

macrophages in the regulation of nickel sensitivity.

Soluble histamine had an inhibitory effect on nickel-induced blast transformation. Even in the absence of exogenous histamine, the receptor type 2 antagonist was able to increase the nickel reaction, which suggests that the suppressive effect of histamine receptor bearing cells is not dependent on excessive amounts of histamine but is a readily expressed ability when nickel-sensitive clones begin to proliferate.

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Clinical Evaluation and Pathomechanism of Urticaria-like Skin Eruption in Systemic Lupus erythematosus

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Abstract. Clinical observations of 10 SLE patients having urticaria-like skin symptoms showed that the clinical process of urticaria found in patients suffering from SLE differs from the classic one. On the basis of histological and immunohistological studies in 5 cases, a characteristic histological manifestation of leukocytoclastic vasculitis of small veins in the upper third of the cutis was found. The various urticaria-like skin symptoms in SLE are caused by immunocomplexes of various components. The continuous presence of urticaria is caused by C-activating formation of anaphylatoxin. The appearance of urticaria in SLE patients is an unfavourable precursor which has been confirmed by statistical analysis.

Key words: Systemic lupus erythematosus; Urticaria; Immunocomplex

Systemic lupus erythematosus (SLE) is not infrequently accompanied by urticaria or by urticaria-like manifestations (1, 2, 3, 4, 5, 8, 10). *Dubois* found urticaria in 6.9% of 520 cases, while *Harvey* found it in 7% of 105. *Estes* found a higher rate of urticaria—13%—in patients suffering from SLE. In our study the proportion was 12.5%.

The urticaria-like skin symptoms prompt the following questions: What are their clinical characteristics; to what extent do they differ from urticaria caused by histamine; are they connected functionally with SLE; what is their importance for the prognosis of the disease?

The purpose of our study was to find answers to these questions raised in the course of clinical observations of 10 SLE patients having urticaria-like skin symptoms and by histological and immunohistological analysis of biopsies made of skin symptoms.

MATERIALS AND METHODS

For 9 years, 10 SLE patients with urticaria-like skin symptoms (on the basis of ARA criteria) were observed (age range 24–57 yrs, average 40.5, all females). The

Table 1. *Differential diagnosis of urticaria-like lesions appearing in SLE*

	SLE	Urticaria
Morphological picture	Small elements; frequent transition to erythema exsudativum multiforme	Various extent elements
Course	Protracted	Rapidly changing
Subjective symptoms	None	Intense itching
Therapy	High dosage steroid (above 60 mg predisone per day) or immunosuppressive agents	Antihistamines
Histology	Leukocytoclastic vasculitis	Increased vessel permeability
Prognosis	Poor	Good

symptoms developed during the active stage of the disease (LE cell positivity, ANA positivity in high titer, hypocomplementemia, arthritis, proteinuria) during corticosteroid management (20–60 mg/day).

Besides urticaria, other skin symptoms such as classic discoid in 2 of the patients, pemphigoid in one and livedo reticularis, were seen.

A histological immunofluorescence examination was made in 5 out of 10 patients. As a control the same analytical method was used for the examination of three bacterial and drug-induced urticarias. One man (32 yrs) and 2 women (48 resp. 58 yrs) were among them.

The fixed histological sections were stained with hematoxylin-eosin and toluidine blue. Immunohistochemical examinations were made on cryostat sections obtained from biopsies, by both direct and indirect methods. Hyland conjugates were used for the immunofluorescence studies. The sections were studied with a Zetopan-Binolux (Reichert) microscope, illuminated with a HBO-200 mercury vapour lamp, using 2×BG 12/3 primary and GG 9/1 mm OG 1/1.5 mm secondary filters.

RESULTS

Clinical observations

Skin symptoms similar clinically to urticaria were lesions of small elements appearing on sites exposed to a continuous stress. The centres of these lesions, which bled slightly, subsequently sank in, leaving an annular outline. Clinically the affection is most similar to erythema exsudativum multiforme. The differences between urticaria-like eruptions as seen in SLE, and classical urticaria are summarized in Table 1.

