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COAGULATION AND FIBRINOLYSIS IN CHRONIC PANNICULITIS[1]

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Abstract. Observations made in an investigation of coagulation and fibrinolysis in panniculitis appeared to warrant the following conclusions: 1) In chronic panniculitis of the limbs the fibrinolytic activity of the plasma and/or vessel walls is often decreased or absent. 2) Coagulation factors, inhibitors of fibrinolysis, and platelet adhesiveness are essentially normal. 3) Decreased fibrinolysis may be the metabolic deficiency responsible for vascular inflammation often found in this group of diseases.

Nodular inflammatory lesions of the lower limbs occur in a group of heterogenous diseases. Clinically, the inflammatory process may be acute and short, but it is often chronic with recurrent spells of painful and sometimes ulcerating nodules over years or even decades. Attempts have been made to classify these diseases on a clinical basis (3, 10, 12). The classification is founded on characteristic clinical features comprising such entities as erythema nodosum and vasculitis nodularis in the acute–subacute group, and erythema induratum and perniones in the chronic group. However, recent contributors (22, 25) oppose such subgrouping of nodular infiltrations and consider the varying clinical and histopathologic signs as different stages of development of the same fundamental disease.

Most pathologists agree that the nodular infiltrates have features in common permitting them to be classified together. First, an involvement of the panniculus adiposus of varying intensity and on varying level, which explains the frequent use of the term "panniculitis" for the entire group of diseases. Second, a mainly granulomatous type of inflammation, occasionally with areas of necrosis. Third, an inflammatory reaction, sometimes leading to obliteration, of cutaneous vessels of different types. This explains the frequent use of the term "nodular vasculitis".

The importance of vasculitis in the pathogenesis of the disease was stressed by Eberhartinger in his review (4) of erythema induratum. On the basis of a clinical and histologic study of 250 cases he concluded that the primary lesion is located in the vessel walls; with but slight modification this view has been endorsed by other investigators (6, 10, 12).

The present investigation was undertaken to demonstrate a biochemical deficiency, if any, of peripheral vessels in chronic panniculitis, mainly of the erythema induratum type. The investigation included a complete study of coagulation factors with special reference to the fibrinolytic activity of plasma and of the vessel walls, in the knowledge that the cutaneous veins, venules and capillaries normally have a high plasminogen activator content (7). Laboratory data were studied for any correlation with clinical and histopathologic findings.

MATERIAL AND METHODS

The material consisted of 11 patients, aged 38-78, with chronic nodular inflammatory lesions of the lower legs (Table I). There were 9 females and 2 males. They were distributed according to anamnestic data and clinical findings among three categories: *erythema induratum*, when painful ulcerating nodules, mainly on the calves, occurred over years; *vasculitis nodularis*, with inflammatory non-ulcerating infiltrates up to a few centimeters in diameter, and located on legs and arms; *panniculitis* for a more extensive and deep infiltration, non-ulcerating but usually more continuous than vasculitis and involving mainly the lower legs. The trunk was not affected in any of our patients, and none reported fever, malaise or other systemic symptoms except fatigue, when the disease was in an active phase.

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Table I. *Clinical and laboratory data of patients*

Patient no. ...	1	2	3	4	5	6	7	8	9	10	11
Sex	♀	♀	♀	♂	♀	♀	♀	♀	♀	♀	♂
Age	44	62	57	47	38	38	62	78	43	47	41
Regions (A = arms, L = legs)	L	L	L	A, L	L	L	A, L	L (left)	L	L	A, L
Aspect (M = medial, L = lateral, E = extensor, F = flexor)	F, M	E, F	All	E	All	E, F	E, F	M	E, F	F, M	All
Ulceration	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes
Total duration (years)	25	4	6	2	4	10	25	8	3	4	13
Bouts per year	½	C	½	3	C	C	1	1	2–3	2–3	C
Correlation to tuberculosis, other infection or disease	No	No	No	No	No	No	No	No	No	No	Tbc pulm. as child, retinitis
Drug intake	No	No	No	No	Anal-gesic?	No	Expect-orans?	No	No	No	No
Season, cold	Spring	No	No	Winter	Summer	No	No	No	No	No	Summer
Venous disease	Varic. veins	No	No	No	No	No	No	No	No	No	No
ESR > 20 mm/1 h	No	42	No	No	22	No	26	22	No	22	No
Tuberculin reaction pos. to conc. weaker than 1/1,000	Yes	No	No	No	No	No	Not exam.	Not exam.	No	No	No
Drug curing temporarily	CS	None	None	None	CS	None	TS	None	None	CS	CS
Clinical diagnosis	EI	EI	VN	VN	VN	EI	EI	UP	EI?	UP	EI?

