

Lipodermatosclerosis: Successful Treatment with Danazol

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Sir,

Lipodermatosclerosis (LDS), also reported as lipodermatolysis, hypodermatitis sclerodermaformis, sclerosing panniculitis, pseudoscleroderma, indurated cellulitis, stasis panniculitis and chronic cellulitis, is characterized by a scleroderma-like induration of the skin and a typical 'inverted champagne bottle' sign. Although considerable progress has been made in understanding the pathophysiology, no unifying therapeutic concept exists and the efficiency of the various treatment options has been reported very controversially. In the present case we describe successful treatment of LDS with the weak androgen danazol.

CASE REPORT

A 73-year-old man presented with a painful reddish-brown induration of the lateral and dorsal right lower leg of at least 4 years' duration (Fig. 1a). The patient's history also revealed a chronic failure of the right heart, coronary heart disease, diabetes mellitus and an arthrodesis of the right knee because of a war injury. His body mass index was 25. Physical examination confirmed a marked palpable induration of the hyperpigmented area on his right lower leg. In addition, signs of venous dilatation could be observed in the right popliteal fossa and at the right thigh. Phlebologic and phlebographic examination revealed venous insufficiency of the medial (11, 16, 21 cm) and lateral (15, 17, 25 cm) *Vv. perforantes*. However, after assessment in the department of vascular surgery, and due to the patient's refusal, surgical treatment was not performed. Nuclear magnetic resonance imaging consistently showed thickening of dermis in the distal right lower leg associated with a relative reduction of the subcutaneous fat tissue. Histopathology of a deep skin biopsy from the indurated area demonstrated a lobular panniculitis with septal and lobular fibrosis as well as pathognomonic oil cysts (Fig. 2). These lipomembranous cysts were associated with an infiltrate of predominantly CD68-positive macrophages.

Continuous administration of danazol 2×200 mg/day markedly improved the pain and led to a significant decrease of induration. As the patient developed hypercholesterolaemia after 7 months of treatment, the dose was reduced to 2×100 mg/day. After 30 months of danazol administration, the patient still revealed a clinical benefit (Fig. 1b). The induration, measured with a Rex Durometer (Buffalo Grove, USA),

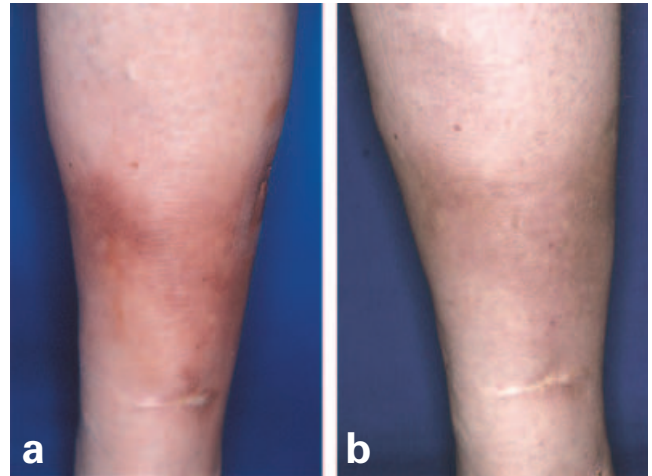


Fig. 1. (a) Lipodermatosclerosis initially presenting as a reddish-brown induration of the lateral and dorsal right lower leg. (b) The same lipodermatosclerotic plaque 30 months after continuous treatment with danazol.

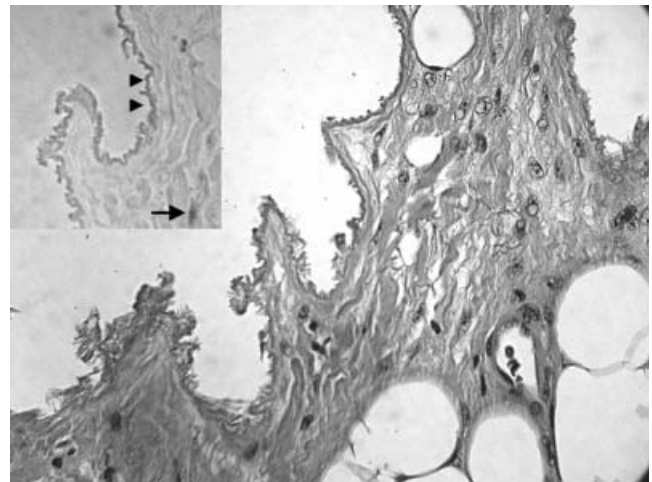


Fig. 2. Histopathology of lipodermatosclerotic tissue: fibrosis of the pannicular septa and cystic fat cell degeneration (H&E staining). Insert: Positive immunohistochemical staining for CD68 of the arabesque-like pseudomembranes (arrowhead) and single histiocytes (arrow).

had decreased from 41 to 28 durometer units and the patient's pain assessment (Visual Analogue Scale 0–10) had decreased from 7 to 3.

