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URTICARIA AND ARTHRALGIAS AS MANIFESTATIONS OF NECROTIZING ANGIITIS (VASCULITIS)*

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ABSTRACT

Although necrotizing angiitis (vasculitis) of the superficial venules and capillaries of the skin is usually appreciated visually as a purpuric papule, a group of patients has been defined in whom all of the skin lesions were urticarial. Microscopic examination of skin biopsy specimens showed fibrinoid necrosis of the blood-vessel walls, an infiltrate containing polymorphonuclear leukocytes, fragmentation of cell nuclei, and extravasation of erythrocytes. Arthralgias were present in 7 of the 8 patients and arthritis in 3 of these. Two of the patients experienced episodes of abdominal pain. A syndrome of chronic refractory urticaria accompanied by arthralgias and occasionally arthritis or abdominal pain and an elevated erythrocyte sedimentation rate was recognized in nonatopic female patients and appears to be a manifestation of an underlying necrotizing angiitis.

Necrotizing angiitis (vasculitis) of the skin usually presents clinically as a variety of lesions that includes macules, papules, pustules, infarcts, ulcers, and scars. The characteristic erythematous papule that does not blanch with the application of external pressure (purpuric papule) is the most typical and constantly present clinical sign [1]. Although descriptions of patients with urticaria as the sole manifestation of cutaneous vasculitis exist in the literature [2–4], the wheal is an infrequently recognized presentation of vasculitis.

A group of patients comprised predominantly of nonatopic women with chronic urticaria accompanied by arthralgias has been delineated. The urticarial skin lesions in these patients showed vasculitis when skin biopsy specimens were examined, and the most consistently abnormal laboratory study was an elevated erythrocyte sedimentation rate. The incidence of vasculitis masquerading as urticaria among individuals with chronic refractory urticaria is unknown, and only through recognition of this entity by examination of skin biopsy specimens can the necessary clinical experience be gained to permit definition of incidence, prognosis, and optimal treatment.

MATERIALS AND METHODS

Patient population. Eight patients with skin lesions that were present as raised wheals that blanched with the application of external pressure were studied. Four of these individuals were referred for the evaluation of chronic urticaria that was refractory to treatment, and vasculitis was discerned by examination of biopsy specimens; the remaining 4 patients were then appreciated from 12 clinic patients with the clinical diagnosis of urticaria based on the evolving concept of a clinical entity. The eruption occurred as crops of lesions that were transient in duration and of generalized distribution. Multiple blood specimens from each patient were collected at the initial interview and serially thereafter; the sera were stored in aliquots at −70°C.

Laboratory studies obtained included: hematocrit, hemoglobin, Westergren erythrocyte sedimentation rate (ESR), white blood-cell count (WBC) with differential analysis, eosinophil and platelet counts, antinuclear (ANA) [5] and rheumatoid [6] factors, serum protein electrophoresis, cold agglutinins, serologic test for syphilis, blood-chemistry profile including lactic dehydrogenase (LDH), hepatitis-associated antigen, blood urea nitrogen, serum creatinine, urinalysis with sediment examination, creatinine clearance, 24-hr urine protein, stool examination for occult blood, electrocardiogram, and chest roentgenogram.

Histopathologic examination. Skin trephine biopsy specimens measuring 4 mm were taken from skin lesions and an adjacent, clinically normal area after infiltrating the periphery of both sites with lidocaine anesthesia. The tissue was fixed in 10% formalin, stained with hematoxylin–eosin, and examined with a light microscope. The histopathologic criteria [1,7] used for the diagnosis of vasculitis are described under *Results*.

Measurement of complement components. Effective molecule titrations were used to measure C1 [8], C4 [9], C2 [10], C3 [11], and C9 [12]. Whole serum complement activity, CH_{50}, was measured as described [13]. C1q [14], C4 [15], C3 [14], C5 [16], Factor B (C3 proactivator) [17], and $C\bar{1}$ inhibitor [18] were measured immunochemically by radial immunodiffusion [19].

