Stasis Papillomatosis with Cardiac Complications and Vein Insufficiency

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ABSTRACT We report the case of a 73-year-old man with massive swelling of the lower extremities, with a chronic and rather uncommon form of stasis dermatitis – stasis papillomatosis. The patient was also diagnosed with severe heart failure, including dilated cardiomyopathy, hypothyroidism that required a substantial dose of exogenous tyrosine, microcytic and megaloblastic anemia, iron deficiency, and type 2 diabetes. The cause of stasis dermatitis lesions is not completely understood. It may be caused by the allergic reaction to some epidermal protein antigen formation or chronic damage to the dermal-epidermal barrier that makes the skin more sensitive to irritants or trauma. It has, however, been suggested that the term stasis dermatitis should be used to refer only to cases caused by chronic venous insufficiency, which belongs to a group of lifestyle diseases and affects both women and men more and more frequently.

KEY WORDS: stasis; vein insufficienty; edema; heart failure

INTRODUCTION

The problem of chronic venous insufficiency affects the vast majority of highly organized societies and belongs to the group of lifestyle diseases. Population-based studies have shown that this condition affects up to 50-60% of women and 10-55% of men (1). Venous stasis, which is the disorder of multifactorial etiopathogenesis, generates a series of tissue disturbances, resulting in chronic venous insufficiency. Stasis dermatitis is not only a manifestation of chronic venous insufficiency but also reflects the severity of the disease. The “leukocyte trap” theory is one of the many hypotheses explaining the pathology of chronic venous stasis (2). Trapped in microcirculation, leukocytes release a number of cytokines and proteolytic enzymes, leading to development of chronic inflammatory lesions of perivascular tissue (2). This inflammatory process is also accompanied by a disturbance in venous wall architecture. Despite many...
explanations, the question of why the permanent venous hypertension causes specific changes in some patients, but not in others, still remains unanswered.

**CASE REPORT**

The patient, a 73-year-old farmer, was admitted to the Department of Vascular Surgery in March 2011 because of persistent, refractory edema of the lower limbs. Upon admission the patient presented with edema of the lower limbs, with brownish hiperpigmentation and numerous flat-topped, brownish, and violaceous papules resulting in a cobblestone appearance. The aforementioned lesions were accompanied by areas of erythema and crusting. The epidermis was rather thin, albeit papillomatous. Ultrasonography of the lesional skin revealed rather thin albeit papillomatous epidermis. The upper dermis was loose, with a finely fibrillar appearance (Figure 1). Orcein staining showed disappearance of elastic fibres in the upper dermis. The dermis contained several blood capillaries with thick walls, occasionally surrounded by a loose lymphocytic infiltrate, and some dilated lymphatic capillaries. It also contained some cells with a brown pigment, most likely hemosiderin. Alcian blue staining showed moderate amounts of mucin in the upper and mid dermis. Toluidin blue stain showed numerous mast cells in the dermis. Periodic acid-Schiff-diaestase (PAS) and amyloid stains were unremarkable (Figure 2).

