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Abnormal Fibrinolysis: The Cause of Lipodermatosclerosis or "Chronic Cellulitis" in Patients with Primary Lymphedema

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Abstract:

Blood fibrinolytic activity was measured in 20 patients with primary lymphedema, ten without and ten with skin changes usually attributed to "chronic cellulitis". The patients with abnormal skin showed reduced fibrinolytic activity, a finding previously described in patients with chronic venous disease and lipodermatosclerosis. It is postulated that changes of "chronic cellulitis" are identical to lipodermatosclerosis and are produced by a similar mechanism, namely reduced fibrinolysis.

The skin changes of thickening and hyperkeratosis which are often found in patients with long standing primary lymphedema have commonly been attributed to high protein concentration in the interstitial fluid (1,2). Some patients develop marked redness, induration and skin pigmentation of the extremity which is thought to result from immune deficiency and recurrent low grade secondary infection (2). This theory remains unproven, however, since microorganisms are seldom cultured from blood or skin during acute attacks (2).

The clinical appearance of these lymphedematous legs closely resembles lipodermatosclerosis of calf skin seen with severe venous disease (3). Marked impairment of both blood and tissue fibrinolysis are found in patients with venous lipodermatosclerosis (4) and this abnormality may be responsible for the development of similar skin changes with lymphedema. Accordingly, we investigated the fibrinolytic activity of blood in two groups of patients with proven primary lymphedema, one with and the other without, liposclerotic skin changes.

Clinical Material:

Twenty patients with primary lymphedema, ten with lipodermatosclerosis (Fig. 1) and ten with "normal" calf skin were selected from patients attending the outpatient department or admitted to the ward for other investigations. The diagnosis of lymphedema was confirmed by lymphography in all twenty patients (Table 1).

No patient had clinical evidence of varicose veins or venous disease. Three patients with lipodermatosclerosis had normal phlebograms while the limbs of the other seven patients were so edematous that phlebography proved technically unsuccessful. The presence or absence of lipodermatosclerosis was judged solely on clinical inspection. An excess of extravascular fibrin was not confirmed by skin biopsy (5).