Evaluation of cryoproteins and immunoglobulins. Blood was drawn into plastic syringes at 37°C and distributed for the isolation of cryoproteins into 2 glass tubes to obtain serum or plasma formed in ethylene diamine tetraacetate (1.4 mg/ml). The specimens were sedimented at 250 × *g* for 10 min at 37°C and the cells and clots discarded. In order to determine cryocrits, 1.0-ml portions of the serum or plasma were transferred

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to calibrated tubes (Clay Adams, Becton, Dickinson Company) that were maintained at 4°C for 24 hr followed by centrifugation at 250 × *g* for 10 min at 4°C.

Serum immunoglobulins IgG, IgM, and IgA [20], IgD [21], and IgE [22] were measured by radial immunodiffusion. Screening for low-molecular-weight [7S] IgM was carried out in 4% polyacrylamide gel [23,24].

RESULTS

The 8 patients (Tab. I), of whom 7 were women and 1 was a man, ranged from 25 to 68 years of age. The skin lesions, which appeared as raised, erythematous, circumscribed wheals that blanched with the application of external pressure, were present in all of the patients. Although the urticaria was chronic and occurred for periods ranging from 3 months to 25 years, an individual crop of lesions was transient, usually lasting fewer than 48 hr and in no instance more than 72 hr. The frequency of episodes of lesions was highly variable and ranged from once daily to once monthly. In most of the patients the eruptions were characterized as being pruritic or as possessing a burning quality, or both. The skin lesions were asymptomatic in patients ND and AS. All areas of the integument were affected in a generalized distribution that included the palms in patient RS and the oral mucous membranes in patients CH and EL. Livedo reticularis was present in a generalized distribution over the skin in patients EL, AS, and RW.

The histopathologic criteria [1,7] used for the diagnosis of vasculitis of the small, superficial venules and capillaries of the skin in biopsy specimens were: endothelial swelling, necrosis of the blood-vessel wall with the presence of fibrinoid material, an infiltrate containing polymorphonuclear leukocytes in and about the blood-vessel walls and scattered in the dermis, fragmentation of nuclei (nuclear dust), and extravasation of red blood cells (Fig.). Each of the skin lesions showed similar microscopic changes. There was edema of the superficial portions of the dermis and an absence of eosinophils in the cellular infiltrate. In addition, similar findings were present in skin biopsy specimens taken from sites of circled lesions following resolution such that the site appeared clinically normal at the time of biopsy 24 hr after being circled in patients FD and RW. Normal skin that had not been clinically involved showed no pathologic changes. Biopsies in 8 control patients with persistent urticaria revealed only edema of the upper dermis and a slight perivascular infiltrate composed of lymphocytes.

Pain and stiffness of the joints occurred in 7 of the patients; these episodes were transient and usually lasted fewer than 72 hr. Multiple joints were affected, most commonly the knees, ankles, wrists, and fingers. In some of the patients the initial episodes of arthralgias and urticaria began simultaneously, and in some patients there tended to be concomitant fluctuations in the skin and joint involvement. In addition, patients ND, RS, and RW described occasional swelling of their joints accompanied by warmth and erythema. Patient RS exhibited a transient effusion of the knee, and examination of a synovial biopsy speci-

TABLE I

Clinical and laboratory features in patients with vasculitis manifested as urticaria

Patient	CH	RS	EL	ND	FD	MT	AS	RW	Normal values
Age, sex	25, F	29, F	68, F	29, F	54, F	38, F	46, F	48, M	
Duration skin lesions	10 yr	3 yr	5 yr	25 yr	3.5 yr	3 mos	2 yr	3 yr	
Arthralgias	+	+	+	+	+	—	+	+	
ESR	66	4	44	40	42	36	60	28	
WBC	5,000	8,500	6,200	8,900	24,800	7,100	3,000	5,100	
ANA	—	—	—	—	1/20	—	—	—	
LDH (units/ml)	215	212	ND	192	166	248	120	190	90–200
Immunoglobulins									
IgG (mg/ml)	9.3	10.4	10.45	15.5	5.9	9.0	13	8.4	7.2–15.8
IgM (mg/ml)	0.75	1.33	1.31	1.11	2.31	1.15	0.88	1.1	0.5–2.0
IgA (mg/ml)	2.8	1.42	2.82	4.12	1.88	1.3	1.15	0.87	1.0–5.6
IgD (μg/ml)	39	12	24	56	11	33	ND	11	15–68
IgE (ng/ml)	<10	<10	<10	<10	<10	<10	150	<10	0–350
7S IgM	—	ND	—	—	+	ND	ND	+	

ND = not done; numbers within boxes are abnormal values.

men showed necrotizing vasculitis involving the venules of the synovium.

