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Vascular and nerve lesions of the diabetic foot – a morphological study

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Abstract

The microcirculation in neuropathic diabetic feet is the subject of the same changes found in other end organs of the diabetic patients. In diabetic neuropathy, abnormal neurogenic regulation of the hemodynamics in the small vessels may contribute to the development of microangiopathy, which is manifested as increased basement thickening. *Material and Methods*: The study has been made on a group of 25 patients: nine with diabetes mellitus type 1 and 16 patients with diabetes mellitus type 2. All patients were affected by peripheral diabetic neuropathy and showed various degrees of lesions on the foot level. All cases required amputations done at the lower extremity of the limbs. Tissue fragments were processed for the standard histopathological exam, using Hemalaun–Eosin, trichromic Szekely and van Gieson staining. *Results*: The histopathological examination revealed on the skin level – ulcerations covering large areas, while entire sections showed hyperacanthosis. At the dermis level, the microscopic panel was dominated by the presence of the inflammatory infiltrate. The absence or the degeneration of the sweat glands, the presence of venous stasis and perivascular bleedings completed the morphological panel of the dermis. On the microcirculation level, the endothelial cells have a flat smooth inflated aspect. In the case of the large arterioles and arteries of muscular type, we observed the presence of the fibrous tissue on the level of media, calcium deposits on intima, mediocalcinosis. *Conclusions*: The identification of vascular and nervous morphological structures in the complicated diabetic foot allows the extension of the knowledge related to the pathological background of this condition. The vascular lesions, which appeared on the microcirculation level, are consequently involving arterioles and arteries of muscular type and are being accompanied by nervous lesions shown through morphological changes of the peripheral nerves. The overall morphological contest of the complicated diabetic foot involves lesions of the epidermis, dermis, and muscles.

***Keywords*:** diabetic foot, microangiopathy, neuropathy.

Introduction

The diabetic foot comprises a heterogeneous group of lesions such as autonomous neuropathy, sensitive-motor neuropathy, diabetic macroangiopathy and micro-angiopathy, joint and bone structural changes, lesions of the sole, skin and nail lesions and also the infection [1, 2]. The management of the foot ulcerations is a multidisciplinary one that reaches out educational, surgical, mechanical, vascular, and microbiological aspects [3, 4]. Nearly all the distal extremity components of the pelvic member are being involved such as tegument, subcutaneous cellular tissue, muscles, bones, articulations, vessels, and nerves [5]. The accurate understanding of these processes is absolutely necessary in order to develop a prevention management and plenty of studies in the field have been undertaken in the last decades [6]. Therefore, due to the dynamics of the impressive epidemiology of the ulcerations and amputations registered in the case of the diabetic patients, there has been made great progress in respect of the diabetic foot pathogenesis and management. These past few decades have been changed by the increasing range of the anti-biotherapy, by perfecting of the exploring invasive and non-invasive angiographic techniques (including the microcirculation), and also by perfecting the exploring techniques of the foot biomechanics [7], which laid the foundation of a primary prevention. The term of "diabetic foot" can associate in different degrees the whole range of the pathogenic changes which are determined by the diabetes mellitus on the level of vessels (both small and large) and nerves, bone skeleton and soft tissues [8], leading to changes in the foot biomechanics, triggering severe infections and tissue destructions, and sometimes, resulting in amputations. Besides the above-mentioned factors, there are also abnormalities of the microcirculation, which can result in the insufficiency of the capillaries incapable of providing the nutrients on the tegument, level [9]. The microangiopathy, commonly met in the condition of the diabetes mellitus, can have a general character [10], and each organ can be affected to a different degree; the clinical aspect is reached when the lesion extends to the point where the function can no longer be regained (the diabetic nephropathy, the diabetic retinopathy).

