Lupus May Be Present With Only Skin Changes

The fact that a patient is antinuclear antibody negative does not rule out the diagnosis of lupus.

BY DIANA MAHONEY
New England Bureau

STOWE, VT. — Skin involvement is one of the most frequent manifestations of lupus erythematosus, yet the cutaneous signs of the disease are not always recognized as such, Dr. Victoria P. Werth said at a dermatology conference sponsored by the University of Vermont.

Although systemic lupus erythematosus (SLE) is estimated to occur in 17-48 per 100,000 individuals, the cutaneous variants are thought to be two to three times more prevalent, said Dr. Werth of the University of Pennsylvania, Philadelphia.

Skin findings in cutaneous lupus are generally categorized into lupus-specific and lupus-nonspecific diseases, based on biopsy findings. "Lupus-specific lesions show histology that is specific to lupus erythematosus, while nonspecific lesions are not histopathologically distinct for the disease and may be seen as a feature of another disease process," she said. Some of the more common nonspecific skin findings include alopecia, vasculitis, and Raynaud's phenomenon.

Although skin disease is the second-most frequent clinical manifestation of SLE, cutaneous lupus does not always meet all the diagnostic criteria for SLE. Rheumatologists need to keep in mind that the diagnosis of lupus erythematosus can be confirmed whether or not the [American College of Rheumatology] criteria for SLE have been met," Dr. Werth said.

Rheumatologists may doubt the diagnosis of lupus in an antinuclear antibody–negative patient with skin manifestations. They have a hard time believing these patients really have lupus. Dermatologists look at these patients differently. "We know they have lupus because we see it all the time," explained Dr. Werth, a dermatologist.

Lupus-specific cutaneous lesions are further subdivided into three categories: acute, subacute, and chronic. "The most recognizable acute presentation is the butterfly rash, which comes on abruptly and heals within hours or days, usually without scarring," Dr. Werth said. Some variations of this rash include bullous formations or blisters.

Subacute manifestations can include annular and/or psoriasiform rashes that are usually highly photosensitive. Chronic cutaneous lupus is "the wastebasket category" for many of the other lupus-specific skin presentations, she said.

The most common chronic cutaneous form is discoid lupus erythematosus, which begins with well-defined scaly lesions that evolve into scarring plaques and often includes follicular involvement that can lead to hair loss. "Early, aggressive treatment for these patients is important in order to prevent permanent, disfiguring scarring and permanent hair loss," said Dr. Werth.

She also discussed several of the following less prevalent manifestations of chronic cutaneous lupus:

- **Chilblain lupus.** Associated with itching, cold, and painful swelling of the extremities and toes.
- **Hypertrophic lupus.** Characterized by wartlike bumps.
- **Lupus profundus.** Causes deep dermal nodules on the upper arms and sometimes on the head, chest, or legs.
- **Lupus tumidus.** Presents as broad, indurated plaques.

Although management for the various lupus subsets does not differ substantially, the clinical distinctions are important because they relate to the likelihood that an individual patient will develop systemic disease, Dr. Werth pointed out.

Nearly all patients with acute cutaneous lupus, and half of those with subacute disease, will meet American College of Rheumatology criteria for SLE. With respect to chronic cutaneous lupus, those with generalized discoid lesions have a 20% chance of developing SLE, those with lupus profundus are estimated to have a 10% chance, those with localized discoid lesions have a 5% chance, and those with lupus tumidus have virtually no chance. "Patients whose skin conditions put them at higher risk should be followed more closely for evidence of systemic disease," she said.

Once a diagnosis of cutaneous lupus has been made, the next step is to evaluate the patient for signs of systemic disease. The initial evaluation should include history, physical examination, CBC, sedimentation rate, antinuclear antibody (ANA) testing, and urinalysis. For ANA-positive patients or ANA-negative patients in whom there is suspicion of SLE, Dr. Werth suggests a panel that includes anti-Sjögren's syndrome A, anti-Sjögren's syndrome B, anti-ribonucleoprotein, anti–double-stranded DNA, and anti-Smith antibodies, as well as complement studies.

Patients with positive findings warrant closer monitoring, "especially those with high titre, anti–double-stranded DNA antibody because of an increased risk for renal problems," she said.

In terms of management, "the first order of business is advising patients to avoid precipitating factors such as heat, certain medications, and sunlight," Dr. Werth said. "I tell my patients they should not go outside without a sunscreen that has a UVB of 30 or more, as well as a UVA blocker, like Parsol 1789." ■

B-Cell Targets Expanding in Lupus, With Promise of Fewer Infections

BY NANCY WALSH
New York Bureau

NEW YORK — Progress toward unraveling the complexities of the B cell and its role in autoimmunity continues, with identification of potential new therapeutic targets for lupus nephritis and early clinical investigations providing insights on what B-cell depletion does—and does not—do.

