

LICHEN MYXEDEMATOSUS WITH GENERALIZED NODULAR PANNICULITIS

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Abstract. A case of lichen myxedematosus of the discrete nodular type also exhibiting numerous, widespread panniculitic nodules is described. A broad-base elevation of the gamma globulins was found, but no isolated abnormal post-gamma proteins. Slight, but persistent signs of liver disease were noted as well as some signs of an auto-immune process.

The demonstration of mucinous material in lesions from patients with a number of clinically somewhat divergent diseases has made it possible to collect all these diseases into a well defined group, the mucinoses. In this group lichen myxedematosus (papular mucinosis) is a rare disease which has been described under different designations since the beginning of this century (for references see 4, 5, 18). Montgomery & Underwood (15) presented a classification of this rare disease into four different types: (1) generalized lichenoid papular eruption; (2) discrete papular forms; (3) localized to generalized lichenoid plaques; (4) urticarial plaques and nodular eruptions that end usually in the lichenoid form. Yet another type of palm-sized plaques was described by Perry et al. (19).

In the following, a case of lichen myxedematosus is described. It seems to be similar to type 2 mentioned above, i.e. with generalized, discrete papules and nodules. In addition, however, our patient has subcutaneous lesions showing a histological picture of nodular necrotizing panniculitis.

CASE REPORT

The patient is a woman, 65 years old. No allergic diseases, malignancies or diabetes are known among her

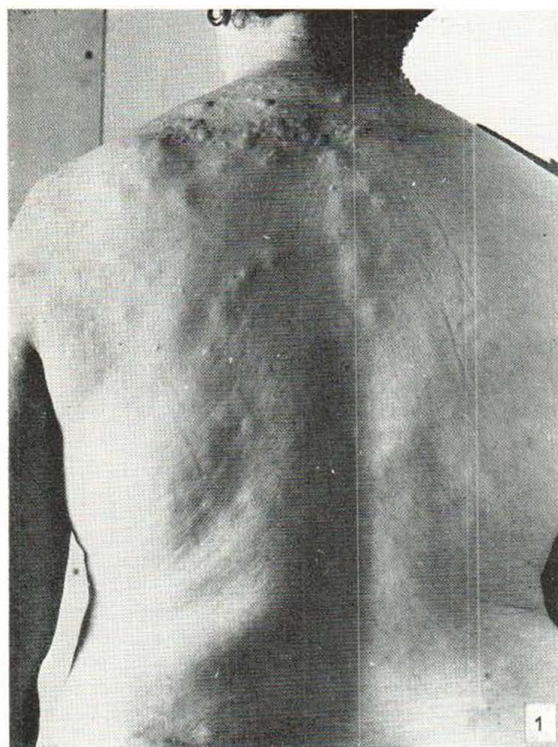
relatives. A son has suffered from tuberculosis, but her other three children are in good health.

During her first pregnancy, at the age of 21 years, she probably had a cystopyelitis (elevated temperature, backache). Since 1962 she has been under intermittent medical supervision because of epigastric pain responding temporarily to antacid drugs and mild sedation. X-rays of the stomach on several occasions were normal, as also were X-rays of the colon and kidneys on one occasion. Her blood pressure has been slightly elevated since 1962 (180/100 to 210/110 without treatment). ESR is often elevated, but with a tendency to vary within short periods of time. Since the end of 1969 she has had two episodes of backache with physical signs compatible with ischialgia. Spinal X-rays showed slight spondylosis.

The first signs of her skin disease were noted in the summer of 1968. At that time the patient noted asymptomatic papules over her shins. An increasing number of such papules and nodules appeared during the following year on the proximal parts of her arms and on her shoulders and back. On admission to the hospital in August, 1969, she displayed the following picture (Figs. 1 and 2). The skin over the ventral side of both lower legs showed discrete, skin-colored, firm, flat nodules, fairly well demarcated from the surrounding normal skin and with a diameter of about 15 mm at the most. Some of these lesions were grouped together. The larger of the nodules had a central, non-ulcerating depression and occasionally showed slight scaling at the periphery. The oldest lesions had a more orange hue than the others, which were skin-coloured with a whitish tinge. All of these lesions gave an impression of an intradermal localization. No atrophy or scarring was visible.