C = continuous, CS = corticosteroids, TS = tuberculostatics, EI = erythema induratum, VN = vasculitis nodularis, UP = unspecific panniculitis.

Histopathology. Biopsy specimens of active lesions comprising epidermal, dermal and subcutaneous tissue were collected for light microscopy. They were stained with hematoxylin-eosin, elastin, periodic acid-Schiff and toluidine blue.

Coagulation studies. Blood samples were collected and treated in the way described previously (15, 21). The following determinations were made: platelet count, platelet adhesiveness (Hellem's method for whole blood), coagulation time, one-stage prothrombin time, prothrombin + factor VII + factor X (Owren's P & P test), factor V, AHF (f. VIII), fibrinogen, euglobulin clot lysis time, fibrinolytic activity of plasma and resuspended euglobulin precipitate on unheated bovine fibrin plates, thrombin time, fibrinolytic split products, plasminogen, inhibitors of plasminogen activation by urokinase, α_2-macroglobulin and antiplasmin. The methods used have been described earlier (1, 5, 13–18, 21). The plasminogen activator of the vessel walls was measured by a modified fibrinolysis autography technique in biopsy specimens of superficial arm veins (20). The vascular fibrinolytic potential of these patients was assayed by determining the fibrinolytic activity of blood samples obtained before application of a tourniquet round the arm or leg and again just before release of the tourniquet 20 min later (19).

RESULTS

Clinic. Data on the patients with chronic panniculitis are given in Table I. A typical patient was a middle-aged woman with a long history of recurrent ulcerating nodules on the lower legs.

The lesions did not appear to be related to tuberculosis or other systemic disease, to hypostasis, to any particular season, or to the use of drugs. The erythrocyte sedimentation rate and tuberculin reaction were usually normal. A favourable response to corticosteroids had been noted in several cases. The diagnoses were: erythema induratum in 6 cases, vasculitis nodularis in 3, and panniculitis in 2.

Histological examination. In most of the cases the findings were the same. Distribution of the cases among such diagnoses as erythema induratum, non-specific panniculitis and the like was not possible. The lesions were invariably confined to the subcutaneous fat. The corium sometimes contained non-specific perivascular round cell infiltrates. The subcutaneous changes varied somewhat in appearance, probably with the age and size of the lesions. In some cases there were advanced necrosis with eosinophil granular material, often containing nuclear fragments. The margins of these necrotic foci showed leukocytes and leukoclasia.

The necroses contained necrotic arteries, veins and capillaries. It could not be decided whether these vessels were in the foci. It is not certain whether the vascular changes were primary, because no such changes were seen outside the nec-

