



Approach to Vasculitis and Bullous Pemphigoid

A patient's history, physical examination and histological analysis are the keys to assessing unfamiliar skin conditions, such as vasculitis and bullous pemphigoid.

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Patients who present to the emergency room (ER) or your office with a skin rash cannot always be convinced that they simply have eczema. They will not be happy, therefore, with a

simple prescription for a topical steroid. So what do you do to initiate the workup of a patient with an unusual cutaneous eruption? This article will focus on vasculitis (small vessel) and bullous pemphigoid to demonstrate a reasonable approach to establish a diagnosis. It also will explain the use of systemic steroids and some immune-modulating alternatives.



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Vasculitis

Presentation. Patients with vasculitis complain of painful, pruritic red bumps, known as purpura, all over the body, (Figure 1). They may also have systemic complaints.

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Figure 1. Palpable purpura as a manifestation of vasculitis.

The examination will reveal palpable non-blanchable erythematous papules, especially on the legs. To prove the papules are non-blanchable, use a pocket-magnifying lens or glass slide to press down on a single lesion to see if it remains erythematous. This is known as diascopy. If you are uncertain of your clinical acumen, a skin biopsy is a must before proceeding further. It is imperative a diagnosis is established before treatment is initiated, otherwise further investigations will be compromised and underlying etiologies may be masked. If possible, biopsy a complete lesion from above the waist with a 4 mm punch biopsy.

Any biopsy taken from the legs will always show some degree of red blood cell (RBC) extravasation, potentially making the pathological interpretation falsely positive. On the laboratory requisition, write down that you are assessing for vasculitis. That way, if the pathologist sees RBC extravasation, neutrophils (and other mononuclear cells), nuclear dust (fragmented neutrophils) and fibrinoid degeneration (fibrin inside

Summary

Approach to Vasculitis & Bullous Pemphigoid

Vasculitis:

- Patients with vasculitis complain of painful, pruritic red bumps all over the body. The examination will reveal palpable non-blanchable erythematous papules, known as purpura, especially on the legs.
- There is no ideal classification of vasculitis because there is such an overlap of these heterogeneous diseases.
- The severity and extent of the inflammatory process determine therapy. The first thing to do, if applicable, is to stop the offending medication or treat the underlying infection.

Bullous Pemphigoid:

- Elderly patients will complain of rather sudden onset of multiple large fluid-filled blisters (Figure 2). On examination, the physician may see red urticoid plaques (1 cm to 4 cm) on the upper body while the lower body shows large bullae.
- Immunosuppressive therapy is usually required to control blister formation. Some patients with pemphigoid, however, undergo spontaneous remission in two to six months, therefore, alternatives to prednisone should be considered. If prednisone is used, a bisphosphonate should be considered.

Table 1

Vasculitis Classification: Hypersensitivity Small Vessel Disease

- Drug induced/serum sickness
- Infection (viral, bacterial)
- Connective tissue disease
- Malignancy (lymphoma, multiple myeloma)
- Henoch schonlein purpura
- Idiopathic

vascular walls), then there will be pathologic support for the diagnosis.¹ Although the final test results will take anywhere from a few days to many weeks, it is a crucial part of the puzzle. It is important because vasculitis is a clinicopathologic process characterized by inflammation and necrosis of small vessels, which can lead to damage of the skin and any other organ (joints, gut, renal, respiratory, neural and cardiac).² If other organs are affected, the patient may have systemic complaints, such as sudden onset of arthralgia, gastrointestinal (GI) pain and bleeding, flank pain and hematuria, dyspnea and hemoptysis, headaches and dysesthesia, or chest pain. The incidence of vasculitis is equal in both men and women. Ten per cent of cases occur in children.

Classification and investigations. There is no ideal classification of vasculitis because there is such an overlap of these heterogeneous diseases.³ Tables 1 to 3 illustrate three major categories. The hypersensitivity group is not uncommon. The author's experience has shown the usual culprits to be medications (prescription, over-the-counter [OTC], vitamins, herbal), infection and idiopathic. A thorough history, especially concentrating on what goes in the mouth other than food and alcohol is, therefore, an extremely important part of the

Table 2

Vasculitis Classification: Large Vessel Disease

- Polyarteritis nodosa
- Giant cell arteritis
- Takayasu's disease/ Buerger's disease
- Kawasaki/Behçet's disease

Table 3

Vasculitis Classification: Granulomatous Vasculitis

- Wegners granulomatosis
- Churg-Strauss syndrome
- Lymphomatoid granulomatosis

workup. The author then proceeds with a biopsy and baseline bloodwork, which includes erythrocyte sedimentation rate (ESR), complete blood count (CBC), urinalysis, hepatitis B and C, anti-streptolysin-O titre (ASOT), antinuclear antibodies (ANA) and rheumatoid factor (RF).

This is usually all the author does before initiating therapy on the first visit. Other investigations to consider, if warranted by history, include Epstein-Barr virus (EBV), cryoglobulins, antineutrophilic cytoplasmic antibody (ANCA), serum protein electrophoresis, blood cultures and skin sample for culture of mycobacterial disease.

