Grand Rounds Review

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases

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A wide differential diagnosis must be considered in a patient presenting with urticarial plaques. Although acute and chronic urticaria are the commonest diagnoses, other differential diagnoses include polymorphous eruption of pregnancy, mast cell disorders, hypereosinophilic syndrome, urticarial vasculitis, pemphigoid, systemic lupus erythematosus, and autoinflammatory disease. This review will specifically address urticarial vasculitis and autoinflammatory syndromes. These entities represent contrasting examples of urticarial-like lesions resulting from either an adaptive immune complex−mediated mechanism (urticarial vasculitis) or an innate immune−mediated mechanism (autoinflammatory disorders), with differing therapeutic implications. In patients presenting with painful, persistent plaques that last more than 24 hours and resolve with bruising of the skin, consideration should be given to a diagnosis of urticarial vasculitis. A biopsy should be obtained to ascertain this diagnosis. In patients presenting with a persistent history of recurrent urticarial plaques associated with signs of systemic inflammation including fevers and elevated inflammatory markers (C-reactive protein [CRP]/serum amyloid A, leukocytosis, and negative connective tissue serologies), consideration should be given to autoinflammatory disorders: the 3 cryopyrin-associated periodic syndromes, Schnitzler syndrome, and familial cold autoinflammatory syndrome 2. Serum protein electrophoresis should be checked to rule out an underlying monoclonal gammopathy. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)**

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A wide differential diagnosis is entertained in a patient presenting with urticarial plaques. Although acute and chronic urticaria are the commonest diagnoses, other differential diagnoses include polymorphous eruption of pregnancy, mast cell disorders, hypereosinophilic syndrome, urticarial vasculitis (UV), systemic lupus erythematosus (SLE), and autoinflammatory disease. This review will specifically describe UV and autoinflammatory syndromes. These entities represent contrasting examples of urticarial-like lesions resulting from either an adaptive immune complex−mediated mechanism (UV) or an innate immune−mediated mechanism (autoinflammatory disorders), with differing therapeutic implications.

When urticarial plaques are persistent and associated with signs of vasculitis such as bruising and with systemic disease, a diagnosis of UV should be considered.[1] The clinical presentation of UV is an example of adaptive immune complex activation; in response to a number of etiologic factors, immune complexes become activated, leading to complement activation and the generation of C3a and C5a, which as anaphylatoxins can activate mast cells (and basophils) to degranulate with the release of preformed histamine with resultant clinical manifestations of urticaria and UV.

In patients with recurrent or persistent fever accompanied by an array of inflammatory symptoms, the possibility that autoinflammatory diseases result from inappropriate activation of the innate immunity (with the absence of significant levels of autoantibodies and autoreactive T cells) needs to be considered. Urticarial rash is a differentiating characteristic in 5 of the autoinflammatory syndromes: the 3 cryopyrin-associated periodic syndromes (CAPS), Schnitzler syndrome, and familial cold autoinflammatory syndrome 2 (FCAS2).

Table I summarizes clinical, histologic, laboratory, and management findings that differentiate chronic urticaria, UV, and autoinflammatory diseases.

CASE 1: URTICARIAL VASCULITIS

A 54-year-old female Native-American ancestry presents for further evaluation of a 2-year history of an urticarial skin eruption lasting for up to a week at a time and resolving leaving either bruising or brown pigmentation on the skin; occasionally she develops blisters on the palms. This rash is generally extremely uncomfortable for her—it is associated with both itching and burning sensations, self-rated as approximately 10/10 in severity, and associated with disruption of her sleep, work, and social life. She cannot swim or teach water aerobics because of them. She missed work because of the symptoms. She additionally has alopecia, inflammatory polyarthritis, pleurisy, and strongly positive serologies including antinuclear antibody (ANA), Sjögren syndrome antigen A (SSA), ribonucleoprotein (RNP), and anti-Smith antibody; urinalysis was normal. Her complement levels are markedly decreased (total, C3 and C4 in addition to C1q) consistent with hypocomplementemia.

Physical examination is significant for discrete and confluent urticarial appearing plaques involving approximately 20% to 30% of the skin (Figure 1, *A*). They measure from 2 to 4 cm

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Abbreviations used
AA- Amyloid A
ANA- Antinuclear antibody
ANCA- Antineutrophil cytoplasmic antibody
CAPS- Cryopyrin-associated periodic syndromes
CINCA- Chronic infantile neurologic, cutaneous, and articular
CRP- C-reactive protein
FCAS2- Familial cold autoinflammatory syndrome 2
GI- Gastrointestinal
HUV- Hypocomplementemic urticarial vasculitis
HUVS- Hypocomplementemic urticarial vasculitis syndrome
MWS- Muckle-Wells syndrome
NUV- Normocomplementemic urticarial vasculitis
RNP- Ribonucleoprotein
SLE- Systemic lupus erythematosus
SSA- Sjögren syndrome antigen A
UV- Urticarial vasculitis

diameter. No bruising is associated with these current urticarial plaques.