Table II. *The components of coagulation and fibrinolytic systems*

	Normal range	Patient no. 1	2	3	4	5	6	7	8	9	10	11
Coagulation time												
glass, min	8– 14	16	6	—	5	—	11	15	8	9	12	16
plastic, min	15– 25	31	11	—	11	—	24	28	24	27	25	28
One-stage prothrombin time, sec	15– 17	16	15	15	14	16	16	15	16	17	16	16
Prothrombin + f. VII + f. X (P & P), %	80–120	110	124	140	148	87	128	82	120	63	148	100
Factor V, %	80–120	100	103	105	80	104	100	135	130	60	103	110
Factor VIII, %	60–160	83	147	104	85	70	214	149	144	138	140	105
Platelets per $mm^3 \times$ 1,000	150–350	330	280	170	350	220	230	300	240	150	315	270
Platelet adhesiveness, %	22– 38	30	38	40	25	32	42	64	31	28	34	42
Fibrinogen, g/100 ml	0.26–0.38	0.40	0.45	0.49	0.36	0.29	0.38	0.59	0.39	0.31	0.46	0.39
Spontaneous fibrinolytic activity unheated fibrin plates, mm^2												
(*a*) plasma	0– 50	18	0	0	0	27	0	0	0	0	0	0
(*b*) resuspend. euglob. prec.	0– 70	29	17	12	32	52	19	0	0	0	0	25
Plasminogen, %	60–140	109	97	105	103	109	122	102	83	80	96	112
Inhibitors of plasminogen activation by urokinase, %	60–140	42	158	111	156	122	58	118	102	245	136	148
Antiplasmin, %	60–140	—	—	—	119	160	101	100	95	101	1	1
α_2-Macroglobulin, %	80–120	85	96	135	56	—	165	88	—	—	—	—
Fibrinolytic split products, mg%	0	0	0	0	0	0	0	0	0	0	0	0

roses. There were signs of extrafocal angiitis with round cells in the adventitia and occasionally also hyperplasia of the intima. These changes were situated around inflammatory cell infiltrates and need not have been primary. In 6 cases no vascular changes were seen with certainty.

There were often lipogranulomas and sometimes also epithelioid cells adjacent to the necroses. Giant cells, usually of foreign-body type, were demonstrated in most cases.

In 6 cases there was severe fibrosis with course septa surrounding the lipogranulomas, which often contained oil cysts. These findings were interpreted as inveterate changes with organization of necroses. The lesions were sometimes very vascularized, but could not be interpreted as angiitis.

Laboratory findings. The coagulation factors and inhibitors of fibrinolysis were essentially normal except in 3 patients (nos. 3, 4, 10) with increased P & P, 1 (no. 6) with increased AHF and 1 (no. 9) with increased urokinase inhibitors (Table II). A high level of fibrinogen was found in 5 (nos. 1, 2, 3, 7, 10). Platelet adhesiveness was increased in 4 patients (nos. 3, 6, 7, 11). In 4 (nos. 7, 8, 9, 10) of the patients no spontaneous fibrinolytic activity could be demonstrated in blood. Remarkably, venous stasis enhanced blood fibrinolysis only slightly in the arms of 5 of the patients (nos. 4, 8, 9, 10, 11), while in the remaining six the response was normal or possibly somewhat low. (Table III).. Three patients failed to develop any appreciable fibrinolytic activity after venous stasis of the legs (nos. 8, 9, 10). Histochemical estimation of the fibrinolytic activity of the venous walls revealed markedly low values for the arms of 6 patients (nos. 1, 3, 7, 8, 10, 11) but normal values for the remaining samples. In 3 patients (nos. 6, 10, 11) samples were obtained from superficial leg veins. The fibrinolytic activity was reduced in 2 of them (nos. 10, 11).

DISCUSSION

As in most cases of inflammatory conditions, in some patients the AHF, fibrinogen and platelet adhesiveness were increased. No coagulation ab-

Table III. *Fibrinolytic activity of the vessel walls*

	Fibrinolytic activity on unheated fibrin plates at the end of venous occlusion				Fibrinolytic activity of veins (arbitrary units)	
	Arm		Leg			
Patient no.	Plasma—mm²	Resusp. euglob. prec.—mm²	Plasma—mm²	Resusp. euglob. prec.—mm²	Arm	Leg
1	176	235	22	54	0	
2	190	293			7.5	
3	88	146	0	18	3.5	
4	51	107	0	25	8.5	
5	100	141	22	38	7	
6	135	218	20	37		4.5
7	96	244	0	81	3	
8	89	120	0	10	3	
9	23	95	0	10	6	
10	0	0	0	0	4	0
11	0	24			0	0.5
Normal range	100–600	160–750	0–150	20–200	7.7±1.8	4.7±2.1

normalities characteristic of chronic panniculitis were demonstrated in the patients. Also, the components of the fibrinolytic system in circulating blood were largely normal.