Lesions of the same kind were found also on other parts of her skin, mainly on the upper part of the back, but also on the sides of the neck, on the upper part of the breasts, on the shoulders and upper arms. Here no orange-colored nodules were seen. Some of the lesions on the upper part of the back were grouped together in a slightly curved band.

Apart from these intradermal lesions, the patient also had an abundance of up to plum-sized, deeply seated, probably subcutaneous, infiltrates. These were not very



Figs. 1-2. Dermal papules and nodules, especially abundant in a band-like region on the upper part of the back, and subcutaneous nodules clearly visible in tangential light. Lesions of these two types were roughly sym-

metrically distributed on the trunk and proximal parts of the extremities. On the distal parts of the extremities and the sides of the neck only dermal lesions were found. The face, hands and feet were free from lesions.

conspicuous at first glance, but many of them became clearly visible in tangential light. Most of these lesions, however, were only evident on palpation. The subcutaneous tissue on the back and in the gluteal region was literally studded with such infiltrates and they were also found on the proximal parts of the legs and arms and in the mammary region.

During the observation time of about 1 year, a moderate number of fresh lesions of both the superficial and deep types have appeared. On the arms, some of these lesions have presented as moderately erythematous and somewhat translucent nodules. It has not been possible to ascertain clinically whether both superficial and deep alterations are present in one and the same lesion.

Histopathology

Numerous punch biopsies were taken, as well as deep scalpel excisions. Two types of lesions were found histologically, corresponding to the clinical impression. The superficial nodules (Fig. 3) exhibited local oedema of the upper and middle corium with upward protrusion of the somewhat flattened and thin epidermis. The collagen bundles seemed to be fragmented and were stained pale blue with hematoxylin and eosin. In sections stained with alcian blue, an alcianophilic material was observed within

the oedema and this material was also slightly stainable with mucicarmine. When stained with toluidine blue solution a clear metachromasia appeared. The alcianophilic and metachromatic properties disappeared after digestion with testicular hyaluronidase. The material was moderately PAS-positive. Stainings for iron, fat and amyloid were negative. In the mucinous oedema there were scattered stellate fibroblast-like cells. Mast cells were present in normal numbers. No lipophages, epithelioid cells or giant cells were found. The reticulin fibres appeared unaltered, but the elastic fibres were slightly fragmented. In some of these superficial biopsies, some small blood vessels showed changes with proliferation of endothelial cells, swelling of the walls and perivascular infiltration especially by lymphocytes and plasma cells, but also some histiocytes. No thromboses were observed. Some sclerosis of the lower dermis often was seen.

The biopsies from the subcutaneous nodules (Figs. 4-5) revealed fat necroses with fibrosis and oedema in which a mucin-like substance with the same appearance and staining properties as in the dermis occurred. A sparse, diffuse, cellular infiltrate consisting largely of lymphocytes and plasma cells was present, but the inflammatory cells were concentrated around small and medium-sized blood vessels, predominantly arteries. These vessels exhibited oedema of their walls and endothelial cell proliferation



Fig. 3. Oedema of the corium with fragmented collagen bundles and scattered fibroblast-like cells. Alcian-blue-PAS, $\times 150$.

almost occluding the lumen in some parts. No thromboses or haemorrhages were seen.

In some of the biopsies the two types of changes were found together and the oedema of the corium continued into the subcutaneous changes.