At present it is generally admitted that there is a close connection between the abnormalities of the microcirculation and the diabetic neuropathy [11–13] proving the fact that microvascular changes are closely linked to the speed decrease in the nervous conduction and vibratory sensitivity, the alteration of the sudomotor function or the decrease in the potential of muscular action [14]. In the case of the diabetic neuropathy, we are dealing with a profound hemodynamics change [12, 15], which opens the arterio-venous shunts, an abnormal

adjustment of the blood flow and, also, an abnormal inflammatory response to the injury. The abnormal neurogenic adjustment of the microvascular hemodynamics can contribute to the development of the microangiopathy manifested through the thickening of the basal membrane of the capillaries and proliferating lesions reported within the artery and arteriole lumen. Today it is generally admitted that the microvascular abnormalities can bring their contribution to the ischemic etiology of the diabetic neuropathy [12].

Due to the scarcity of descriptive information on the morphological changes accompanying the diabetic foot, our present study aims to identify the vascular and nervous lesions common to this pathology and tries to establish a pattern of the evolution closely linked to the gravity of the illness.

Material and Methods

The study has been made on a group of diabetic patients affected by peripheral diabetic neuropathy clinically (by testing sensitivity, bilateral loss of the Achilles and patellar reflexes) and, also, nervous conduction velocity proven. The diabetic patients showed various degrees of lesions on the foot level (ulcerations, gangrenes). All patients have been tested through common biochemical procedures. The total number of the patients was 25: nine patients suffering from diabetes mellitus type 1 (five men and four women) and 16 patients suffering from diabetes mellitus type 2 (10 men and six women). The lifetime of the illness ranged from 10 to 30 years (the medium was of 20 years). All cases required surgical intervention, which consisted of amputations done at the lower extremity of the limbs. Tissue fragments were processed for the standard histopathological exam, using Hemalaun–Eosin (HE), trichromic Szekely and van Gieson staining.

Results

The histopathological examination revealed specific microscopic changes which fundament the pathogenic background of the particular lesions of the diabetic foot. On the skin level, all the cases presented ulcerations covering large areas, while entire sections showed hyperacanthosis (Figure 1). At the dermis level, the microscopic panel was dominated by the presence of the inflammatory infiltrate, mainly formed of the mononucleate cells but associating, at times, polymorphonuclear neutrophils (Figure 2). The absence or the degeneration of the sweat glands (Figure 3) completed the morphological panel of the skin in the area under investigation. Other revealing aspects on the dermis were sustained by (i) the presence of venous stasis and by the perivascular bleedings which supported the pathological context of the hemodynamical disorders (Figure 4) and (ii) the existence of some areas bordered by necrosis, the disorganization of the histoarchitecture in those areas, resulting in the destruction of the vascular structures as well (Figure 5).