However, clearly abnormal values were obtained for the fibrinolytic activity of the venous walls. The panniculitis group as a whole had abnormally low spontaneous fibrinolytic activity. The vascular fibrinolytic potential of these patients assayed by venous stasis was low in 5 (about 40%) cases. It is known from an investigation of a large series of controls (24) that only 5% of normals develop low fibrinolysis on venous stasis of the arms. In six of the patients the content of plasminogen activator in the vessel walls, as assayed by a histochemical method, was decreased. Isacson & Nilsson (9) have shown a decreased fibrinolytic activity of the vessel walls in about 40% of patients with deep venous thrombosis and superficial thrombophlebitis and thereby demonstrated an association between a metabolic defect of the venous walls and a clinical manifestation. Our patients were not examined with phlebography. It is, however, known from clinical experience that panniculitis does not predispose to deep venous thrombosis or thrombophlebitis. In the present material there was no demonstrable tendency to thrombosis or to any hypostasis. Furthermore, preliminary results (8) obtained in patients with an acute panniculitis of the erythema nodosum type (with less marked involvement of vessel walls) indicate a normal fibrinolytic potential.

Most pathologists regard a degenerative and obliterative inflammation of vessel walls as an important part of the picture found in chronic panniculitis. Actually, many authors believe that the vascular change precedes necrosis of the adipose tissue, the degeneration of fat thus being secondary to a nutritional deficiency ("Wucher-atrophie"). It is possible however, that an initial inflammatory process of adipose tissue may later involve also the vessel walls, which might explain the absence of vasculitis in some of the present cases. More important for evaluating the intensity and area of inflammation is probably the age of the lesion from which biopsy specimens are obtained (4, 11, 12). The ages of the lesions varied widely in the present material, besides which a single biopsy can never reflect a complete picture of the complicated dynamics of inflammation.

When vasculitis is demonstrated in early infiltrates, it usually involves both arteries and veins (4, 12). According to some investigators, inflammation appears first in venous walls, later also in arteries (4, 6). The primary site of the inflammatory process within vessel walls seems to be the adventitia and media (4, 6) whence it spreads to, and obliterates, the intima. It is interesting to note that the plasminogen activator, found to be deficient in about 45% of our patients, is located in the adventitia of unaffected veins (20).

Recently, Cunliffe (2) found the spontaneous blood-fibrinolytic activity to be decreased in 3

patients with "cutaneous vasculitis". During treatment with phenoformin and ethyloestrenol the activity increased and the patients improved. It is possible that different clinical types of cutaneous vasculitis belong to the same group from an aetiologic and pathogenetic point of view, a possibility thoroughly discussed at the International Congress of Dermatology (23) in 1957. Such a group should include allergic vasculitis, nodular vasculitis, polyarteritis nodosa cutanea, subacute nodular migratory panniculitis, cold panniculitis, and erythema induratum. Differences in clinical appearance and course of diseases belonging to this group may be due to the type and site of vessels involved, as well as to the type and intensity of inflammation.

We found thus that in chronic panniculitis the content of plasminogen activator in the vessel wall is often small and/or the amount of plasminogen activator released from veins is often decreased. It would appear warranted to assume that this decreased fibrinolytic activity leading to vascular disease (or vice versa) may be an important feature of the pathogenetic background of chronic panniculitis.