Biopsies were consistent with UV, showing superficial and deep perivascular and interstitial polymorphonuclear infiltrate with nuclear dust, leukocytoclasis, and red blood cell extravasation. Direct immunofluorescence studies of skin biopsy specimens showed IgM, IgA, and C3 involving the blood vessels; discontinuous weak IgM and IgA and C3 staining along the basement membrane zone was also noted.

A final diagnosis of SLE with hypocomplementemic UV (HUV) was made. The diagnosis of UV was based on the clinical manifestations of painful urticarial plaques lasting for more than 24 hours, occasionally associated with bruising by history and resolving with postinflammatory hyperpigmentation, the laboratory finding of hypocomplementemia, and the histology demonstrating changes of UV. The diagnosis of SLE was made based on the wide range of clinical and serological manifestations of alopecia, inflammatory polyarthritis, pleurisy, and strongly positive serologies including ANA, SSA, RNP, and anti-Smith antibody.

She was started on oral antihistamines (loratadine), oral prednisone 30 mg daily (weaning as tolerated to zero over months), and antimalarial medication hydroxychloroquine (because smoking can hasten the clearance of hydroxychloroquine from the system and reduce its efficacy, she was additionally advised to stop smoking). Nonsteroidal anti-inflammatory drugs in moderation were recommended. If refractory, methotrexate, mycophenolate mofetil, or azathioprine was recommended as consideration.

Urticarial vasculitis

General aspects

Introduction. UV is a diagnosis that requires clinicopathologic correlation. It is characterized in the skin by an inflammatory injury of dermal capillaries and postcapillary venules, with clinical signs varying from urticaria to signs of frank vasculitis. The diagnosis requires clinical manifestations of urticaria and the objective finding of vasculitis.

As with any vasculitis, many organs can be affected. Although clinical presentation generally involves skin, additional involvement of almost any other organ may be present, including musculoskeletal, pulmonary, renal, gastrointestinal (GI), and cardiac and ophthalmologic. The term "urticarial vasculitis" encompasses a wide spectrum of disease, varying from mild and limited disease to life-threatening organ involvement.

Precipitating factors may be similar to those associated with any vasculitis: infection, medication reactions, autoimmune reactions, and underlying malignancies are all possible underlying etiologies and should be sought. Frequently, the UV is idiopathic (of unknown cause).

The syndrome is thought to be driven by deposition of immune complexes in the skin predominantly, which activates the complement cascade, and therefore low complement levels are often noted. Low complement levels denote a more severe form of the disease; therefore, when UV is observed with hypocomplementemia, there is likely to be more organs involved.

Nosology/classification. Currently, the following classification of UV is generally accepted:

- normocomplementemic urticarial vasculitis (NUV),
- hypocomplementemic urticarial vasculitis (HUV),

and "urticarial vasculitis" is a term used for patients who have urticarial plaques and the skin pathology findings of leukocytoclastic vasculitis. UV generally can be divided into 2 groups according to complement levels, that is, NUV and HUV.[2]

The nomenclature and classification of HUV have been debated. HUV represents a continuum of the same disease, ranging from isolated urticarial lesions to a more systemic disease associating vasculitis. Although a specific syndrome called hypocomplementemic urticarial vasculitis syndrome (HUVS) has been described, it is not well delineated and is on the spectrum of HUV.[2]

A classification of UV is outlined in Table II. Table III presents a summary of identified etiologies,[3-8] Table IV summarizes systemic involvement,[9-13] Table V describes the suggested workup,[14] and Table VI provides an approach to management.[15]

Epidemiology. Although UV is rare, there are no epidemiologic studies that are population based describing the incidence and prevalence of this disorder. Most reports detail that women are more often affected (comprise 60% to 80% of reported patients). UV can occur at any age but is commonly reported in the fourth decade of life.

Etiologies and associated conditions. Like other forms of vasculitis, identified etiologies include medications, infections, autoimmune disease and malignancies, and other miscellaneous causes and often remain unidentified (idiopathic). Described etiologies are outlined in Table III.[3-8] Most instances of NUV are idiopathic.

Pathophysiology. It is thought that immune complexes (antigen antibody complexes secondary to antigens above) in the blood are deposited in vessel walls. These antigen antibody complexes activate the classic complement pathway such as C3A and C5A, leading to mast cell degranulation that leads to urticarial plaques, by increasing vessel permeability and chemotaxis of neutrophils. IL-1 is also thought to play a role.

Complement antibodies against their components cause conformational changes leading to pathological activation or inhibition of complement with organ damage and/or limited capacity of the immune system to clear immune complexes and apoptotic debris.[16]