DISCUSSION

LDS is most common in middle-aged and elderly women. The most common clinical finding in LDS

is the scleroderma-like induration of the skin. This induration may comprise the whole circumference of the calf, leading to the typical 'inverted champagne bottle' sign. A more localized plaque variant has been reported as well. The degree of skin induration can be effectively measured by the use of a durometer (1). Other clinical findings of LDS are various degrees of erythema, hyperpigmentation, oedema and further accompanying signs of venous insufficiency. In some cases, ulceration of the lipodermatosclerotic skin can occur and LDS is significantly correlated with a delayed healing of these skin ulcers (2). The leading subjective symptom of chronic LDS is pain (3).

The pathophysiology of LDS has not been completely clarified yet, but several possible mechanisms have been proposed in recent years. Venous insufficiency is undeniably correlated with LDS (4, 5). However, a considerable subset of patients reveals no apparent venous abnormalities, suggesting pathophysiological mechanisms not simply related to stasis. These patients are often overweight or obese. Bruce et al. proposed that venous hypertension might be the linking pathogenic key factor for both groups of patients (3).

Various treatments including compression therapy, surgery of the chronic venous insufficiency, excision of the lipodermatosclerotic skin with subsequent split skin transplantation and vasodilative drugs have been suggested for LDS (6, 7).

The anabolic steroid stanozolol has been reported as an effective treatment for LDS (8). Stanozolol is a derivative of testosterone with an estimated anabolic/androgenic ratio of between 30:1 and 100:1. It has been hypothesized that the fibrinolytic activity of stanozolol is at least partly responsible for this effect.

To our knowledge, this is the first report on danazol for the treatment of LDS. Danazol is a weak androgen with associated anabolic properties. Notably, it inhibits the release of gonadotropin-releasing hormone and therefore the secretion of gonadotropins (9). According to these mechanisms, danazol is therapeutically established for the treatment of endometriosis, benign fibrotic breast disease, premenstrual syndrome and gynaecomastia. Furthermore, danazol increases the level of C₁ esterase inhibitor and is administered to patients suffering from hereditary or acquired angio-neurotic oedema (Quincke's disease). Similar to stanozolol, danazol has fibrinolytic properties. Danazol increases the levels of protein C, protein S, antithrombin III and plasminogen, whereas the levels of plasma fibrinogen, plasminogen activator inhibitor and the expression of CD62 (P-selectin) on platelets are decreased. This results in a decreased thrombogenesis

and enhanced fibrinolysis, which might partly explain the efficacy in LDS. However, possible side effects should be critically taken into account: danazol exhibits mild androgenic side effects such as virilization in females, acne, oily skin and weight gain. It is contraindicated during pregnancy or breast feeding. In men, prostatic disease should be excluded. Further possible adverse effects are mild elevation of liver transaminases and fluid retention. Therefore patients with serious cardiac, hepatic and renal dysfunction should be carefully monitored, as well as patients with diabetes mellitus. Like other anabolic drugs, danazol can increase the level of LDL (low density lipoprotein) cholesterol and decrease the level of HDL (high density lipoprotein) cholesterol. However, danazol remarkably reduces lipoprotein(a) in the serum, which reduces the risk for atherosclerosis (10). In our patient, a mild hypercholesterolaemia could be controlled by the reduction of the dose. Otherwise, no severe side effects were observed during 30 months of maintenance therapy.

REFERENCES

1. LeBlanc N, Falabella A, Murata H, Hasan A, Weiss E, Falanga V. Durometer measurements of skin induration in venous disease. *Dermatol Surg* 1997; 23: 285–287.
2. Nemeth AJ, Eaglstein WH, Falanga V. Clinical parameters and transcutaneous oxygen measurements for the prognosis of venous ulcers. *J Am Acad Dermatol* 1989; 20: 186–190.
3. Bruce AJ, Bennett DD, Lohse CM, Rooke TW, Davis MD. Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol* 2002; 46: 187–192.
4. Kirsner RS, Pardes JB, Eaglstein WH, Falanga V. The clinical spectrum of lipodermatosclerosis. *J Am Acad Dermatol* 1993; 28: 623–627.
5. Greenberg AS, Hasan A, Montalvo BM, Falabella A, Falanga V. Acute lipodermatosclerosis is associated with venous insufficiency. *J Am Acad Dermatol* 1996; 35: 566–568.
6. Ahnide I, Bjellerup M, Akesson H. Excision of lipodermatosclerotic tissue: an effective treatment for non-healing venous ulcers. *Acta Derm Venereol* 2000; 80: 28–30.
7. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; 30: 603–621.
8. Helfman T, Falanga V. Stanozolol as a novel therapeutic agent in dermatology. *J Am Acad Dermatol* 1995; 33: 254–258.
9. Jenkin G. Review: The mechanism of action of danazol, a novel steroid derivative. *Aust N Z J Obstet Gynaecol* 1980; 20: 113–118.
10. Crook D, Sidhu M, Seed M, O'Donnell M, Stevenson JC. Lipoprotein Lp(a) levels are reduced by danazol, an anabolic steroid. *Atherosclerosis* 1992; 92: 41–47.