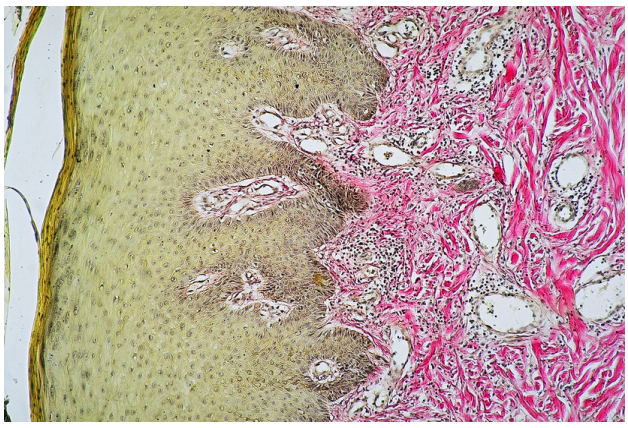

Figure 1 – ***Epidermis showing hyperacanthosis (van Gieson stain, ob. 10×).***

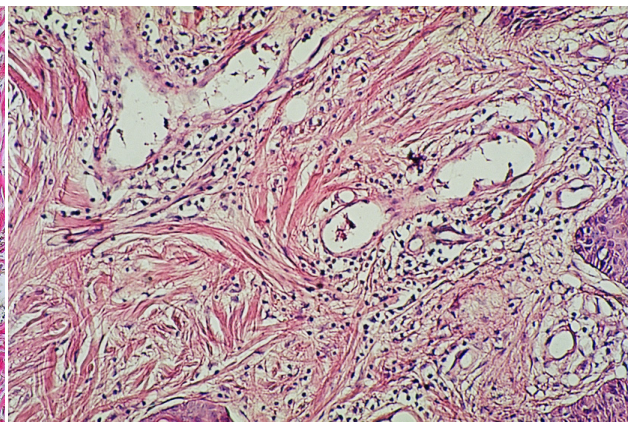

Figure 2 – ***Chronic inflammatory infiltrate in the profound dermis (HE stain, ob. 10×).***

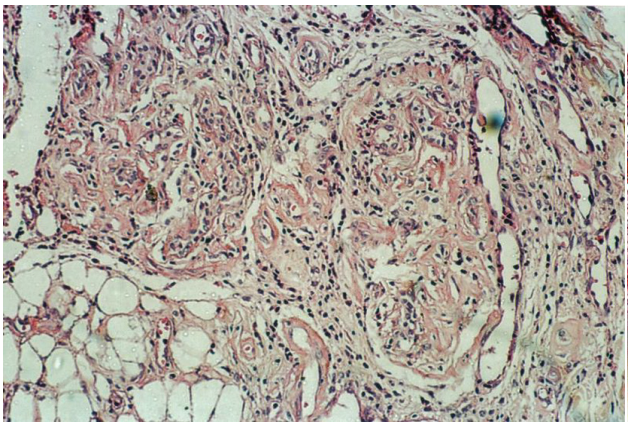

Figure 3 – ***Disorganization and degenerative lesions of the sweat glands (HE stain, ob. 20×).***

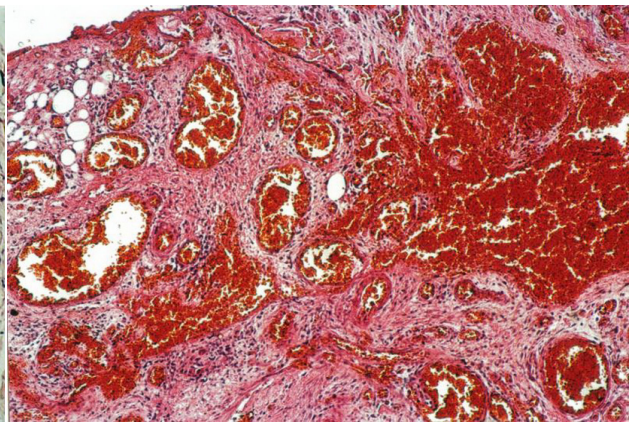

Figure 4 – ***Inflammatory infiltrate in the connective tissue; venous stasis (hemodynamics disturbances) (HE stain, ob. 20×).***

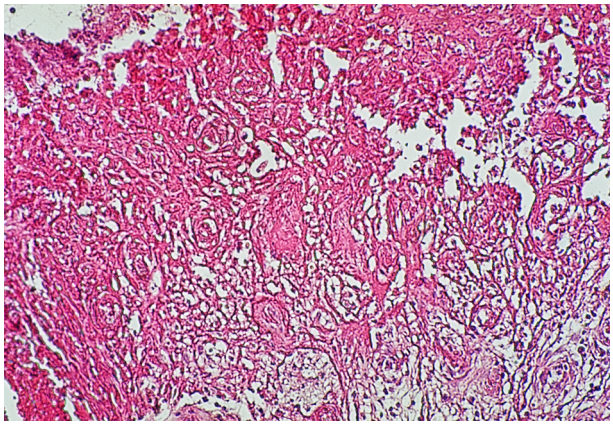

Figure 5 – ***Necrosis area associated with the disorganization of the histoarchitecture, which also involves the destruction of the vascular structures (HE stain, ob. 20×).***

The focus upon the vascular elements has allowed the identification of several more types of lesions. These lesions have been classified according to a systematic sequence and conveying the significance of the evolution related to the severity rate. They are listed below:

▪ on the microcirculation level the endothelial cells have a flat smooth inflated aspect;

▪ in the case of the meta-arterioles, small and medium arterioles:

– presence of the chronic inflammatory infiltrate arranged in concentric layers ("muffs") around them, sometimes penetrating to the media level (Figure 6);

– inflated shape of the endothelial cells, on a well-developed subendothelial layer.

