Persistent urticarial eruption in an asthmatic patient

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CASE REPORT

The patient is a 36-year-old Caucasian woman referred to our service for assessment of a pruritic eruption of 1 year's duration. The eruption typically involved her face, neck, trunk, and extremities, and, on occasion, her tongue, lips and eyelids, and was associated with symptoms of pruritus and low grade pain of a burning nature. The lesions lasted for six to forty-eight hours, leaving a dusky pigment upon healing. She had been treated with cimetidine (400 mg bid), astemizole (10 mg qd), and hydroxyzine (25 to 50 mg qid) without improvement. She was also maintained on 30 mg/day of prednisone and prn nebulized albuterol for steroid-dependant asthma. She had eliminated a variety of foods and food additives from her diet, and changed her brands of detergents, soaps and cosmetics, all to no avail.

The patient noted that sun exposure worsened the eruption. Cold exposure, mechanical pressure, exercise, and emotional stress did not trigger or worsen the eruption. She had had no infections or treatment with other medications that could be implicated as a cause. She denied symptoms of flushing, diarrhea, bone pain, hemoptysis, fever, weight loss, epistaxis, arthralgias, oral ulcers, hematuria, alopecia, abdominal pain, or Raynaud's syndrome. She avoided the ingestion of aspirin, nonsteroidal anti-inflammatory agents, and foods and food additives known to be high in salicylate content.

The past medical history was pertinent for the presence of allergic rhinosinusitis and steroid-dependant asthma of 18 years' duration. Her reactive airway disease typically had worsened during the fall and winter seasons, upon ingestion of salicylates, following exposure to grass pollen, dust, cigarette smoke, and perfumes, and during respiratory infections. Her asthma had not been controlled by inhaled steroids, cromolyn sodium, and beta agonists. Methotrexate had been started several years prior to her present illness as a steroid-sparing agent, but was discontinued because of abnormal liver function studies. Prior allergy (epicutaneous) testing had revealed positive tests to dust and several seasonal allergens. Immunotherapy had not been not been instituted by her referring physician.

The family history is positive for asthmatic bronchitis in the patient's brother and maternal aunt. There is no family history of connective tissue disorders, thyroid disease, cancer, or similar skin disorders.

PHYSICAL EXAMINATION

The pulse rate was 84 beats/min, blood pressure 112/78 mm Hg, and temperature 37 °C. The nasal turbinates were pale and edematous. The thyroid was mildly enlarged and nontender. Lung examination revealed bilateral inspiratory and expiratory wheezes. One to five-cm indurated urticarial lesions were present on the face, neck, trunk, and extremities, including the palms and soles. The lesions were red, palpable, and nontender (Fig 1). Several had coalesced or cleared centrally, leaving a serpiginous red margin. Dermatographia and Darier's sign were absent. The remainder of the examination was unremarkable.

LABORATORY EVALUATION

The white blood cell count was 13,800 cells/mm^3 with a normal differential count. Her hemoglobin and hematocrit, erythrocyte sedimentation rate, urinalysis and blood chemistry were normal. Chest roentgenography revealed apical pleural thickening on the left but was otherwise unremarkable. Computerized tomography of the paranasal sinuses was within normal limits. She had a weakly positive fluorescent antinuclear antibody titer (8 IU/mL; normal = <7.5 IU/mL), and a positive perinuclear antineutrophil cytoplasmic antibody titer (normal = <1:16). The serum C4 was 11.3 mg/dL (normal = 15.5−38 mg/dl). RAST to food and inhalant allergens was negative. The following tests were also negative: antibodies to hepatitis B and C, cryoglobulins, cytoplasmic anti-neutrophil antibody (c-ANCA), antithyroid antibodies, rheumatoid factor, and anti-ds DNA, anti-Ro and anti-La, anti-Smith, anti-nRNP, anti-mitochondrial, and anti-parietal cell antibodies. Thyroid

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Figure 1. Skin eruption seen on the lower extremities of the patient. Annular, erythematous urticarial lesions are seen surrounded by a clear halo, varying between 1 and 5 cm in size. Some of the larger lesions represent coalescence of smaller urticarial lesions. The lesions were generalized and associated with a burning sensation.

function, C3 and CH50 levels, and a serum protein electrophoresis were all normal.