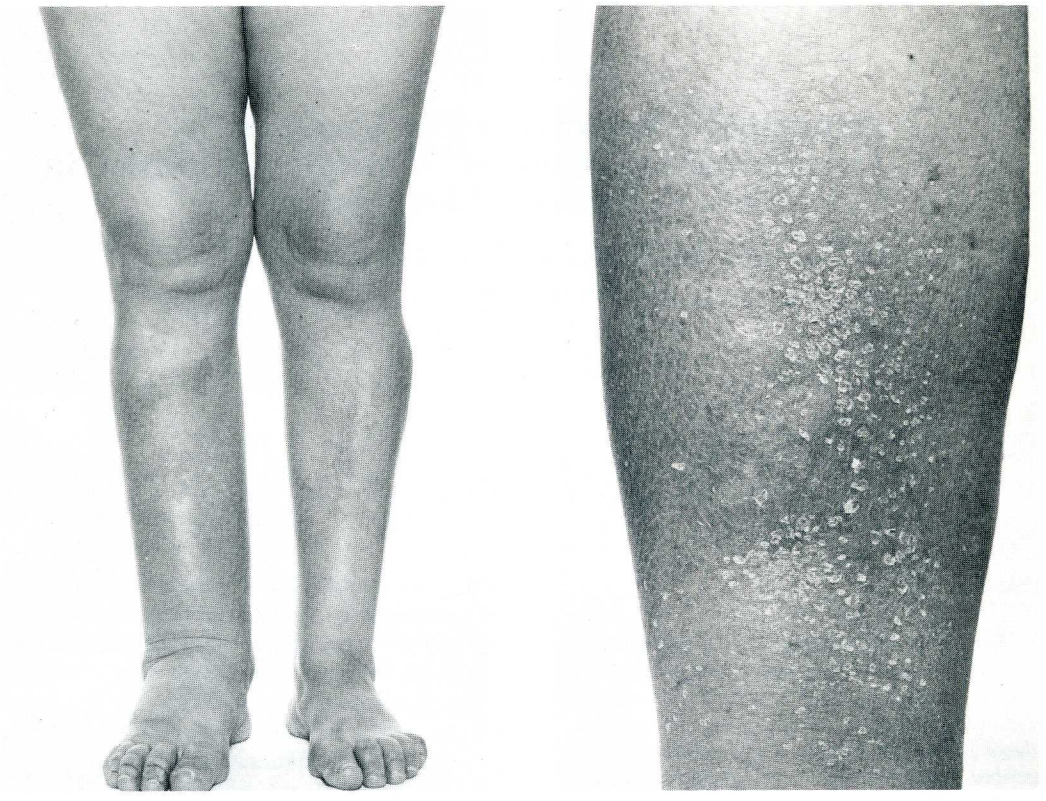

Fig. 1. Primary lymphedema and lipodermatosclerosis of the right leg (above) with close up view (upper right). Ulceration of the ankle with long-standing severe primary lymphedema (right).

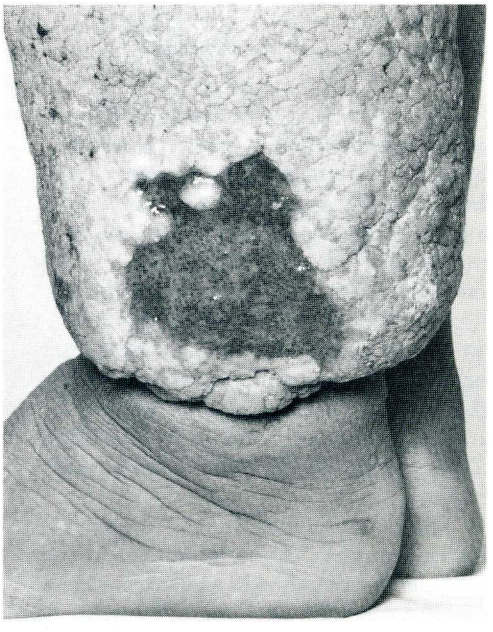

Table 1
Clinical and Lymphographic Findings

	Lymphedema without Skin Changes # Patients	Lymphedema and Liposclerosis # Patients
Swelling		
Unilateral	8	6
Bilateral	2	4
Degree of Swelling		
Marked	2	3
Moderate	6	7
Mild	2	0
Lymphography		
Distal hypoplasia	6	8
Proximal and Distal Hypoplasia	2	0
Proximal Obstruction and Distal Distension	2	2
Average Length of History	7.6 years	13.0 years

Methods:

A 5 ml blood sample was taken between 0930 and 1030 from an antecubital vein of fasted subjects without congesting the vein and three indices of fibrinolytic activity were tested — the dilute blood clot lysis time (DBCLT) using the technique of Fearnely et al (6), the euglobulin lysis time (ELT) by the technique of Nilsson and Olow (7), and the plasma fibrinogen (CWF) using the clot weight method of Ingram (8). Previous estimation of blood fibrinolytic activity in normal healthy ambulant subjects showed a range in our laboratory (dependent on age and sex) for DBCLT of 180-480 minutes, of ELT 60-80 minutes, and of plasma fibrinogen 300-400 mg/dl.

Results:

Blood fibrinolytic activity in both groups of patients are shown in Table 2. In patients without skin changes the levels fell within the expected range for age and sex. On the other hand, fibrinolytic activity of the ten patients with lipodermatosclerosis was depressed.

Because the ten patients with lipodermatosclerosis were significantly older than control subjects a depression of fibrinolytic activity by 5% (9) and a rise in plasma fibrinogen by 15% (10) were expected. Even if these age adjustments are made, however, the statistical significance of the results is unaltered.