▪ in the case of the large arterioles and arteries of muscular type:

– presence of the fibrous tissue on the level of media (Figure 7);

– mediosclerosis through the transformation of the fibrous tissue localized in the media (Figure 8);

– calcium deposits on intima level (Figure 9);

– calcium deposits on media level – mediocalcinosis (Figure 10);

– arteriole obstruction due to the massive development of the intima through the excessive proliferation of the subendothelial connective tissue, followed, sometimes, by a fibrous change (Figure 11);

– thromboses, sometimes associated with the connective transformation of the thrombus (Figure 12).

The focus on the nervous elements has pointed out the presence of the peripheral nervous structures with minor changes and obvious aspects showing degeneration also sustained by the decreasing in Schwann cells (Figure 13), facts that eventually have resulted in the disappearance and homogeneity of the nervous fibers (Figure 14). It is worth mentioning the presence of the myositis on the level of the muscular tissue in the context of the lesions under study (Figure 15).

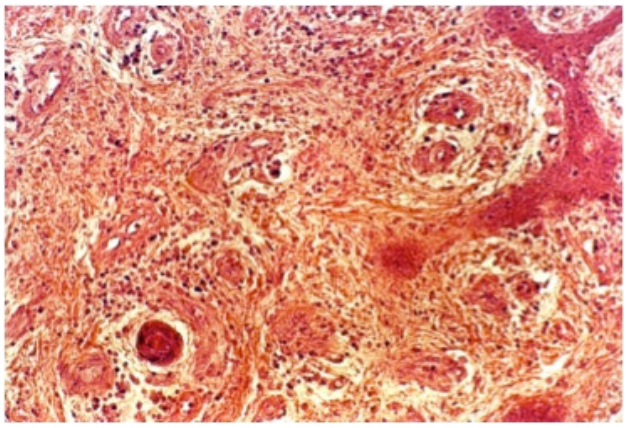

Figure 6 – ***Inflammatory process localized in the dermis; the vascular elements are surrounded by lymphocytes (HE stain, ob. 20×).***

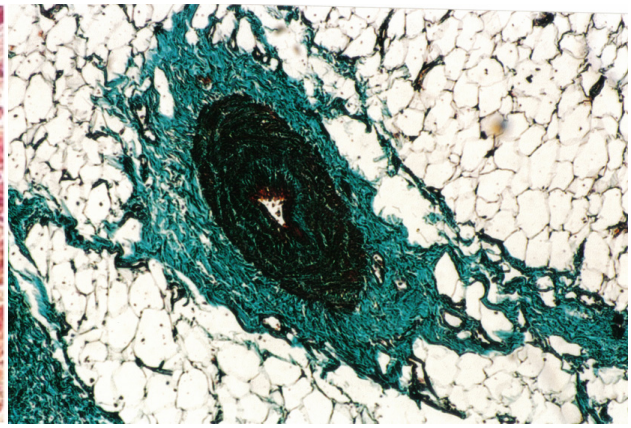

Figure 7 – ***Arteriole with fibrous changes (trichromic Szekely stain, ob. 10×).***