The patient was diagnosed with chronic venous insufficiency, which is an indication for compression treatment. However, the diagnosis of heart failure limited the use of standard/classic compression methods in that patient. This limitation was due to high risk of excessive pressure and volume overload of the heart ventricles that could consequently result in heart failure exacerbation. Furthermore, Doppler ultrasound suggested the possibility for alternative compression treatment. The ankle-brachial index was 0.8, and it was decided that "short stretch" compression, a multi-layer compression system, would be appropriate. Additionally, the "short stretch" compression treatment was preceded by two weeks of lymphatic manual massage of the main nodal points (popliteal and inguinal areas). The massage technique allows improved lymphatic drainage of the affected area of the lower extremities. Continued treatment resulted in a reduced calf circumference by 2 cm. At the same time, the patient was under constant cardiology observation. The next step in the treatment plan was to utilize the aforementioned multi-layered compression system (based on a "short stretch" bandage; stretch range 40%). The interface pressure was established at 10-15 mm/Hg and adjusted with a Kikgel device. Consequent four weeks of compression therapy resulted in further reduction of edema in the posterior calf/lower extremity due to restoration of normal/regular redistribution of lymphatic drainage to capillaries. Additionally, after six weeks compression stockings (2nd degree compression) were intro-
It should be noted that this patient had a long history of hypertension, gout, and paroxysmal atrial fibrillation that was treated with electrical cardioversion procedures and amiodarone. During the hospitalization period, the patient was diagnosed with venous thrombosis of the lower limbs (Figure 3). Standard therapy with the use of low molecular weight heparins (enoxaparinum) was conducted. Because of the skin lesions, a specimen was collected for histopathological diagnosis. The patient was also diagnosed with hypothyroidism, heart failure, and type 2 diabetes. The diagnosis of hypothyroidism was then confirmed by the hormonal tests: TSH 24 – normal values 0.25-4.00 mIU/L, FT4 6.5 (ref 9-20). Ultrasonography (USG) showed that the thyroid gland was the regular size, but with slightly heterogeneous echogenicity of thyroid tissue. A gradually leveling dose of thyroxin was administered, and the euthyrosis was achieved at the dose of 137.5 mg/day. The echocardiographic examination revealed a significant heart enlargement (RVDD-3: 4 cm; LVIDD-6: 4 cm; LA-5: 7 cm), a generalized disorder of left ventricular contractility (EF: 44%), and a significant tricuspid regurgitation III/IV which helped to confirm heart failure and lead to a preliminary diagnosis of dilated cardiomyopathy of New York Heart Association (NYHA) class III. The deterioration of cardiac systolic function was also confirmed by the elevated levels of B-type natriuretic peptide-648.7 pg/mL (ref 0-100). Electrocardiogram (ECG) examination showed the presence of the atrial fibrillation, with an average ventricular rhythm of 75/min, and a segment of the left branch of the bundle of His.

Additionally, laboratory data on blood morphology revealed severe anemia with HGB 9 g/dL (N: 12.0-16.0 g/dL), that could have been one of the reasons for fatigue and intolerance for exertion, which the patient had complained about. The anemia was microcytic (MCV 75.3 fL, N: 80.0-94.0 fL) and hypochromatic (MCH 22.4 pg, N: 27.0-32.0 pg), other parameters of blood analysis (leukocytes and thrombocytes) were within normal ranges. Based on the above mentioned observations oral iron supplementation was started. Within the three next weeks, the increase of HGB level up to 10.6 (MCV=78.4 fL and MCH=24.1 pg) was noted. The patient felt better than before the period of iron supplementation. Thus the oral iron supplementation was continued. The level of C-reactive protein (CRP) remained at a slightly elevated level (8.255 mg/L, ref 0-5).

In May 2011, the patient was admitted to the Cardiology Clinic for a treatment of the advanced heart failure and implantation of the stimulating and re-synchronizing systems. Immediately after the patient’s admission, echocardiography (including transesophageal examination) was performed. Apart from the previously diagnosed problems the examination showed the thickened wall pericardium, and also the thrombosed inferior vena cava and almost entirely thrombosed left atrial appendage. A few hours after the patient’s examination, cardiac arrest occurred due to the mechanisms of ventricular fibrillation. The patient was successfully resuscitated but required mechanical ventilation for a short period of time afterwards. The patient also underwent thoracic tomography (64-row CT angiography), which showed significant, generalized impairment of contractile function (EF 31%), with the concomitant contraction asynchronism. In addition, the examination showed the symptom of the reflux of contrast from the right atrium to the enlarged inferior vena cava and hepatic veins, pulmonary artery enlargement (44 mm), and the enlargement of mediastinum lymph nodes and soft tissue swelling. Due to the large amount of contrast used in the procedure no examination towards the diagnosis of pulmonary embolism was performed (D-dimer-3041.4 mg/L/FEU, cut-off threshold of 500 mg/L/FEU). The treatment with low molecular weight heparin (enoxaparinum) was conducted. The implantation of the cardioverter-defibrillator (CRT-D) (ICD) was partially successful. The reason for this procedure not being completely successful was the lack of the proper coronary sinus that disabled the implantation of the left-ventricular lead/electrode. However, it was decided to implement this electrode epicardially and with the use of cardiac surgery methods.