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REFERENCES

1. Cronberg, S., Nilsson, I. M. & Silwer, J.: Studies on platelet adhesiveness in von Willebrand's disease. Acta Med Scand *180:* 43, 1966.
2. Cunliffe, W. J.: An association between vasculitis and decreased blood—fibrinolytic activity. Lancet *I:* 1226, 1968.
3. Duperrat, B. & Monfort, J.: Les allergides vasculaires hypodermiques. Proc 11th Intern Congr Dermat 1957, *II:* 182, 1959.
4. Eberhartinger, Chr.: Das Problem des Erythema induratum Bazin. Ein Beitrag zur Kenntnis der rezidivierenden subakuten nodösen Gefässprozesse am Unterschenkel, Arch Klin Exp Derm *217:* 196, 1963.
5. Ganrot, P. O.: Determination of α_2-macroglobulin as trypsin-protein esterase. Clin Chim Acta *14:* 493, 1966.
6. Gans, O. & Steigleder, G. K.: Histologie der Hautkrankheiten. Die Gewebsveränderungen in der kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs. Springer-Verlag, Berlin, Göttingen and Heidelberg, 1955, I: 505.
7. Haustein, U.-F.: Die Lokalisation der fibrinolytischen Aktivität in der Haut. Arch Klin Exp Derm *226:* 83, 1966.
8. Isacson, S. & Möller, H.: In preparation.
9. Isacson, S. & Nilsson, I. M.: In preparation.
10. Leczinsky, C.-G.: Nodular vasculitis, clinical and histological studies based on some 400 cases. Preliminary report. Proc 11th Intern Congr Dermat 1957, *II:* 185, 1959.
11. Lever, W. F.: Histopathology of the Skin, p. 243. Pitman Medical Publishing Co., Ltd., London, 1967.
12. Montgomery, H., O'Leary, P. A. & Barker, N. W.: Nodular vascular diseases of the legs. Erythema induratum and allied conditions. JAMA *128:* 335, 1945.
13. Niléhn, J. E.: Separation and estimation of "split products" of fibrinogen and fibrin in human serum. Thromb Diath Haemorrh *18:* 3, 1967.
14. Niléhn, J. E. & Nilsson, I. M.: Demonstration of fibrinolytic split products in human serum by an immunological method in spontaneous and induced fibrinolytic states. Scand J Haemat *1:* 313, 1964.
15. Nilsson, I. M., Blombäck, M. & Ramgren, O.: Coagulation studies in hemophilia. Acta Med Scand *170:* 665, 1961.
16. Nilsson, I. M., Krook, H., Sternby, N.-H., Söderberg, E. & Söderström, N.: Severe thrombotic disease in a young man with bone marrow and skeletal changes and with a high content of an inhibitor in the fibrinolytic system. Acta Med Scand *169:* 323, 1961.
17. Nilsson, I. M. & Olow, B.: Determination of fibrinogen and fibrinogenolytic activity. Thromb Diath Haemorrh *8:* 297, 1962.
18. — Fibrinolysis induced by streptokinase in man. Acta Chir Scand *123:* 247, 1962.
19. Nilsson, I. M. & Robertsson, B.: Effect of venous occlusion on coagulation and fibrinolytic components in normal subjects. Thromb Diath Haemorrh *20:* 397, 1968.
20. Pandolfi, M., Robertsson, B., Isacson, S. & Nilsson, I. M.: Fibrinolytic activity of human veins in arms and legs. Thromb Diath Haemorrh *20:* 247, 1968.
21. Paraskevas, M., Nilsson, I. M. & Martinsson, G.: A method for determining serum inhibitors of plasminogen activation. Scand J Clin Lab Invest *14:* 138, 1962.
22. Pierini, L. E., Abulafia, J. & Wainfeld, S.: Idiopathic lipogranulomatous hypodermitis. Arch Derm (Chicago) *98:* 290, 1968.
23. Proc 11th Intern Congr Dermat 1957, vol. *II:* 155–199, 1959.
24. Robertsson, B. & Nilsson, I. M.: Personal communication 1969.
25. Röckl, H.: Die Bedeutung der Histopathologie für die Diagnostik knotiger Unterschenkel-Dermatosen. Zugleich ein Beitrag zur Frage der Existenz des Erythema induratum Bazin. Hautarzt *19:* 540, 1968.

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