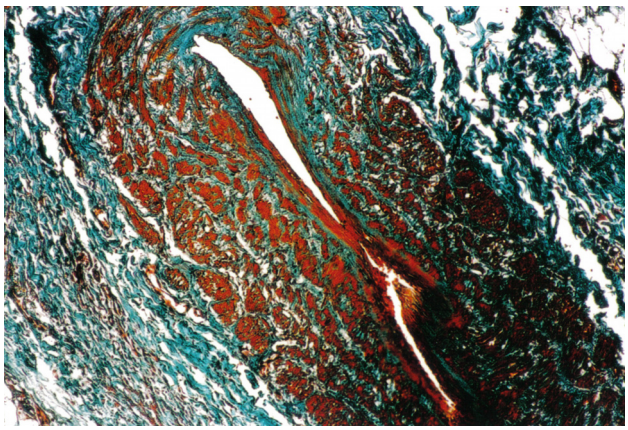

Figure 8 – ***Fibrosis that tears the muscular fibers (trichromic Szekely stain, ob. 10×).***

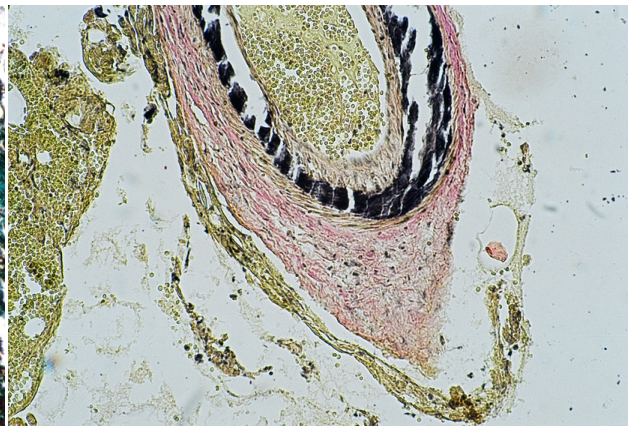

Figure 9 – ***Mineralization on the intima level (van Gieson stain, ob. 20×).***

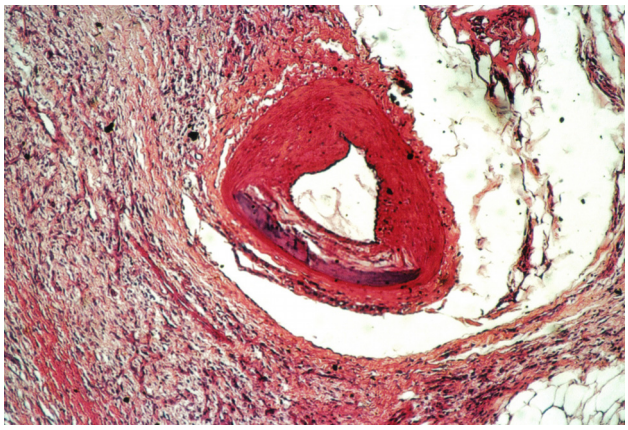

Figure 10 – ***Mediocalcinosis limited to the media (HE stain, ob. 10×).***

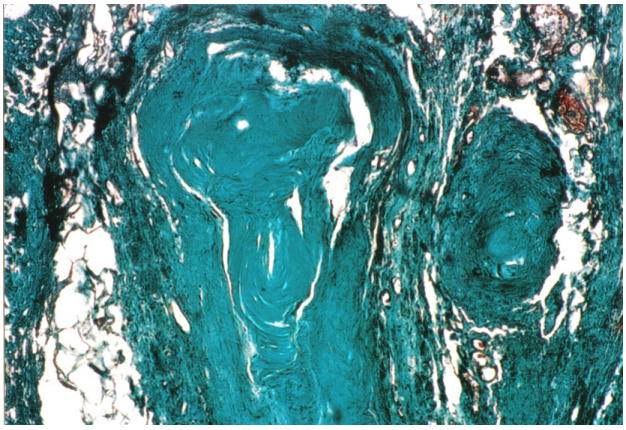

Figure 11 – ***Intima with excessive proliferation of the subendothelial layer, and the subsequent obstruction of the lumen (trichromic Szekely stain, ob. 20×).***