QUESTIONS

1. Based on the initial history, physical examination, and laboratory results, what diagnosis would you consider in this patient to be the most likely explanation for her skin eruption?
   a. Solar urticaria
   b. Chronic idiopathic urticaria
   c. Churg-Strauss syndrome
   d. Systemic lupus erythematosus
   e. Systemic mastocytosis
   f. Urticarial vasculitis
   g. Aspirin sensitivity

DIFFERENTIAL DIAGNOSIS

Chronic Idiopathic Urticaria

By definition, a diagnosis of chronic urticaria requires the persistence of the skin eruption for 6 weeks or longer. In contrast to acute urticaria, the etiology of chronic urticaria is identified in only 10% to 15% cases, hence most cases are of unknown etiology.[1–3] Typically, chronic urticaria occurs more commonly in women, and is characterized by the occurrence of pruritic wheals lasting less than 24 hours. The wheals may appear annular due to central clearing, but only rarely result in residual pigmentation.[1] The lesions may be associated with angioedema in about half the cases.

Chronic urticaria may result from reactions to food additives such as benzoic acid, sodium benzoate and the azo dyes. In one placebo-controlled study, 10% of patients with chronic urticaria reacted to the oral administration of these food additives.[1] Complement-mediated urticaria may be associated with serum sickness secondary to the administration of heterologous sera or drugs, or occur following the administration of blood products and radiocontrast media. The "first pass syndrome," where activation of the alternative pathway of complement follows renal dialysis using cuprophane membranes, may also occur.[7] These syndromes, however, seldom result in chronic urticaria unless exposure to the offending agent continues. Chronic urticaria may also be associated with autoimmune thyroiditis. Cases with autoantibody directed against the high affinity IgE receptor (FcϵRI), which can cross-link the receptor and lead to mast cell and basophil degranulation, have also been reported.[1,4,5] Our patient had no evidence of these risk factors to explain her urticaria.

Against a diagnosis of chronic idiopathic urticaria in our patient are the findings that the lesions were painful, that they persisted for more than 24 hours, and that they left a pigmented residual upon healing. In addition, the eruption did not respond to treatment often considered to be relatively effective in treating chronic urticaria (H_1 and H_2 blockers, corticosteroids).

Aspirin Sensitivity

Urticaria may be induced by drugs that inhibit arachidonic acid metabolism, such as the salicylates. One-third of patients with chronic urticaria may flare after ingestion of aspirin.[8] Aspirin sensitivity can also cause angioedema, anaphylaxis, or present as a syndrome of rhinitis, nasal polyps, hyperplastic sinusitis, and steroid-dependant asthma. Interestingly, simultaneous skin and respiratory sensitivity to salicylates is uncommon.

Our patient gave a history of exacerbations of her asthma when exposed to aspirin, and hence a carefully performed salicylate challenge would be pertinent to the understanding of her airway disease. The patient, however, had avoided the ingestion of aspirin, nonsteroidal anti-inflammatory drugs, and azo dyes during the time she suffered from the skin eruption. In addition, she avoided foods known to be high in salicylate content. The usual lack of involvement of both the skin and respiratory tracts in aspirin-sensitive patients also militates against salicylate-related urticaria in this patient. Furthermore, urticaria due to these drug sensitivities does not ordinarily result in residual pigmentation.

Systemic Mastocytosis

The clinical presentation of systemic mastocytosis may vary from a rela-

tively asymptomatic variant to a sometimes fatal, fulminant, systemic disease.[11] The classic cutaneous manifestation of mastocytosis is urticaria pigmentosa, an eruption characterized by the appearance of diffuse, reddish brown macules, papules or nodules. A positive Darier's sign (stroking a skin lesion induces urtication) is diagnostic. Nearly 30% of adults with mastocytosis have systemic disease.[12] In addition to urticaria, symptoms may include flushing, pruritus, rhinitis, asthma, nausea, vomiting, diarrhea, cramping pain, steatorrhea, bone pain, and peripheral neuropathy. Anaphylactoid reactions with hypotension and cardiovascular collapse may also occur. Patients may also have hepatosplenomegaly and lymphadenopathy. Monoclonal gammopathy, eosinophilia, anemia, and raised alkaline phosphatase may be found on laboratory examination. The diagnosis is established by bone marrow or skin biopsy, and/or measurements of 24-hour urinary histamine, histamine products, and leukotrienes. Plasma heparin and mast cell tryptase levels may also be elevated.[11,12]

Our patient did not have hepatosplenomegaly, lymphadenopathy, or skin lesions typical of systemic mastocytosis, nor a positive Darier's sign, making this diagnosis an unlikely cause of her urticaria. Further, she did not complain of bone pain, flushing, gastrointestinal or neuropsychiatric symptoms typical of this disorder, and her routine laboratory studies were normal. Hence, a diagnosis of systemic mastocytosis is unlikely in this case.