Seven of the patients were afebrile whereas temperature elevations as high as 103°F occurred in patient FD and appeared to precede each episode of urticaria. Only 2 of the patients exhibited symptoms or signs indicating involvement of the gastrointestinal tract. Abdominal pain associated with nausea, vomiting, and diarrhea that lasted about 72 hr occurred with some but not all episodes of urticaria in patient RW. Abdominal pain also occurred in patient AS, in whom an abnormal D-xylose test was present without concomitant renal disease. Allergic rhinitis was present in patient EL, in whom seasonal exacerbations occurred but in whom a family history of similar problems was absent. None of the patients showed sensory or motor abnormalities on neurologic examination, and there was no evidence of pulmonary disease by history, physical examination, or radiologic evaluation.

Therapeutic regimens over the years in all of the patients had included various combinations of antihistamines, tranquilizers, and prednisone with minimal or no benefit. Neither these medications nor any other agents could be related to the eruption.

Normal laboratory studies included hematocrit, hemoglobin, eosinophil and platelet counts, cold agglutinins, serologic tests for syphilis, serum glutamic oxalacetic transaminase and alkaline phosphatase, hepatitis-associated antigen, blood urea nitrogen, serum creatinine, urinalysis with sediment examination, 24-hr urine protein, creatinine clearance, stool examination for occult blood, electrocardiogram, and chest roentgenogram.

In only 1 patient (RS) was the erythrocyte sedimentation rate not elevated, and this was the case on two determinations. In the other 7 patients the erythrocyte sedimentation rate was consistently elevated, with the number of determinations ranging from one to three. The serum level of lactic dehydrogenase was elevated in 3 of the patients. The white blood-cell count in patient FD was elevated with the maximum level being 32,400 with 86 polymorphonuclear leukocytes, 6 band forms, 6 lymphocytes, 1 monocyte, and 1 basophil. In contrast, the white blood-cell count was low in patient AS with the minimum value being 3000 with a normal differential count.

Rheumatoid factor was present only in patient RW, in whom the titer was 20,240. The antinuclear factor was positive in only 1 of the patients (FD), without other serologic abnormalities suggestive of lupus erythematosus. Cryoglobulins were absent in all of the patients; however, a cryofibrinogen was present in patient RW at a level of 5%. Quantitative analysis of serum immunoglobulins showed only occasional borderline abnormalities in the levels of IgG, IgM, IgA, and IgD, with no elevation of levels of IgE. A small IgM-M component was present in patient FD, and a low-molecular-weight (7S) IgM occurred in the serum of 2 of the patients (FD and RW). Hypocomplementemia (Tab. II) with depression of the levels of the early components—C1, C1q, C4, and C2—occurred in patients RW and AS. In addition, in patient AS the levels of both C3 and C9 were diminished. In 4 of the 6 patients without hypocomplementemia, the levels of C9 were elevated.

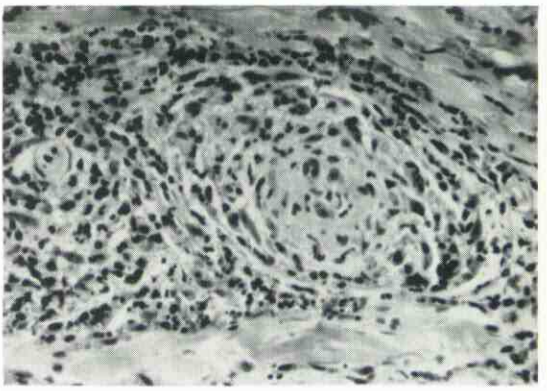

FIGURE. Detail of small blood vessel in superficial portion of dermis showing fibrinoid necrosis of the vessel walls, an infiltrate with many polymorphonuclear leukocytes, nuclear dust, and a few erythrocytes (H & E, × 195).