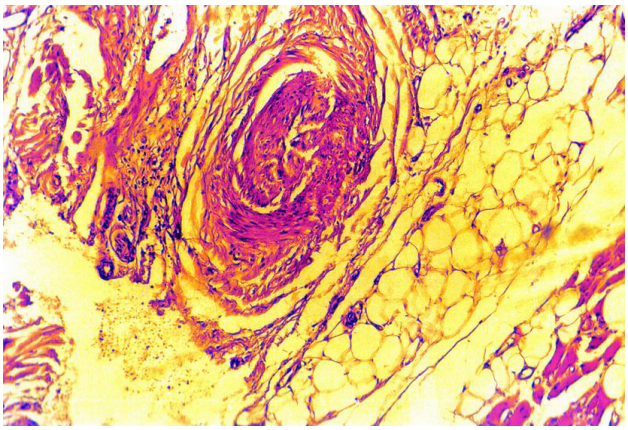

Figure 12 – ***Thrombosis associated with the connective organization of the thrombus (HE stain, ob. 20×).***

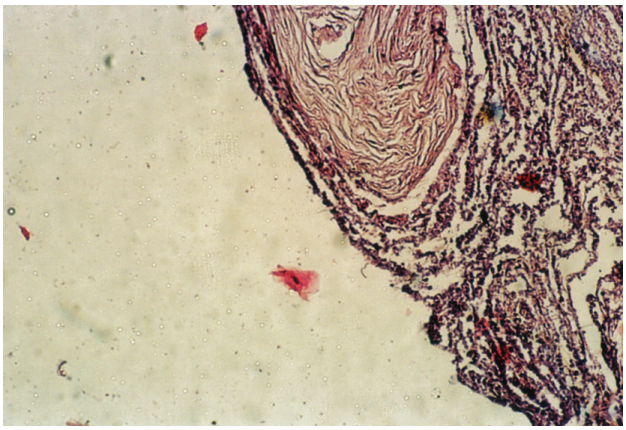

Figure 13 – ***Peripheral nerve associated with a significant reduction of the Schwann cells (HE stain, ob. 20×).***

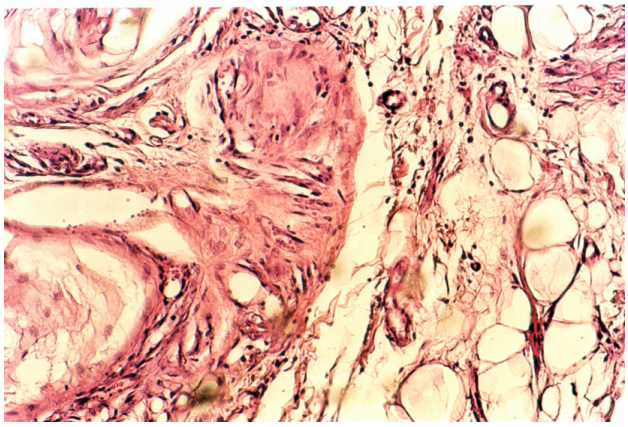

Figure 14 – ***Nerve with inflated Schwann cells and homogeneous axons (HE stain, ob. 20×).***

