Understanding Pemphigus and Pemphigoid

By Michelle Greer, RN

These autoimmune diseases are so rare that they often are difficult to diagnose, and while there is no cure, there are effective treatments to put them in remission.

Mike woke up one morning with pain on the right side of his mouth. Looking at it in the mirror, he saw what looked like a small sore, and he brushed it off. But after a week, it was getting worse. He went to a dentist, who ordered an antifungal rinse, which did nothing for it. The dentist referred him to a periodontist, who promptly removed all of his wisdom teeth and ordered a different type of rinse. A month later still with no relief, he noticed a small sore beginning in the lower lid of his left eye. At first, he didn't connect the two sores, but after some time, both were progressing.

Eight months and as many physicians later, Mike received yet another diagnosis: mucous membrane pemphigoid. Not only was he confused because he didn't know what it was, he was also frustrated that it took so long and so many doctors to figure out what the sores were. Yet he also was relieved because he thought he would finally get the appropriate treatment.

Unfortunately, the relief he felt only lasted a little while, and the frustration and confusion continued. Mike was prescribed prednisone, a powerful steroidal anti-inflammatory that seemed to help temporarily. But each time the dose was tapered, the sores would flare up again. The high-dose steroids eventually caused diabetes, and for a few weeks, he required insulin to control his high blood sugar. Then, he was prescribed an immunosuppressant, and he ended up in the hospital with a rare fungal infection. Finally, he saw a dermatologist with expertise in his disease who prescribed intravenous immune globulin (IVIG) therapy in addition to the prednisone and immunosuppressant. At last, the blisters healed, and he was able to discontinue all other medicines after six months. Unfortunately, it was not before Mike had permanent scarring in his left eye, leaving him with partial visual difficulties. He also was very underweight because the sores in his mouth made eating painful for him. At one point, Mike weighed only 170 pounds, not a lot for his 6-foot-1-inch frame. While his doctors wanted to put in a feeding tube, he refused.

What Are Pemphigus and Pemphigoid?

Mike's story is not unusual for people with pemphigus or pemphigoid. These conditions represent a group of rare autoimmune blistering diseases in which the immune system mistakenly attacks skin and/or mucosa. In pemphigus, desmogleins (which are essentially the glue of the epidermis) are attacked. In pemphigoid, the basement membrane of the epidermis is attacked. In either case, when this occurs, the skin separates and blisters form because fluid and cells that should normally remain below the dermis seep through.

Pemphigus and pemphigoid can occur at any age and in any race or gender, but there is some evidence that the incidence of pemphigus is somewhat higher in those of Jewish ethnicity.

There are different types of pemphigus and pemphigoid (see Table 1). The type of pemphigus or pemphigoid determines the location and nature of the blisters. In pemphigus, blisters will mainly be very superficial and rupture easily, and once they heal, there is no scarring. In pemphigoid, blisters will be deeper and are not as fragile. In the cicatricial (i.e., scarring) pemphigoid type, there is frequent scarring that occurs mainly when the blisters are in the mucous membranes such as the eyes and throat, which can lead to permanent disability.

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How Are Pemphigus and Pemphigoid Diagnosed?

Pemphigus and pemphigoid are diagnosed through special testing. One test, immunofluorescence, uses a dye to look for the presence of antibodies that are responsible for the attack on self. There are two types of immunofluorescence: direct and indirect. With indirect immunofluorescence, blood is drawn to look for the presence of antibodies. With direct immunofluorescence, the tissue is stained with a dye and examined under a special microscope to look for antibodies. The ELISA test measures the levels of autoantibodies to specific skin molecules targeted by pemphigus and pemphigoid. Another diagnostic measure may include rubbing an area near a blister. In pemphigus, it is likely the top layers of skin will be rubbed off when this is done (known as Nikolsky's sign).

How Are Pemphigus and Pemphigoid Treated?

Once a diagnosis is made, treatment almost always begins with high-dose oral steroids. These steroids are powerful anti-inflammatory drugs that suppress the immune system. In many cases, this is enough to control the disease and stop the attack on self so that blister formation ceases and existing blisters heal. Unfortunately, as in Mike's case, this treatment has significant side effects that can be so severe that the therapy is not tolerable.

Immunosuppressants often are prescribed to suppress the immune response, but this treatment may not result in the attack on self subsiding. Immunosuppressants also can cause significant side effects that result in undesirable immune suppression, which can then result in unusual infections. And these infections lead to additional treatments with antibiotics and other therapies and may result in hospitalization.