Therapy. The severity and extent of the inflammatory process determine therapy. The first thing to do, if applicable, is to stop the offending medication or treat the underlying infection.

With regards to the medication, if it is a lipid-soluble product, there will be a slow release of the agent over many weeks and, therefore, recovery

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will take longer than if the patient had been taking a hydrophilic drug.

The small vessel hypersensitivity vasculitis usually only has skin involvement. The skin changes, however, may represent the initial signs of systemic vasculitis or manifestation of underlying disease.

If a patient has limited cutaneous involvement and no systemic complaints, the author will reassure him/her that bedrest will suffice. There is no benefit in using topical steroids, as they do not penetrate adequately to the mid- and deep-dermis,

If cutaneous manifestations are extensive or systemic complaints are severe, immunosuppressive therapy should be prescribed along with bedrest to make the patient more comfortable and minimize internal organ damage.

where the inflammatory reaction occurs. The author explains to patients that, although they have a painful condition, it will spontaneously resolve, without scarring, in four to eight weeks. Systemic therapy, such as prednisone, should not be used because the side effects can far outweigh the benefits (see section on side effects of therapy). If you feel it is reasonable, antihistamines and/or nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered for pain management.

If the cutaneous manifestations are extensive, or systemic complaints are severe, immunosuppressive therapy should be prescribed, along with bedrest, to make the patient more comfortable and minimize internal organ damage. The main medica-

tion is prednisone. The typical dose ranges between 50 mg and 80 mg, depending on the size of the patient (0.5 mg/kg/day to 1.0 mg/kg/day). The author maintains this dose until no new purpura are developing and there is some evidence of resolution of pre-existing lesions. This usually takes five to seven days. Since small vessel vasculitis is an immune-complex-mediated process that releases mediators of inflammation from neutrophils and results in high local levels of interleukins and cytokines, the steroids should be tapered slowly over three to six weeks, depending on the patient's response. The author often drops the dosage by 10 mg increments every five days until 30 mg is reached. At that time, the dosage may be decreased by 5 mg every five days, until discontinued.

Generally, even with bedrest, the purpura on the upper part of the body resolve first, and after many weeks, red macules (non palpable) are still present on the lower legs. If these are not painful and are blanchable, further therapy is not warranted, as these will resolve spontaneously. Conversely, if resolution does not occur, additional immunosuppressive therapy, such as intravenous (IV) pulse steroids, azathioprine, cyclophosphamide, mycophenolate mofetil or cyclosporine should be considered. These will not be discussed further in this article. Before introducing these agents, ensure the workup for all underlying etiology of small, medium and large vessel vasculitis is completed.

Side effects of therapy. The side effects of long-term steroids (*i.e.*, three months or longer, giving more than 4,000 mg in total) are numerous and well documented (*i.e.*, hypertension [HT], electrolyte disturbances, fluid retention, osteoporosis, osteonecrosis, peptic ulcer disease [PUD], hyperglycemia, glaucoma, cataracts and pseudo tumor cerebri). They always should be reviewed with the patient. This article will highlight two of the most prominent side effects, which can occur very early, even with short duration therapy.

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Within the first few days, mood alteration is not uncommon, and can be rather upsetting to the patient and the family, if not forewarned. The mood change can be one of elation (*i.e.*, energy to do housecleaning or watch television all night) or depression (*i.e.*, tearful or suicidal thoughts).

The other serious side effect is osteonecrosis of a long bone (*i.e.*, femur or humerus). Recent literature suggests a course of steroids for as little as one to two weeks may result in osteonecrosis many months to years later.⁴ Patients, therefore, should be warned to notify their physician if they experience hip or shoulder pain, as early treatment before the collapse of the bone may be beneficial.

Bullous Pemphigoid

Presentation. An elderly patient, who is feeling relatively well, complains of rather sudden onset of multiple large, fluid filled blisters (Figure 2). On examination, the physician may see red urticoid plaques (1 cm to 4 cm) on the upper body while the lower body shows large bullae. The common differential diagnosis of bullae includes pemphigoid, pemphigus, bullous lupus and epidermolysis bullosa acquisita. As all of these diseases have varying degrees of severity and systemic complications, it is important to establish the diagnosis before initiating therapy.⁵

Investigations. The gold standard is a biopsy for hematoxylin-eosin (H&E) and direct immunofluorescence (DIF). Bullous pemphigoid is an autoimmune disorder that results in subepidermal blisters as seen with H&E and linear deposition of immunoglobulin G (IgG) and complement 3 (C3), as seen with DIF. An H&E biopsy is taken by making a linear 1 cm x 0.4 cm incision from the edge of a bullae, so that at least 4 mm of normal or erythematous-appearing skin is present, and into the bullae. Do not worry that this may cause the rest of the



Figure 2. Large tense bullae of bullous pemphigoid.

bullae to collapse. Place the sample in a standard formalin-filled biopsy bottle. Fill out the pathology requisition, making sure to write: "bullae assess for pemphigoid." The 1-cm size and transition from normal to bullous skin allows the pathologist to determine at what level in the skin the bullae occurs (pemphigus in the epidermis, the rest between the epidermis and dermis). The DIF 4 mm punch biopsy should be taken about 1 cm to 2 cm away from a bullae in normal-looking skin and placed on a saline-soaked gauze in a sterile urine specimen bottle. Send it immediately to the lab, or, ideally, in a phosphate-buffered normal saline transport media. Again, a pathology requisition is used, but write in big letters: "for DIF." Assess for pemphigoid and notify the lab that it is coming so they do not place the specimen in formalin.