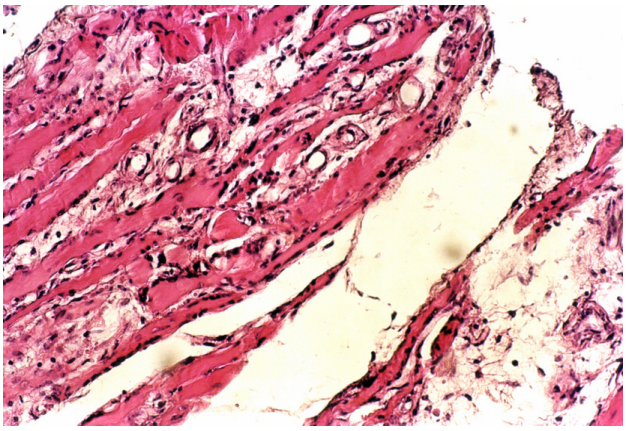

Figure 15 – ***Myositis (HE stain, ob. 20×).***

Discussion

The notion of "small vessel disease" on the level of the diabetic foot was introduced in 1959 by Goldenberg S *et al.* [16]. The concept according to which microcirculation is involved in the pathogenesis of the diabetic foot has went through multiple changes over the past years. Nevertheless, there are evidences of the structural changes in the microcirculation which do not allow the denial of this concept [9] and which sustain the involvement in the pathogenic mechanism of the diabetic foot complications. The endothelium dysfunction plays an important part in the pathogenesis of the diabetic microangiopathy [10, 17–22]. It precedes the apparitions of the microvascular lesions and it is proven by the decrease in the dilating response to the vasoactive agents and also through alterations of the anti-thrombotic properties of the endothelium [19, 20, 23]. According to the hemodynamics hypothesis, in the early stages of the diabetes there is registered an increase of the microvascular blood flow and capillary

permeability. All these determine an endothelium injury, which results in its consecutive sclerosis and microvascular hyalinosis. Along with sclerosis and arteriolar hyalinosis, the thickening of the basal membrane [22, 24], has also been proven through studies of light and electron microscopy, and it was admitted to be the main characteristic of the diabetic microangiopathy. It has been proven that these abnormalities are directly related to the capillary pressure and there are more accentuated on the foot level due to the hydrostatic influence exerted by the orthostatic position. The microvascular sclerosis determines a structural "closure" of the capillary wall, which affects the vasodilatation and turns other vascular responses into a particular way on the level of the lower limbs. Recent studies have proven that microangiopathy on the foot level cannot be viewed as an obliterating microangiopathy [19] (as it is commonly recorded in retinopathy and diabetic nephropathy), and its presence alone is insufficient to cause a foot lesion. Despite of these aspects, the microcirculation (especially, on the level of capillaries and small and medium arterioles) is affected in the case of the diabetic patients. Ischemia, secondary to the multi-segmental arterial disease, induces additional abnormalities of the microcirculation functions, which overlap the pre-existent structural microvascular changes and functional microangiopathy [9]. The latter is caused by the loss of the sympathetic tonus associated with the decrease or total loss of the hyperemia response to any inflammatory process [10], the increase of the arteriolar resistance and, also, the increase of the circulation through the arterio-venous shunts. By this mechanism, a decrease of the blood quantity is being produced which actually reaches the capillary level and has final consequences upon the nutritive circulation of the tissues on this level. The alterations of the microcirculation can also explain the late healing noticed at the patients suffering from diabetes mellitus [25, 26], and, even more, the raise of the suspiciousness in the case of diabetic foot infections [17].

However, the influence of the microvascular changes in relation with the appearance of the lesions on the diabetic foot, the role played by the vascular mediators in diabetes, and the influence of all these exerted upon the microcirculation require further studies and recordings [27–29].

Our present study makes a difference by identifying the vascular and nervous changes on the level of cutaneous areas, along with the presence of the inflammatory infiltrate on the dermis, structural modifications of the sweat glands, and myositis. The microvascular lesions have been associated, during the evolution of the diabetic foot complications, with the lesions found on level of the small and medium arterioles. The nervous involvement is sustained by the morphological changes on the level of the peripheral nervous structures.

Conclusions

The identification of vascular and nervous morphological structures in the complicated diabetic foot allows the extension of the knowledge related to the pathological background of this condition. Within the context of the evolution of diabetes mellitus, the vascular lesions, which appeared on the microcirculation level, are aggravating; they are consequently involving arterioles and arteries of muscular type and are being accompanied by nervous lesions shown through morphological changes of the peripheral nerves. The overall morphological contest of the complicated diabetic foot (compulsorily accompanied by complications) involves lesions of the epidermis, dermis, and muscles.

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