Churg-Strauss Syndrome

The Churg-Strauss syndrome is characterized by the development of systemic vasculitis in patients with allergic asthma.[13] The syndrome typically presents with fever, malaise, weight loss, skin lesions, bronchospasm, and pulmonary infiltrates. An infiltrate on chest roentgenography occurs 93% of the time, while peripheral neuropathy, abdominal complaints, cardiac and renal involvement occur in 63%, 42%, 38%, and 38% of cases respectively.[13,14] Laboratory evaluation invariably demonstrates a raised erythrocyte sedimentation rate and eosinophilia. The diagnosis is confirmed by skin biopsy, which demonstrates a granulomatous vasculitis involving the small and medium-sized blood vessels, and by demonstrating a positive perinuclear antineutrophil cytoplasmic antibody which is present in about 66% of cases. Untreated, the mortality associated with the syndrome is high with less than 4% surviving five years.

Our patient's findings do raise the possibility of the Churg-Strauss syndrome. The presence of lung, sinus, and cutaneous involvement are compatible with the diagnosis, as is the finding of a positive perinuclear antineutrophil cytoplasmic antibody.[15] Nonetheless, the normal erythrocyte sedimentation rate, the absence of eosinophilia, neuropathy, gastrointestinal and cardiac involvement and the normal chest roentgenography all argue against the diagnosis.

Systemic Lupus Erythematosus

Urticaria can be a presenting feature of systemic lupus erythematosus.[16,17] The urticaria in these cases is usually a manifestation of leukocytoclastic vasculitis. It typically occurs in patients with obvious serologic and clinical evidence of systemic lupus. In one study, 10 of 143 patients with systemic lupus erythematosus developed urticaria, 90% of whom had evidence of systemic disease; seven of the nine patients who were biopsied had evidence of leukocytoclastic vasculitis.[18]

With the exception that her urticarial rash was photosensitive, our patient had none of the clinical findings to suggest a diagnosis of systemic lupus erythematosus, such as polyarthragias, fatigue, hair loss, and nephritis. In addition, although her fluorescent antinuclear antibody was positive and the C4 level was slightly depressed, antinuclear antibodies considered more specific for lupus erythematosus (dsDNA, Smith's antibody) were negative.

Urticarial Vasculitis

Urticarial vasculitis is a form of leukocytoclastic vasculitis involving postcapillary venules.[1,2,19–21] Clinically, the lesions are painful (patients often describe a burning sensation), may persist for more than 24 hours and evolve into palpable purpura, often leaving a residual pigmentation upon healing. Systemic involvement resulting in angioedema, arthritis, abdominal or chest pain, fever, episcleritis, uveitis and nephritis, and obstructive airway disease may occur. In a recent review of 72 cases of urticarial vasculitis, angioedema was present in 30%, arthralgias in 49%, lung disease in 21%, and abdominal pain in 17%.[20] The majority of the patients had urticarial lesions lasting more than 24 hours (64%); 32% of patients complained of a burning sensation at the site of the eruptions. In 35% of patients the urticaria evolved into palpable purpura.[20] The diagnosis is established by skin biopsy.

Although the presence of perinuclear antineutrophil cytoplasmic antibody is not typical of urticarial vasculitis, our patient's clinical findings are compatible with this diagnosis.

QUESTION

1. Which therapy or therapies may be useful in the management of this patient's skin eruption?
   a. Increasing her prednisone dose to 1mg/kg/day.
   b. Methotrexate
   c. Hydroxychloroquine
   d. Cyclophosphamide
   e. Colchicine
   f. Nonsteroidal anti-inflammatory agents
   g. Azathioprine
   h. Dapsone
   i. Pentoxifylline

DISCUSSION

Our patient's course is most compatible with a diagnosis of urticarial vasculitis. Her skin lesions persisted for longer than 24 hours, were painful, palpable, and left a residual pigmentation. This diagnosis was confirmed by a skin biopsy which revealed leukocy-

toclasis and perivascular polymorphonuclear leukocyte infiltration involving postcapillary venules (Fig 2).