Table 2
Blood Fibrinolytic Activity in Primary Lymphedema

Subjects (n)	M:F ratio	Age	DBCLT (min)	ELT (min)	CWF (mg/dl)
No skin changes (10)	1:9	39.0	372 ± 121‡	149 ± 60	354 ± 52
Liposclerosis (10)	0:10	57.6	927 ± 453*	233 ± 90**	583 ± 132***

‡$\bar{x}$ ± SD
DBCLT = Dilute blood clot lysis time; ELT = Euglobulin lysis time; CWF = plasma fibrinogen; M = Male; F = Female

*p = 0.0015; **p = 0.05; ***p = 0.000073

Discussion:

High pressure, generated within calf veins of postphlebitic legs during exercise, is transmitted via incompetent perforating veins to overlying venules and capillaries (11). As a result dermal capillaries distend and elongate while inter-endothelial pores widen (12) thereby allowing increased leakage of larger molecules into the pericapillary space (13). Patients with venous disease associated with redness, pigmentation and induration of calf skin (lipodermatosclerosis) uniformly show fibrin deposition around dermal capillaries of affected skin (5). This response may result from supersaturation of tissues with escaping fibrinogen and a consequent increase in polymerization of fibrinogen to fibrin (14). Patients with lipodermatosclerosis are known to have defective fibrinolysis (4) which hinders fibrin breakdown and favors fibrin deposition.

The macromolecular interstitial leak associated with venous disease does not occur with primary lymphedema because these patients have normal calf-muscle pump function. However, larger molecules that escape from plasma under physiological conditions are poorly cleared from the interstitial space as a result of obstructed or malfunctioning lymphatics. Over many years this dysfunction leads to accumulation of interstitial protein and subcutaneous fibrosis. Although nearly all plasma protein moieties in lymphedematous interstitial fluid have been verified, there is no selective increase of any one protein fraction (15).

Lipodermatosclerosis and subsequent necrosis and ulceration in venous disease are attributed to a selective overaccumulation of fibrin in interstitial tissues. Skin necrosis and ulceration in patients with primary lymphedema although less common does occur (Fig. 1). Presumably, excessive and selective fibrin accumulation is held in check by adequate fibrinolysis in the vast majority of patients with primary lymphedema. However, defective fibrinolysis may play a critical role in the small subgroup of patients with lymphedema and "lipodermatosclerosis" of calf skin.

From a large series of patients with primary lymphedema seen at St. Thomas Hospital (2) we have found this small cohort of ten patients with lipodermatosclerosis. This subgroup had more severe lymphedema for a longer period than the ten control patients and these factors may also be relevant to the development of cutaneous changes. Nonetheless, examination of the plasma fibrinogen level and blood fibrinolysis of these 10 patients shows significant impairment of systemic fibrinolytic activity similar to that described in patients with venous lipodermatosclerosis. These findings suggest that changes of "chronic cellulitis" found in patients with lymphedema occur in patients with defective or exhausted fibrinolytic activity and may, therefore, result from prolonged tissue fibrin accumulation rather than secondary bacterial infection.

Because fibrinolytic enhancement with anabolic steroids improves the quality of the skin of patients with venous lipodermatosclerosis (16) these agents may have a role in treatment of patients with lipodermatosclerosis associated with primary lymphedema.

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Waiting for Genius

Do not let us fall victims to the naive illusion that problems like cancer, mental illnesses, degeneration, or old age...can be solved by bulldozer organizational methods, such as we used in the Manhattan project. In the latter, we had the geniuses whose basic discoveries made its development possible — the Curies, Rutherfords, Einsteins, Niels Bohrs, and many others. In the biological field, ... these geniuses have not yet appeared, and we are still waiting for them. No mass attack will replace them, and it is they who will determine the rate of progress toward the solution of these problems. No one can tell in which section of the biological sciences they will appear — in all probability, in one of the least fashionable ones. But when they do appear, it is our job to recognize them and give them the opportunity to develop their talents. This is not an easy task, for they are bound to be lone wolves, awkward individualists, nonconformists, and they will not fit well into any established organization.

E.B. Chain: The Quest for New Biodynamic Substances, Perspect. Biol. Med. 10:208, 1976