The most experience with B-cell depletion in lupus thus far is with rituximab. This drug selectively targets the intermediate-stage B cells, though not stem or plasma cells, and causes significant decreases in markers of T-cell activation. "The risk of infection is limited because IgG is conserved," Dr. Gregg Silverman said at a rheumatology meeting sponsored by New York University.

A recent open study of rituximab that included 10 patients with biopsy-proven proliferative glomerulonephritis showed "very impressive" results, Dr. Silverman said. Patients received four weekly infusions of 375 mg/m^2, and in 8 of the 10 patients, partial remission of nephritis was seen within a median of 2 months. Five of these patients went on to complete remission by a median of 3 months (Arthritis Rheum. 2005;52:501-13). More studies are needed with rituximab in lupus, however, particularly to establish the optimal regimen.

Another ongoing investigation involves the autoreactive B-cell survival factor BAFF (also known as BLyS). BAFF, a tumor necrosis factor, can be blocked a number of ways, such as through decoy receptors and with anti-BAFF monoclonal antibodies, explained Dr. Silverman, professor of medicine at the University of California, San Diego.

One anti-BAFF monoclonal antibody, belimumab (LymphoStat-B, Human Genome Sciences, Rockville, Md.) has been tested in a phase I trial that included 70 lupus patients, and found to be safe, with no clinically significant differences from placebo in adverse events. It also significantly reduced levels of circulating B cells and anti–double stranded (ds) DNA antibodies, which are seen in high titers in lupus nephritis. A phase II trial that includes 449 patients now has been initiated, according to the company's Web site.

Abetimus (LJP 394, Riquent, La Jolla Pharmaceutical Co., San Diego), an agent that induces tolerance in B cells against anti–ds-DNA antibodies was investigated in a 76-week blinded study that randomized 230 patients to 16 weekly doses of 100 mg of the active drug or placebo, then alternating 8-week drug holidays and 12 weekly doses of 50 mg of the drug or placebo.

In this trial the primary efficacy outcome—prevention or delay of subsequent renal flare in patients with a history of lupus renal disease—was not met (Arthritis Rheum. 2003;48:442-54). But an ad hoc retrospective analysis found that in the subset of patients with high levels of anti–ds-DNA antibodies there were 67% fewer renal flares and time to renal flare was longer. A new multicenter trial is planned that will test three different doses of abetimus, he said. ■

Each Infusion Costs $5,000

IVIG Access *from page 1*

immune therapy are Medicare eligible and have been the first to start experiencing access issues, said Marcia Boyle, president of the Immune Deficiency Foundation (IDF). Ms. Boyle and Mr. Kruger said that private insurers are following Medicare's lead and also are starting to cut IVIG payments.

At the same time, supplies of the hard-to-make therapy—it takes up to a year to create—have tightened, partly because of rising demand.

From 2000 to 2005, manufacturers increased supplies by 60%, but it still was not enough, Julie Birkhofer, executive director, North America, of the Plasma Protein Therapeutics Association (PPTA), said in an interview.

Another problem: Much of the supply is tied up in physician offices, and they have stopped offering infusions because of the decreased payments.

The IDF and others say that patients have begun migrating to hospitals as physicians shut down infusion services, but that hospitals also are curbing IVIG infusions as the lower reimbursement hits them. The physician's office is considered a safer environment than a hospital for an immune-compromised patient. Infusions, usually given monthly, generally cost $5,000.

CMS has been reimbursing physicians for the average sales price plus 6%, and in 2006, added a $69-per-infusion payment to cover administrative costs.

In 2005, CMS was paying hospitals 83% of the average wholesale price, which was a slightly higher reimbursement. But in 2006, hospitals also were moved to the average sales price plus 6% rate, which Lewin estimated as a 9% shortfall between the acquisition cost and the Medicare payment, said Ms. Birkhofer. Hospitals were also given an additional $75 for administration.

The PPTA, the AAAAI, and others are seeking an add-on payment for the product and to assign Health Care Common Procedure Codes to each brand of IVIG.

Currently, all 10 available brands are bundled under one code, which gives physicians an incentive to prescribe the lowest-cost IVIG, said Ms. Birkhofer. That can affect patient access and care because not every patient can tolerate the same brand of IVIG, she said.

PPTA has received a legal opinion that CMS can adjust the payment through a rule or some other administrative mechanism. ■