Less than a month later the patient was admitted to the Cardiology Clinic once again. Cardiac catheterization and coronarography ruled out the possibility of constrictive pericarditis and the presence of sig-
significant changes in the epicardial vessels of the heart. The patient qualified for the further pharmacological treatment and ICD.

DISCUSSION

In our case report, a man was diagnosed with severe heart failure, including dilated cardiomyopathy (DCM), hypothyroidism (that required a substantial dose of exogenous tyrosine), microcytic and megaloblastic anemia and iron deficiency, and a recently diagnosed type 2 diabetes.

The clinical assessment revealed that one of the predominant symptoms was the massive swelling of the lower extremities with a chronic and rather uncommon form of stasis dermatitis, namely stasis papillomatosis. The patient's hypothyroidism was most likely the result of taking amiodarone for a period of several months in the initial treatment for paroxysmal atrial fibrillation. Since then, the general symptoms of gradually accumulated thyroxine deficiency had been increasing. Those symptoms were not recognized previously.

Edema of the lower limbs of varying degrees are a part of many disease entities, having both endocrine and, even more likely, cardiovascular grounds (3-5). Notable causes also include kidney failure, cirrhosis, pulmonary hypertension, and the negative impact of several drugs, including the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and calcium channel blockers.

Taking into consideration the substantial incidence of heart failure, clinical assessment, and the echocardiographic parameters of our patient, the origin of edema could be put down to advanced heart failure (6). Blankfield et al. concluded that 33% of patients had edema due to heart damage, and 42% of patients with edema were later diagnosed with pulmonary hypertension (3).

Simple hemodynamic parameters are not sufficient for the justification of a significant exacerbation of symptoms. It is advised to assume that there is a difficulty with the outflow through the inflamed lymph. Rheologically inefficient mediastinal lymph nodes and pelvis may also be the cause.

Mediastinal adenopathy in patients with severe heart failure and the consequent edema was analyzed by Erly et al. (7). It affected close to 81% of the patients with the ejection fraction below 35%. Enlarged lymph nodes in the pelvis and the simultaneous increase of the lymph drainage disorders can lead to significant chronic inflammation, fibrosis, secondary swelling of the lower limbs, and disorders in the proper functioning of organs the in lower pelvis. These may include the malfunction of the bladder as well as the distal segment of the gastrointestinal tract (8). Very prolonged sedentary position, which is usually observed in the case of ortopnoe dyspnea in patients with heart failure, favors the stagnation of fluids in the lower limbs, already occurring during the first 4 hours of taking a sedentary position (9). Critically increased body weight may also have great importance in the formation and persistence of edema of the lower limbs (10-12). In our the body mass values were increased and the BMI was 27.

The very obvious cause leading to venous insufficiency of lower limbs, massive edema formation, and subsequent complications was deep vein thrombosis. Ultrasound of the lower limbs confirmed thrombosis, damage of valves, and progressing post-thrombotic syndrome. In the period of active lesions, ultrasound examinations were significantly impeded by the skin oedema and induration. Chronic venous insufficiency is currently regarded as one of the most common causes of lower limb edema (13-16). Simple theories explaining the malfunctioning of veins, perforators, and valves as the result of pressure changes and simple thrombosis observed in the patient are of relatively little importance. The cause of this malfunction should rather be investigated in terms of the chronic activation of leukocytes which seem to be constrained and trapped by inefficient microcirculation, leading to the release of large amounts of cytotoxic.