Laboratory examinations

The initial haemoglobin values were 12.2 g%; there was a subsequent tendency to decreased values, the lowest value being 9.3 g%. MCH and MCV were at the upper normal limits, MCHC normal. WBC, differential counts and thrombocytes were within normal limits. Reticulocytes were slightly elevated on most occasions, with a maximal value of 3.8%. ESR 65–100 mm per hour; there was often diffuse demarcation between plasma and red blood cells. Bone marrow smears were only slightly abnormal with a non-specific reactive picture, on one occasion with a slight increase in number of plasma cells of normal appearance. Haptoglobin was normal on all three occasions tested (115–128 mg per 100 ml). Serum level of iron, triglycerides, total lipids, cholesterol, protein-bound iodine and serum electrolytes were all within normal limits, as also was the tri-iodo-thyronine uptake. The tests for liver function showed increased values on several occasions for thymol turbidity (7.0 units) and for glutamic-oxaloacetic-transaminase (SGOT) (50 units). Bilirubin, alkaline phosphatases, SGPT and SLDH were normal, as also was the galactose tolerance test. Liver biopsy showed a slight and non-specific fatty degeneration. Tests for blood coagulation gave normal results. In the urine both red and white blood cells were found in low to moderate numbers and on some occasions also sparse hyaline casts. These findings were reflected in the results of the quantitative sediment.

Protein electrophoresis on paper and agarose at pH 8.6 revealed a slight depression of the albumin values (3.2 g per 100 ml). Most conspicuous was a pronounced broad-base elevation of the gamma globulin fraction. No

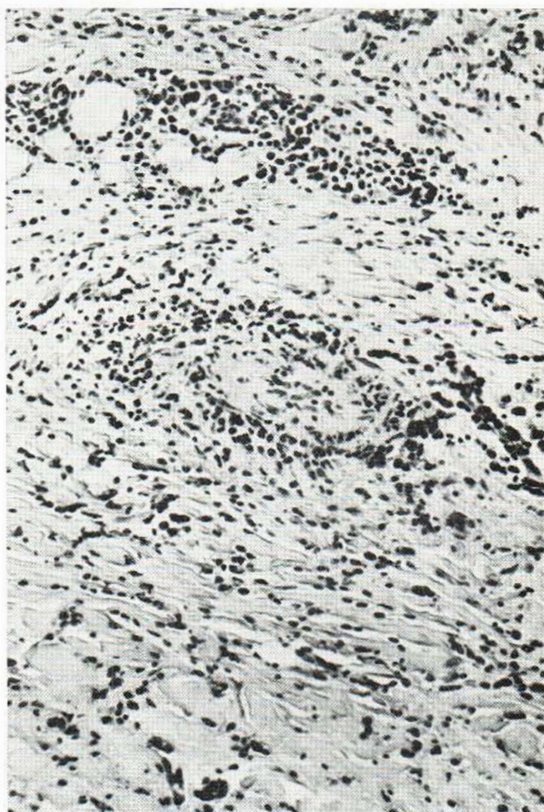


Fig. 4. Subcutaneous fibrosis with inflammatory infiltrates predominantly around the vessels. Hematoxylin and eosin, $\times 150$.

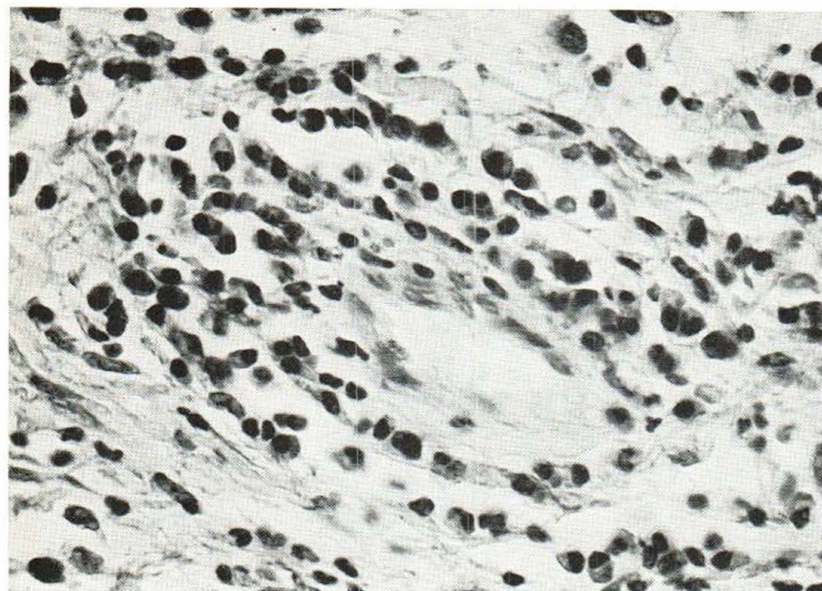


Fig. 5. A small subcutaneous blood vessel surrounded by lymphocytes and plasma cells. Inflammatory cells are also seen within the wall of the vessel, which exhibits some oedema. Hematoxylin and eosin, $\times 600$.

