has only recently been described.

In one patient with aortitis and a high serum IgG4 level of 1,560 mg/dL, treatment with rituximab resulted in a decrease to 390 mg/dL within 2 months. Currently the patient's serum IgG4 level is 26 mg/dL (normal is below 135 mg/dL), Dr. John H. Stone reported.

Remarkably, the treatment appears to affect only IgG4 and not other IgG subclasses, suggesting that the agent is depleting CD20-positive B cells that evolve into the short-lived plasma cells which produce this antibody, and thus making a good case that this process is pathologic, said Dr. Stone, director of clinical rheumatology at Massachusetts General Hospital, Boston.

In another aortitis patient who had been treated with steroids but couldn't tolerate the side effects – and whose IgG4 levels increased when the steroids were discontinued – rituximab had an equally abrupt effect. At 1 month following treatment, her IgG4 levels had fallen to 31 mg/dL. And in a 68-year-old man who previously responded to steroids, but who flared and was being treated with various disease-modifying antirheumatic drugs, serial rituximab decreased his IgG4 level with each dose until it normalized.

**Remarkably, the treatment appears to affect only IgG4 and not other IgG subclasses.**

**DR. STONE**

Ten patients with aortitis, including seven with IgG4 elevation, have been treated with rituximab as part of this series, and IgG4 levels declined quickly in all seven, while all other IgG subclasses remained stable, he said.

IgG4-related aortitis was first described in 2009 by Dr. Stone and his colleagues, who published on the case of a 67-year-old patient who developed dissection of the ascending aorta in the setting of IgG4-related disease, thereby linking IgG4-related systemic disease with this newly recognized subset of noninfectious aortitis, and adding to a growing list of conditions, such as autoimmune pancreatitis, that are associated with IgG4-related systemic disease.

At surgery, a transmural lymphoplasmacytic infiltrate was detected in the aorta, and on immunohistochem-

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