Soon after the biopsy, the patient developed a flare in her urticaria. The dose of prednisone was increased to 60 mg/day and tapered over the next 2 weeks. However, her urticaria worsened when the prednisone dose was reduced to 40 mg/day. She was then started on colchicine 0.6 mg twice daily. Within a week of starting colchicine her urticaria resolved and she has been in remission since. Two months after starting colchicine, the patient developed laryngeal fullness, chest discomfort and dysphagia. Upper endoscopy was normal and her symptoms were thought to represent an adverse reaction to colchicine. These symptoms resolved when the drug was discontinued.

The differential diagnosis of chronic urticaria and the features that may help differentiate between chronic idiopathic urticaria and urticarial vasculitis are listed below and in Table 1, respectively.

IgE-(Immune) mediated Urticaria
- Allergens: Drugs, food, latex, insect venom

Physical urticaria
- Pressure, cold, vibratory, solar and cholinergic

Complement-mediated and Inflammatory states
- Serum sickness syndrome
- Urticarial vasculitis
  - Systemic lufus erythematosus, rheumatoid arthritis, Sjogren's syndrome
  - Hepatitis B and C
  - Schnitzler's syndrome

Iatrogenic
- Opiates, radio-contrast media
- Aspirin, nonsteroidal antiinflammatory drugs
- Tartrazine dyes and bisulfites

Associated with underlying disease
- Urticaria pigmentosa
- Systemic mastocytosis

Miscellaneous
- C_3b inactivator or Carboxypeptidase N deficiency
- Familial amyloidosis deafness syndrome
- Occult infection (Viral, parasitic, bacterial)
- Malignancy: Lymphomas and solid tumors
- Thyroid disease

Idiopathic
- Auto-antibody to FcER1 receptor
  - Autoimmune thyroid disease associated

Urticarial vasculitis may be a primary disorder or occur in association with other diseases including Lyme disease, viral infections (hepatitis B and C, infectious mononucleosis), cryoglobulinemia, IgA and IgM paraproteinemias, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome.[25] In addition to urticarial vasculitis, patients with IgM paraproteinemia may develop disabling bone pain, hyperostosis, and fever (Schnitzler's syndrome).[24] Cimetidine, procainamide, food additives, and ultraviolet light exposure have also been reported to cause urticarial vasculitis.[25]

Two pathologic varieties of urticarial vasculitis have been described: normocomplementemic and hypocomplementemic. The latter syndrome, referred to as the hypocomplementemic urticarial vasculitis syndrome, has been reviewed in detail recently.[20,21] It is an uncommon disorder resembling systemic lupus erythematosus, and may result in polyarthralgias, glomerulonephritis, and positive antinuclear antibodies.[20] One report of hypocomplementemic urticarial vasculitis was reported with life-threatening pulmonary hemorrhage.[23] The hypocomplementemic urticarial vasculitis syndrome is characterized by activation of the classical pathway of complement, low C1q levels, and IgG autoantibodies to C1q.[22] Patients with normocomplementemic urticarial vasculitis are less likely to develop systemic diseases.

Treatments that have been shown to be useful in the management of urticarial vasculitis include aspirin, indomethacin, colchicine, dapsone, hy-