The prognosis of urticaria occurring in SLE is not favourable. Of 89 patients suffering from SLE,

8 died during the observation period of 9 years. Four of these 8 patients showed urticaria-like symptoms. Mortality in SLE accompanied by urticaria-like skin symptoms is statistically considerably greater ($\chi^2 = 13.24$; $c = 0.26$; $p = 0.0013$). It is remarkable that all patients died of lupus nephritis.

Histological study

The histological results obtained were the same, as regards their main features, in all the SLE patients. The stratum papillare was edematous. Around the subpapillate capillaries an infiltrate consisting of polymorphonuclear leukocytes, numerous eosinophil cells, some lympho- and histiocytes containing numerous nucleated fragments were found. The walls of both capillaries and small veins became edematous, loose and resolved partly. Numerous mastocytes stained metachromatic with toluidine blue were detected in the perivascular infiltrate. The histology of our 3 control cases—though their background symptoms were varied—was similar and corresponded to that observed in the urticaria-like symptoms of SLE patients. Thus, both in the background of urticaria-like skin symptoms of SLE patients and in control cases the histological characteristics of leukocytoclastic vasculitis located on the skin surface were to be seen.

Immunohistological study

The results obtained by direct and indirect immunofluorescence methods concerning both the SLE urticaria and the control group are summarized in Table II. Granular fluorescence consisting of immunoglobulins and complements of various types, located in the junctional zone, being characteristic of classic SLE, was observed in only one patient suffering from SLE. This is due to the fact that the other patients were treated with steroids. In investigating the immunocomplex (IC), special attention was paid, not to the junctional zones, but to the immunocomplexes appearing in the damaged vein walls and serving as the basis of the symptoms. IgE, the most frequent immunoglobulin, was found in immunocomplexes within the veins and vein walls. The presence of immunocomplexes causing venous damage in our control cases was confirmed by complement bond. Immunoglobulins could not have been revealed in veins. Intensive fluorescence of cells in the perivascular infiltrate (plasma cells) was observed

Table II. Direct and indirect immunofluorescence in urticaria-like lesions of patients with SLE and of control cases

Conjugates . . .	Direct						Indirect								
	Anti-IgG	Anti-IgA	Anti-IgM		Anti-IgE		Anti-C ₃	Anti-fibrinogen		Anti-IgG	Anti-C3				
Type of fluorescence . . .	a	a b	a	c b	a	c b	a	c b	c	b	b	d a	c	b d	
SLE															
1	-	-	-	-	-	+	+	-	-	+	-	-	+	-	+
2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-
4	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-
5	+	+	-	+	+	-	-	-	+	+	-	-	-	-	-
Control															
1	-	-	+	-	-	+	-	-	+	+	+	-	-	-	-
2	-	-	+	-	-	-	-	+	-	-	+	-	-	+	-
3	-	-	+	-	-	-	-	+	-	-	-	+	-	+	-

a = Granular fluorescence in the dermo-epidermal junction. b = Fluorescence in the plasma of cells of dermal infiltrate. c = Fluorescence of the walls of subepidermal capillaries and small vessels. d = Nuclear fluorescence in the epidermis.

in the direct immunofluorescence study, in some cases even in complement and fibrinogen in all our control cases.

DISCUSSION

The clinical parameters of our 10 urticaria patients showed SLE activity. Urticaria in SLE differs even clinically from the classic urtica, which suggests the presence of other agents beside histamine. This was proved by histological and immunohistological studies, where the fundamental change was seen in the form of leukocytoclastic vasculitis. Clinical and laboratory observations indicate definitely that leukocytoclastic vasculitis is induced by IC. This seems to confirm the existence of a syndrome described recently as urticaria accompanied by hypocomplementemia in the form of skin vasculitis and arthritis where IgG and C3 deposits were found in the dermo-epidermal zone (9). However, changes characteristic of SLE (LE cells, antinuclear factor) in these patients could not be detected. The immunocomplexes in the vein walls and capillaries were represented by IgE and C in most cases (cases 1, 4, 5) and were in one case also accompanied by IgM (case 5). As regards case 2, C fluorescence was found in the walls of subepidermal capillaries and small veins by the indirect method, thus indicating the presence of immunocomplexes capable of binding C.