isolated post-gamma globulin fraction was detected either by these two electrophoretic methods or by starch gel electrophoresis. On immunoelectrophoresis IgG was markedly elevated to 3 550 mg per 100 ml (normal values 910–1 960) and IgA was slightly elevated to 240 mg per 100 ml (normal values 89–212). IgM and IgE were present in normal concentrations. In lipoprotein electrophoresis a broadened lipoprotein band was found in the region of the beta-globulins, corresponding to the prebeta- and beta-lipoproteins. No Bence-Jones protein was present in the urine, and protein electrophoresis of the concentrated urine also showed a normal picture.

The electrocardiogram was normal.

Tests for autoimmunity

Blood group serological tests revealed weak auto-antibodies of the type anti-I. Elution of antibodies from the patient's erythrocytes showed weak, incomplete, non-specific antibodies demonstrable by the indirect antiglobulin test, but not by the enzyme technique. The direct antiglobulin test was positive when a wide-spectrum antiglobulin serum and a specific anti-IgG-globulin serum were used, but negative with antiglobulin sera against the other immunoglobulin classes and with an anti-complement serum. These findings gave reason to suspect an acquired haemolytic anaemia, but the rate of red cell destruction was within normal limits with the methods used (radioactive di-isopropyl-fluoro-phosphate and osmotic fragility tests).

On two occasions antinuclear factors were demonstrated in the serum, diluted 1:10, by the fluorescent antibody technique.

The fluorescent antibody technique was also used in an investigation of a possible increase in the amount of immunoglobulins in punch biopsies from the skin lesions. Cryostat sections were incubated with specific rabbit anti-sera against IgG, IgA, IgM, IgD and IgE and then

incubated with an FITC-labelled anti-rabbit-globulin conjugate obtained by goat immunization. These tests revealed a slightly increased fluorescence with use of the anti-IgA- and anti-IgM-globulin sera in the subcutaneous tissue at the site of the necrotizing panniculitis. The fluorescence was so weak, however, that no firm conclusions could be drawn. With all the other anti-sera the results were negative.

Examinations with regard to possible internal malignancy

The following X-ray examinations were performed, all yielding normal results: lungs and heart; bones of the extremities, pelvis and skull; the entire digestive tract from oesophagus to colon; spleen; intravenous urography and selective renal angiography on both sides. Determinations of the amount of amylase in the urine and in the duodenal juice gave values within normal limits. Otolological, ophthalmological and gynaecological examinations revealed no noteworthy findings.

DISCUSSION

The clinical picture of the skin lesions in this patient appeared to point either to a metabolic or to a fibromatous disease process, when the superficial lesions alone were considered. The deep lesions, on the other hand, were indicative of a panniculitis devoid of symptoms. The histopathological examinations revealed a mucinous substance present in both types of lesions while all signs of lipoidal substances, amyloid and fibromatosis were absent.

Histopathologically, the dermal lesions are com-

patible with the diagnosis lichen myxedematosus (18). Slight endothelial thickening and slight paravascular cell infiltrates are encountered (10, 12), but the vasculitis is unusually pronounced in our case. On searching the literature we have found two descriptions of mucinoses with dermal changes probably of the same nature as in our case (1, 26). No subcutaneous nodules are mentioned, however, in either of these two patients and in one of them (26) some of the lesions showed dermal necrosis. In the paper of Montgomery & Underwood (15) reference is made to a case with lichen myxedematosus beginning as subcutaneous nodules and later developing into erythematous, indurated, umbilicated plaques. This case thus seems to be similar to our patient, with reservation for the lack of further details in their description.