Therapy. Immunosuppressive therapy is usually required to control this immune-mediated blistering disease. Some patients with pemphigoid, however, undergo spontaneous remission in two to

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six months, therefore, alternatives to prednisone should be considered.⁶ Other medications capable of suppressing the mediators of inflammation are the combination of tetracycline, 500 mg four times daily (qid) and nicotinamide 500 mg three times daily (tid), while using a potent topical steroid, such as 0.5% clobetasol propionate cream (tid) to any new urticoid/pre-bullous lesions.⁷

Once the formation of new blisters ceases and healing of existing lesions begins, the cream can be used on an as-needed (PRN) basis. Next, tetracycline can slowly be tapered. The author recommends decreasing by 500 mg once daily (od) every month until the patient is taking 500 mg od. Then taper by 250 mg od per month until discontinued. Even if new pre-bullous lesions appear, the topical steroid should be able to keep them from becoming bullous. Finally, nicotinamide can be tapered by 500 mg every month until discontinued. The risk-benefit ratio is very good for these two medications. No bloodwork needs to be monitored. Unfortunately, these medications are not always tolerated, as the tetracycline may cause GI upset and nicotinamide may cause excessive facial flushing. If either of these or other side effects are too great, prednisone or mycophenolate mofetil is the next choice.

Prednisone is an inexpensive time-tested immune modulator. It dampens the whole of the immune system, however, not just the desired antibody production arm. If it is going to be used, all the side effects, as listed earlier, must be reviewed with the patient. The usual duration of therapy ranges from as little as three months to longer than 18 months. Depending on the size of the patient, dosage should start at between 50 mg and 80 mg od.

The author drops the dosage by 10 mg every two weeks until it reaches 30 mg od, at which time it should be dropped by 5 mg every three weeks. During this time, expect a few urticoid plaques and even some bullae to develop. The author has

patients use a very potent topical steroid on newly developing lesions, rather than increasing the dose of prednisone. These lesions demonstrate that the lowest dose of prednisone is being used for disease control.

If, at any time, a large number of bullae occur, this suggests higher doses of oral steroids over a longer period will be needed. At this point, the author initiates azathioprine as a steroid-sparing agent, but this medication will not be reviewed in this article.⁸ Once it is established that oral steroids are beneficial and tolerated, add in a bisphosphonate (an example would be intermittent etidronate and calcium in the patient-friendly Didrocal[®] Intermittent Cyclical Therapy three month pak). Using bisphosphonates is now considered to be the standard of care for patients who must be on long-term steroid therapy, as these medications prevent or reduce the loss of vertebral and trochanteric bone.^{9,10}

Mycophenolate mofetil is an immunomodulatory drug that inhibits the *de novo* pathway of purine synthesis, while leaving the salvage pathway intact.¹¹ It preferentially inhibits both lymphocyte proliferation and antibody formation. It is quite expensive, however. The author starts with 500 mg od for three days. If there is not excessive GI upset (*i.e.*, nausea, anorexia, vomiting, abdominal cramps or diarrhea), increase to 500 mg bid and up to 1 g bid, if required. Once no new blisters are developing and old lesions are healing, decrease by 500 mg a day every two months. As before, use a potent topical steroid for any urticoid flares. This reinforces to the patient and the physician that the lowest possible dose to control the disease is being used. There are seldom clinically significant nephrotoxic, hepatotoxic, neurotoxic or hypertensive side effects. Leukopenia has been documented, therefore, periodic CBC, as well as liver function tests (LFT) and creatinine should be considered (every six to eight weeks).

Conclusion

The patient's history and physical examination may be supplemented by histological analysis to arrive at a correct diagnosis when assessing unfamiliar skin conditions, such as vasculitis and bullous pemphigoid. It is important to take all the appropriate investigational steps before deciding if therapy is needed.

Depending on the etiology and severity of small vessel vasculitis, avoid prednisone therapy whenever possible. Even if a short course of steroids are deemed necessary, there are certain side effects, such as mood alteration and osteonecrosis, that should be discussed with the patient.

Immunosuppressive therapy is often considered for bullous pemphigoid, however, there are alternatives to prednisone, such as tetracycline with nicotinamide or mycophenolate mofetil. If long-term prednisone is the chosen therapy, then a bisphosphonate should be used as an adjuvant to minimize steroid induced osteoporosis. [CME](#)

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