The presence of IgE in connection with the skin symptoms of SLE patients is not surprising.

Granular fluorescence along the basal membrane, consisting of IgE was observed in 3 out of 25 SLE patients, was determined on the basis of skin biopsies by Provost & Thomasi (11). The role of immunoglobulins of IgE type in activating C should also be taken into consideration. Ishizaka et al. reported on the protein C binding capacity of aggregated IgE in case of myeloma (7). In our case 1, 4, 5, an IgE capable of binding C, as mentioned above, was found. Except for one case (No. 3) the complement in the walls of capillaries and small veins in the presence of SLE urticaria-like skin symptoms was detectable by both direct and indirect immunofluorescence techniques. There is an essential difference from the situation observed with SLE urticaria-like symptoms, i.e. immunocomplexes (in every case this means immunoglobulin complexes being able to bind direct or indirect complements) were found chiefly within the cells but in the cytoplasm in the control groups. The fluorescent cells on the field of infiltration—on the basis of histology—are most likely micro- or macrophages. This difference deserves special mention, as it indicates the normal function of phagocytes in control cases and the functional damage of phagocytes by SLE patients (6).

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Cutaneous Periarteritis nodosa Occurring during Pregnancy

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Abstract. In 9 reported cases of periarteritis nodosa accompanying pregnancy, 7 patients developed systemic periarteritis nodosa during pregnancy and died in post-

partum phase, but full-term infants survived. In 2 cases a cutaneous form of periarteritis nodosa was diagnosed 12 and 4 years before pregnancy and women survived.

We now report the first case of cutaneous periarteritis nodosa beginning during pregnancy. After a thorough 4-year follow-up and a review of the literature we suggest that the successful maternal outcomes may be related to the milder prognosis of cutaneous periarteritis nodosa compared with the systemic form, and that there is apparently no relation between the maternal and the infant involvement in periarteritis nodosa.

Key words: Periarteritis nodosa; Cutaneous form; Pregnancy; Survival

Eight cases of periarteritis nodosa (PAN) and pregnancy were reviewed in 1978 (1). In one of them, cutaneous PAN was diagnosed several years before pregnancy (4). Another similar case was described by Szinnyai (9). We report here the first case of cutaneous PAN occurring during pregnancy.

CASE REPORT

A 25-year-old primigravida developed during the sixth month of pregnancy a painful, violaceous livedo reticularis of both legs (Fig. 1) with myalgia. On admission a month later, the patient was pale, with severe asthenia, anorexia and weight loss. Temperature was 37.6°C, BP 120/70. Laboratory studies showed a Hgb of 10 mg, a WBC count of 7 800 and an ESR of 83 mm, total serum protein was 7.4 ml/100 ml with a rise in the alpha-2 fraction on electrophoresis. Coombs test and Hb electrophoresis gave normal results, as did the hepatitis-associated antigen test, the liver function, and the kidney function studies. Tests for cryoglobulinemia, MNI, rickettsia proved negative. EKG and chest X-ray were normal.

Biopsy of the skin lesions revealed necrotizing vasculitis of the arterioles (Fig. 2) with focal panniculitis in the hypodermis. Fibrinoid necrosis was found on the inner arteriolar wall, the media was thickened, the internal elastic lamina disrupted, fibroblasts and polymorphonuclear leukocytes were prominent.

Three weeks after admission fever (39°C) appeared, cutaneous lesions progressed to necrosis and ulceration, pain and myalgia increased and peripheral neuritis of the legs and feet occurred, causing unilateral foot drop. BP remained at 120/70, however. A cesarean section was performed in the 37th week of pregnancy, delivering a 3000 g healthy boy. Careful examination of the placenta did not reveal infarcts or necrotizing arteritis. Postoperatively the patient was given 120 mg Prednisolone daily.

Clinical improvement with normal temperature began only a month later and prednisone was then progressively decreased. After a 4-year follow-up, the boy shows no signs of vasculitis; the patient has deep atrophic scars on the legs and permanent foot drop.