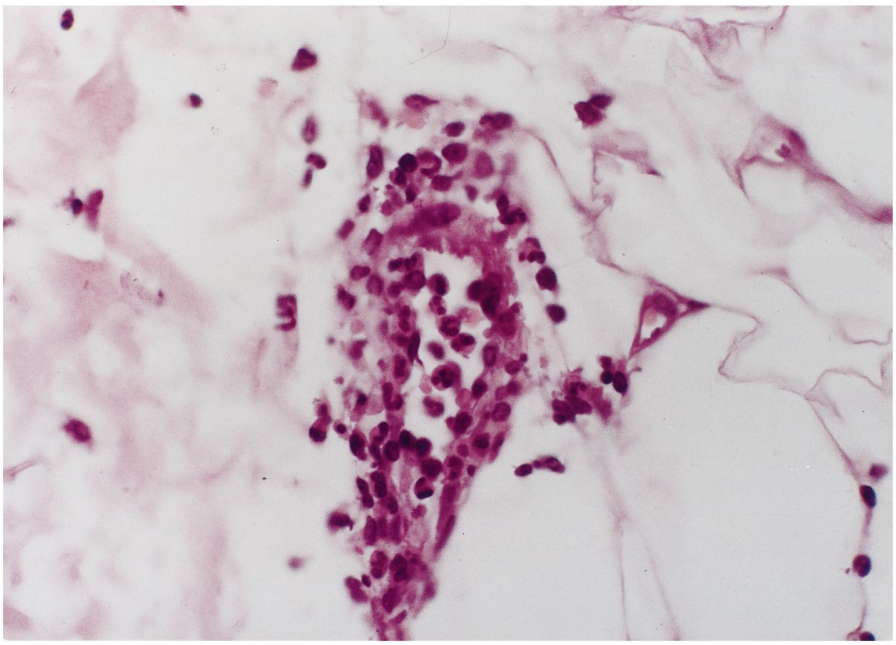


Figure 2. Biopsy of the urticarial lesion revealed leukocytoclastic vasculitis involving postcapillary venules. There is neutrophil invasion of vessel walls, perivascular accumulation of neutrophils, nuclear dust and red blood cell extravasation.

Table 1. Differentiation Between Chronic Urticaria and Urticarial Vasculitis

Feature	Chronic Urticaria	Urticarial Vasculitis
Clinical		
Fever*	−	++/−
Arthralgia	−	++/−
Abdominal pain	−	++/−
Purpura*	−	++
Pruritis	+++	++/−
Burning pain	−	++/−
Pigmentation	−	+++
Duration >24 hrs	−	+++
Systemic disease		
Chronic obstructive pulmonary disease/ asthma	+/−	++/−†
Uveitis	−	++/−†
Renal disease*	−	++/−†
Arthritis	−	++/−†
Serositis	−	+/−†
Laboratory data		
Erythrocyte sedimentation rate	N‡	↑ ↑
Antinuclear antibody	−	++/−
Complement levels*	N	↓ ↓/N
Serum immune complex*	N	↑ ↑/N
Histopathology		
Inflammatory cells	Mononuclear cells	Neutrophils
Location	Perivascular	Perivascular Within vessel wall
Endothelial swelling	−	++
Extravasation of red blood cells*	−	++
Leukocytoclasis*	−	++
Fibrin deposition	+/−	++/−
Immunofluorescence		
C3	−	++
Immunoglobulins	+/−	++
Treatment		
	H_1/H_2 blockade‡ Steroids	Dapsone Colchicine Steroids Cytotoxics

* Major criteria for urticarial vasculitis.
† Features of hypocomplementemic form.
‡ N = normal H_1/H_2 = histamine receptor types 1 and 2.

droxychloroquine, pentoxifylline, and prednisone.[1,19,20,21,25,26] Dapsone may be more effective in patients with vasculitis complicating systemic lupus erythematosus.[25] Hydroxychloroquin, which acts by inhibiting lysosomal enzyme release and interleukin-1 production, has also been shown to be effective in the primary cutaneous form of urticarial vasculitis. Colchicine inhibits neutrophil chemotaxis and stabilizes lysosomal membranes, but toxic side-effects may limit its use more than some of the other therapeutic options.[25] In cases with necrotizing lesions or systemic involvement, corticosteroids, azathioprine, and cyclophosphamide may be indicated.[25] We chose colchicine in our patient due to its additional potential as a steroid-sparing agent in bronchial asthma.

FINAL DIAGNOSIS

Urticarial vasculitis

SUMMARY

This case demonstrates the importance of recognizing urticarial vasculitis in patients with chronic urticarial eruptions. The salient points in history that point towards the diagnosis of urticarial vasculitis include the presence of painful urticarial lesions that last longer than 24 hours and that heal leaving residual pigmentation. In some cases the urticaria may evolve into palpable purpura. An associated systemic illness that may resemble systemic lupus erythematosus should also suggest the diagnosis, which is established by skin biopsy. Histopathology reveals a leukocytoclastic vasculitis involving postcapillary venules. When associated with systemic vasculitis, the urticaria is likely to be of the hypocomplementemic variety, with immunoglobulin and complement deposition on biopsies, and with serum complement studies demonstrating classical pathway activation, low C1q levels, and anti-C1q precipitins. A variety of agents have been used in the management of urticarial vasculitis, including aspirin, nonsteroidal anti-inflammatory agents, corticosteroids, colchicine, dapsone, hydroxychloroquine, and cytotoxic agents such as cyclophosphamide and azathioprine.

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