DISCUSSION

Although urticaria is both encountered frequently and recognized easily, skin biopsies rarely are performed in patients with this clinical presentation. A group of patients comprised predominantly of female individuals was recognized, in whom chronic refractory urticaria accompanied by arthralgias was present. The recurrent urticarial eruptions occurred in crops in the skin and occasionally mucous membranes, were of transient duration lasting fewer than 72 hr, and were generally pruritic. All patients had received medical attention over a period of years and had obtained minimal or no relief from a variety of medications.

Skin biopsy specimens showed a necrotizing vasculitis involving the superficial blood vessels of the dermis, and this was morphologically indistinguishable from vasculitis manifested as palpable purpura [1]. These findings contrast with those reported in classical urticaria, in which the predominant finding is edema in the dermis in early lesions; occasionally there are a few cells scattered in the dermis associated with a perivascular infiltration of lymphocytes in older lesions but without fibrinoid necrosis of the blood-vessel wall [25]. The fact that the vasculitis is apparent in the skin biopsy specimens taken at a time when the lesion has subsided suggests that a mediator emanating from the site of vasculitis results in the local change of vascular permeability; the transient nature of the urticarial reaction could imply consumption of substrate or the development of a

TABLE II

Complement system in patients with vasculitis manifested as urticaria

Patient	CH	RS	EL	ND	FD	MT	AS	RW	Normal values[a]
					Hemolytic assays (units/ml)				
CH_{50}	234	194	210	211	171	214	73	88	150–250
C1	202,000	166,000	262,000	268,800	216,000	248,000	31,900	55,000	141,300–287,900
C4	245,000	232,000	212,000	374,800	456,000	256,000	18,500	94,000	145,000–380,900
C2	25,200	18,500	21,400	19,500	17,400	25,500	700	6,100	15,500–27,400
C3	19,800	ND	26,000	23,000	29,500	ND	ND	18,600	10,600–26,100
C9	230,000	256,000	165,000	310,000	144,500	296,000	83,200	206,000	136,900–219,600
					Complement proteins				
C1q (μgN/ml)	27	23	26	32	27	30	8.2	10	18–38
C4 (μg/ml)	534	310	359	490	309	661	130	153	158–745
C3 (mg %)	90	135	148	134	182	168	62	94	91–198
C5 (μg/ml)	90	126	146	149	114	126	ND	106	65–184
$C\bar{1}INH$ (mg %)	2.7	2.6	2.5	3.5	3.5	3.8	2.0	3.0	1.6–3.7
Factor B (%)	108	78	130	133	155	120	172	108	60–160

[a] Based on an analysis of 50 randomly-selected healthy hospital personnel (±2 SD).

ND = not done; numbers within boxes are abnormal values.

refractory state as the limiting step in the production of the clinical lesion.

There were no consistent abnormalities when the specimens manifesting necrotizing angiitis were examined by direct immunofluorescence techniques, as was also the case in the examination of biopsy specimens in patients with palpable purpura. Others [26,27] also have noted that the presence of immunoglobulins, complement proteins, and fibrin in cutaneous vasculitis is highly variable. Immunofluorescence studies of blood-vessel damage created by an Arthus reaction in the skin of the guinea pig [28] or in the joint of the rabbit [29] showed that the immunoglobulins and complement proteins deposited in the blood-vessel walls are no longer detectable by 18 and 2 hr, respectively. It therefore seems possible that the variability of findings in patients reflects variation in the age of the lesion studied. Alternatively, the mechanism may not involve the deposition of immunoglobulins or complement.

Another cutaneous sign that appeared in 3 of the patients was livedo reticularis. This vascular reaction is thought to represent involvement of arterioles which reside in the deeper dermis with resultant dilation of small subpapillary venules [30]. Livedo reticularis has been reported to occur in patients with polyarteritis nodosa [31] and in necrotizing angiitis associated with cryoglobulinemia [32].

Arthralgias that were transient in duration were present in 7 of the patients and appeared to coincide with the episodes of urticaria on some occasions in the majority of the group. Moreover, in 3 of the patients there was arthritis by history, and in 1 patient an effusion was documented by physical examination. In the latter instance, a synovial biopsy specimen showed necrotizing vasculitis of venules identical to the process observed in the superficial dermis. It is possible to speculate that the joint symptoms and signs have a pathogenetic mechanism comparable to the urticarial skin lesions.