Malignant atrophic papulosis (Degos' syndrome) also has a somewhat similar histological picture, but necrotic changes of the epidermis, as a consequence of changes in the endothelium of small arteries and subsequent thrombosis, seem to be characteristic of this disease (17). Nevus elasticus (24), fibromatosis lenticularis disseminata (2, 23) and pseudoxanthoma elasticum (9) can be ruled out on histological grounds.

The subcutaneous lesions do not resemble any of the types of generalized panniculitis known. Non-febrile cases of Weber-Christian's relapsing nodular non-suppurative panniculitis have been described (13), but the absence of epitheloid cells, foam cells and giant cells in the infiltrates of all biopsies, as well as the dermal changes, are inconsistent with this diagnosis, as well as with the subcutaneous lipogranulomatosis of Rothmann-Makai (22).

The presence of a continuous mucinous infiltrate from the dermis to the subcutaneous fat seems to tie the two types of lesions together, and to indicate that both are different reflections of the same disease process. It is also reasonable to assign the disease to the mucinoses, the most probable diagnosis being lichen myxedematosus of the discrete nodular form combined with subcutaneous necrotizing nodular panniculitis.

Two cases of lichen myxedematosus associated with signs of myelomatosis have been described (14, 18). An abnormal protein migrating in the post-gamma region has also been found in several cases (3, 6, 8, 11, 14, 20). Most of these cases,

however, have been of the Arndt-Gottron type of mucinosis (scleromyxedema) (10), i.e. the generalized lichenoid papular form, and not of the nodular type as in our patient. Apparently no such protein was found in the two cases of Rudner (21). In our case no definite signs of myelomatosis were present. The gamma globulins showed a marked broad-base elevation, but no post-gamma globulin was detected by any of the three electrophoretic methods used. Various internal malignancies can cause a diversity of cutaneous symptoms. Our examinations revealed nothing abnormal in this respect, however.

Certain immunological studies were performed also on some of the cases described previously. Thus, McCarthy et al. (14) found positive immune fluorescence for gamma₂-globulin in sections of skin from their patient. With the same technique Fowlkes et al. (8) found IgG and IgM, but not IgA, in the skin from their patient. In view of these findings, some importance might be attached to the weak fluorescence indicating the presence of IgA and IgM in the skin sections from our patient, as well as to the serologic signs of an autoimmune process which were found. The combination of two autoimmune diseases, Hashimoto's disease and dermatomyositis, with scleromyxedema in one and the same patient (16) is also very interesting in this context.

The slight abnormality in the liver function tests must be evaluated in relation to previous reports in which disturbed liver function is considered as a likely cause of lichen myxedematosus. Thus, both von Fischer (7) and Tappeiner (25) have proposed this mechanism, mainly on the basis of a pathological electrophoretic pattern and of pathological liver function tests (25).

It thus seems possible that lichen myxedematosus is a cutaneous pattern of reaction with different causes. It seems probable that myeloma or pre-myeloma can be one cause, and autoimmune mechanisms and liver disease other possibilities which deserve further investigation.

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Addendum. Since the preparation of the manuscript the clinical picture has changed considerably. During the summer of 1970, i.e. about two years after the start of the disease, the patient was treated with cyclophosphamide. Initially she was given 200 mg a day intravenously during 9 days. After an interval of one week the treatment was continued with 100 mg a day orally for a total of 2 weeks during the next 4 week period. The treatment was discontinued twice during this period due to a tendency to low WBC counts (2900). After that she received 50 mg a day for another week. She then complained of symptoms of mucosal irritation and so the drug was discontinued (after a total dose of 4250 mg during 6 weeks). One month and a half after cessation of treatment a certain improvement of the changes was noted. The improvement has continued ever since and at the last control (February 1971, about 2 $\frac{1}{2}$ years from the start) most of the subcutaneous nodules had disappeared and the dermal lesions had flattened, especially on the upper arms. Of course, it is not possible to ascribe with certainty this improvement to the cyclophosphamide treatment even if the relation in time between treatment and improvement is striking.