The underlying reason of stasis dermatitis lesions is not completely understood. One of the hypotheses claims that this type of eczema is caused by an allergic reaction to some epidermal protein antigen formation which in turn results from the increased hydrostatic pressure. Another hypothesis suggests that chronic damage to the dermal-epidermal barrier makes the skin more sensitive to irritants or trauma (17).

It has, however, been suggested that the term stasis dermaliths should be used to refer only to cases caused by chronic venous insufficiency, which has been supported by the observation that classical flush ligation and saphenectomy done on the patients suffering from saphenous vein insufficiency and stasis dermatitis lead to complete remission of skin lesions at 8-12 weeks after the surgery with the absence of any recurrence (18).

Some studies have shown that on the cellular level the formation of stasis dermatitis may be preceded by the influx of the monocytes and macrophages, gathering around the small vessels of skin (19). The histopathological picture of the lesional skin biopsy
in our patient seems to support this hypothesis. The formation of perivascular infiltrates is accompanied by a proliferation of blood vessels in the papillary layer of the skin which seems to be the result of metalloproteinases involvement (20). The brown color of the lesions is usually associated with the deposition of hemosiderin which is the result of the breakdown of red blood cells that leak out of vessels due to increased hydrostatic pressure.

Massive overgrowth of tissue is then equivalent to the amount of collagen re-growth that responds to fibrinogen extravasation and simultaneously operating hydrostatic pressure, which is elevated in venous and lymphatic vessels. Abnormal amounts of extracellular matrix are also a barrier to oxygen and nutrients, leading to ulceration and tissue necrosis (14). An important factor in regulating fibrotic processes in such situations is transforming growth factor, beta 1 (TGF-B1).

Lower limb venous insufficiency usually coexists with the primary or secondary insufficiency of venous and lymphatic vessels (21-23). Additionally, the increased number of fibroblasts, adipocytes, keratinocytes, and massive protein-rich exudations (that favor a bacterial growth) may result from a long-term advanced lymphedema (21).

An important disease entity that should be considered in the differential diagnosis and the diagnosis of the causes of such severe swelling occurrences as in our patient are unusual forms of constrictive pericarditis. Recently, the focus has shifted to the variability of the disease progress, the limited penetration of a wide variety of symptoms, and clinical assessment of this intriguing disease (24-26). On the basis of the echocardiographic examination there was a suspicion of constrictive pericarditis. However, the cardiac catherization procedure did not confirm the presence of the actual disease. This lack of clear confirmation of the disease might have been the result of atrial fibrillation (with a rapid periodic ventricular rhythm), and the observed instability of the sternum that remained after the resuscitation of the patient.

After treatment with thyroxine, employment of iron supplementation (which leads to the improvement of blood cell count parameters), and also implementation of the latest methods for the treatment of heart failure (angiotensin-converting-enzyme (ACE) inhibitors, diuretics, a cardioverter-defibrillator with the resynchronizing function) the patient’s general condition was significantly improved. Furthermore, substantial reduction of edema in the shin area and the improvement of the skin were observed (this included the disappearance of severe inflammation, filtration, and the epithelialization of erosions). This case of unusual and extensive skin lesions in the shin area of the leg constitutes a valuable observation in cases of massive lesions, since the circumstances included the simultaneous presence of severe heart failure, hypothyroidism, and anemia.

The differential diagnosis in case should also consider other unusual skin manifestations that may be accompanied by the abnormalities in hematopoetic cells. One of them may be pachydermatous eosinophilic dermatitis connected to chronic peripheral blood eosinophilia, described recently by Salomon et al. (27). In such a condition, the lesions are particularly extensive on the extremities and in the genital region. The hands and fingers are stubby and stiff. However, all patients showed persistent peripheral eosinophilia, leukocytosis, and elevated serum IgE level. Those were, however, not observed in our patient.

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