Transient and episodic involvement of the gastrointestinal tract occurring with some episodes of urticaria was present in patient RW, while in patient AS the frequency of the urticarial eruptions was so continuous that it was difficult to relate an episode of abdominal pain to a specific crop of lesions. This clinical association is reminiscent of patients with hereditary angioedema, in whom the attacks of cutaneous angioedema may be associated with transient abdominal pain [33]. It thus seems likely that the full syndrome includes vasculitis with secondary edema in the gastrointestinal tract, joints, and skin but that the episodic nature and ready visibility of the skin favor recognition of the cutaneous manifestations above the others. Although this syndrome does not appear to include involvement of kidneys, cardiopulmonary system, or central nervous system, which are frequently involved in more usual forms of necrotizing vasculitis, it is possible that in some cases it may be the forerunner of typical necrotizing systemic vasculitis inasmuch as urticaria and arthralgias have been noted as early manifestations of clinical polyarteritis nodosa [34] and of hepatitis antigen-associated vasculitis [35]. Urticaria and arthralgias may be very prominent features of serum sickness; however, the clinical evolution of

these patients is quite distinct.

The most consistent laboratory abnormality observed in these patients is an elevated erythrocyte sedimentation rate. Although this abnormality is a nonspecific indicator of inflammation, its elevation in patients with urticaria should suggest a search for vasculitis, as the sedimentation rate is normal in classic urticaria and in hereditary angioedema [33]. Since lactic dehydrogenase is present in the skin [36], it is possible that the slight elevation of serum lactic dehydrogenase noted in 3 patients may be ascribed to this source, as there was no evidence of a liver or hematologic abnormality in the other laboratory studies. A cryofibrinogen was present in patient RW, and it should be noted that the array of skin lesions reported in patients with cryofibrinogenemia includes Raynaud's disease, necrosis, petechiae, cold urticaria, and curious indurated areas of swelling of the skin in children [37]. In the serum of 2 patients (FD and RW) the presence of low-molecular-weight (7S) IgM was demonstrated. Such a protein was previously noted in 1 patient with episodes of angioedema clinically indistinguishable from the hereditary form [24].

Neither the chemical mediators nor the mechanism by which such materials might be formed and released are apparent from this initial recognition of the syndrome. An immediate hypersensitivity reaction, namely IgE-mediated release of histamine or eosinophil chemotactic factor of anaphylaxis, is unlikely as the patients were nonatopic, the serum levels of IgE were not elevated, the patients were refractory to management with antihistamines, and the urticarial lesions were devoid of eosinophils [38]. In addition to histamine, many substances can enhance local vascular permeability, but based on the data available from local, individually administered agents, it is not possible to favor a particular mechanism. A consideration of the action of several of the mediators injected into the skin does not reproduce the clinical picture. Injection of bradykinin into skin [39] results in the formation of both erythema and whealing and the production of pain rather than pruritus when applied to the base of a vesicle. Injection of prostaglandin E_1 into the skin produces a wheal accompanied by prolonged erythema lasting as long as 10 hr without pruritus [40]. Serotonin does not cause a wheal when injected into the skin [41].

Anaphylatoxins can also elicit local changes in vascular permeability and thus it is relevant to consider their action in 2 patients manifesting abnormalities of the complement system. Further, it should be noted that McDuffie et al [4] recently reported 4 patients with urticaria and hypocomplementemia. Anaphylatoxins, which are reaction products of the activation of the complement system resulting from the cleavage of both C3 and C5, induce the formation of local erythema, whealing, and pruritus. The reaction induced by C3a may be abolished by the oral administration of an antihistamine [42]; however, the effect of these agents on C5a has not been analyzed. C5a appears to be more active than C3a on a molar basis [43], and studies with isolated smooth muscle indicate that its action can be independent of histamine release [44]. Therefore, it is not possible to eliminate this as a potential mediator.

The appreciation that this clinical syndrome is based on necrotizing vasculitis has not been a principal consideration in previous management programs. With regard to the present group of patients, such medications as antihistamines, tranquilizers, and prednisone have not been effective, and experience with cytotoxic agents has not yet been accumulated.

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