IVIG in high doses can be a very effective treatment. IVIG usually is given at 2 grams per kilogram every month, although some physicians may prescribe the dosing differently. Severe side effects of IVIG include renal failure, increased risk of blood clots, and aseptic meningitis. The

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Table 1. Types of Pemphigus and Pemphigoid

Pemphigus Type	Description
Pemphigus vulgaris	Most common type. Blisters are soft and fragile and may form in the mouth first and then spread to the skin and even genitals. Blisters are frequently painful but not itchy, and in the mouth make chewing and swallowing difficult.
Pemphigus foliaceus	Less severe type. Blisters may form on the scalp and face first and then spread to the chest and back. Blisters are not usually painful and are superficial and form crusts.
Pemphigus vegetans	Thicker sores mainly in groin and under arms.
IgA pemphigus	Caused by IgA (an antibody) binding to the epidermal cells. May resemble pemphigus foliaceus or may appear as small pustules.
Paraneoplastic pemphigus	Associated with certain forms of cancer. Blisters form inside the mouth and may affect the lungs, leading to a fatal outcome.
Pemphigoid Type	**Description**
Mucous membrane pemphigoid	Affects the eyes, mouth and throat. A clinical form called cicatricial pemphigoid can result in blindness if it involves the eyes, and respiratory compromise if it involves the deeper parts of the throat.
Bullous pemphigoid	Limited to the skin with blisters presenting predominantly on the abdomen, groin, back, arms and legs. The blisters may itch and be painful.
Gestational pemphigoid	Blistering rash starting around the navel and spreading to the entire body, typically in the second trimester.
Epidermolysis bullosa acquisita	Blistering rash on the skin without involvement of mucosal surfaces. Blisters are usually smaller than in pemphigoid.

risk of these side effects can be minimized by assessing risk factors prior to therapy, as well as selecting an appropriate IVIG brand, premedicating properly and running the infusion at an appropriate rate. Other less severe side effects include headache, nausea, vomiting, fatigue, malaise and blood pressure fluctuations. These side effects are most often rate- or batch-related. The rate-related complication can be managed by slowing or pausing the infusion and then resuming it. The batch-related complication can be managed by premedicating prior to and after the infusion. Premedications are usually acetaminophen and diphenhydramine.

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A relatively newer therapy is rituximab, which can be used alone or in combination with IVIG. Again, this will depend on the prescribing specialist. Rituximab is a monoclonal antibody, meaning it is made from immune cells that are all identical to one parent cell. Monoclonal antibodies target specific immune cells. Rituximab targets B cells. Depleting B cells is effective in halting immune attacks such as pemphigus and pemphigoid. But side effects due to induced B cell immunodeficiency can be serious and require testing for certain infections such as hepatitis B prior to therapy, as drugs such as rituximab can reactivate these conditions. Reported side effects of rituximab include renal failure and other severe reactions. Another severe side effect called progressive multifocal leukoencephalopathy (PML) is a progressive condition that results in death. Although these side effects are concerning, most people receive this therapy without issue. There are proper infusion precautions that can be taken, as well as up-front assessment of any risk factors.

There is currently no cure for pemphigus or pemphigoid, only remission. The goal of any therapy is to achieve quick remission with the least amount of steroidal medication. Once initial control of the disease is achieved, doses of steroids are tapered with the ultimate goal of discontinuation. A person is considered to be in full clinical remission when he or she does not need to take medications to remain lesion-free.

The Awareness Campaign

The International Pemphigus & Pemphigoid Foundation (IPPF) is currently funding the Awareness Campaign with the goals of increasing pemphigus and pemphigoid knowledge, reducing diagnostic timelines and improving treatment protocols. The campaign includes training lectures for the 62 dental schools in the U.S., where an estimated 4,500 new dentists graduate each year; two videos, one from expert clinicians and one based on patient testimonies; a fellowship program (funded by IPPF) that will allow side-by-side training with leading pemphigus and pemphigoid experts; and a consensus meeting (hosted by IPPF) that will bring the greatest pemphigus and pemphigoid minds together to redefine existing diagnostic and treatment practices to result in improved patient care. Collectively, the videos, training, fellowship program and consensus meeting underscore the need for early detection and intervention. The videos will be available on www.pemphigus.org.

Awareness Increases the Odds

Pemphigus and pemphigoid are conditions that are so rare that they are not in the forefront of a physician's mind when assessing what appears to be a simple blister or rash. That's why it is important to raise awareness of these autoimmune diseases so that earlier detection and intervention can be possible (see The Awareness Campaign sidebar). A prompt and accurate diagnosis will lead to faster initiation of the appropriate treatment and, ultimately, to better outcomes that will decrease or eliminate the chance of long-term and/or permanent complications.

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