Vascular Leg Ulcers: Histopathologic Study of 293 Patients

Cosimo Misciali, MD, Emi Dika, MD,* Carlotta Baraldi, MD,* Pier Alessandro Fanti, MD,* Michele Mirelli, MD,† Andrea Stella, MD,† Marco Bertoncelli, MD,* and Annalisa Patrizi, MD**

Abstract: Vascular leg ulcers remain a challenge for the modern health care, and a systematic pathological study on this kind of lesions has not been reported so far. A total of 293 consecutive white patients with chronic leg ulcers (present for a minimum of 6 months and up to several years) referred to the Wound Care Unit (Dermatology, University of Bologna) between March 2008 and June 2011. Thirty-four patients affected by other than vascular ulcers, neoplastic or inflammatory conditions, were excluded. The remaining 259 patients affected by vascular leg ulcers were enrolled in this study. Assessment of the patients general health, skin biopsy, and vascular Doppler of the lower limbs were performed to determine the etiology and to formulate an appropriate management plan, whereas 2 punch biopsies of 3 mm were performed on the border and on the bed of each ulcer. Doppler evaluation showed the presence of vascular hemodynamic impairment in 259 patients. Of these, 181 (69.9%) patients were affected by venous insufficiency, 58 (22.4%) by venous and arterial insufficiency, and 20 (7.7%) by arterial insufficiency. Histopathologic features revealed significant differences, thus, reflecting the clinicopathologic correlation with the underlying hemodynamic impairments. In conclusion, histopathologic and hemodynamic data correlation could provide the basis for future analysis of leg ulcers pathogenesis and may improve treatment protocols. We should underline that this observational study represents a single-institute experience and that larger series are needed to confirm our observations.

Key Words: biopsy, vascular leg ulcers, pathology, diagnostic procedure, hemodynamic impairment

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INTRODUCTION

In developed countries, approximately 1% of the general population suffers from vascular leg ulcers (VLUs).[1] The etiopathogenesis of VLUs is multifactorial and still partially unknown. Obesity, deep-vein thrombosis, diabetes, peripheral arterial occlusive disease, and chronic venous incompetence represent the most common risk factors for developing an ulceration of the lower extremities.[2]

From the Departments of *Specialised, Experimental and Diagnostic Medicine, Section of Dermatology, and †Vascular Surgery, University of Bologna, Bologna, Italy.

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Reprints: Carlotta Baraldi MD, Department of Specialised, Experimental and Diagnostic Medicine, Section of Dermatology, University of Bologna, Via Massarenti 1, Bologna 40138, Italy (e-mail: carlotta.baraldi@gmail.com).

About 85% of lower-extremity (lower leg and ankle) ulcers are accounted for venous leg ulcers as a result of the progression of chronic venous insufficiency. Valvular incompetence causing venous reflux is frequently observed and has been postulated by many authors as the primary cause of the vein wall weakness and dilatation.[3]

The gold-standard protocol treatment for the majority of VLUs includes debridement, infection control, moist wound healing, appropriate dressings, and compression therapy, which together lead to consistent wound improvement.[4]

The authors herein report on a clinicopathologic study in patients with chronic VLUs of arterial, venous, or mixed arterial and venous origin with the aim of highlighting differences in their histopathologic features.

Over a 2-year period, all consecutive patients with clinical diagnosis of VLU were assessed using vascular Doppler, duplex sonography, and swab culture and skin biopsies. The histopathologic features were evaluated and correlated with the hemodynamic impairments.

MATERIALS AND METHODS

A total of 293 consecutive white patients with chronic leg ulcers (present for a minimum of 6 months and up to several years) referred to the Wound Care Unit (Department of Dermatology, University of Bologna) between March 2008 and June 2011. Thirty-four patients affected by other than vascular ulcers, neoplastic or inflammatory conditions, were excluded. Patients affected by diabetes or arterial hypertension were included only if the underlying disease was under control.

When admitted and after signing informed consent, a dual approach was taken with each patient involving:

- Arterial and venous vascular Doppler with GE Healthcare Medical System Logic 7;
- Skin biopsy.

If clinical signs of wound infection were present, swab cultures for bacteriologic and mycological culture analysis were performed, and a systemic antibiotic was prescribed on the basis of a specific antibiogram.

Venous disease was confirmed through color venous duplex ultrasonography. A venous reflux was defined as significant if retrograde blood flow persisted for longer than 1 second after manual calf compression and release.

Doppler assessment was used to determine the ankle brachial pressure index (ABPI) and to exclude arterial disease. An ABPI below 0.8 denotes the presence of arterial disease. In calcified arteries (ie, diabetic and uremic patients), an ABPI test may be unreliable; thus, a color duplex

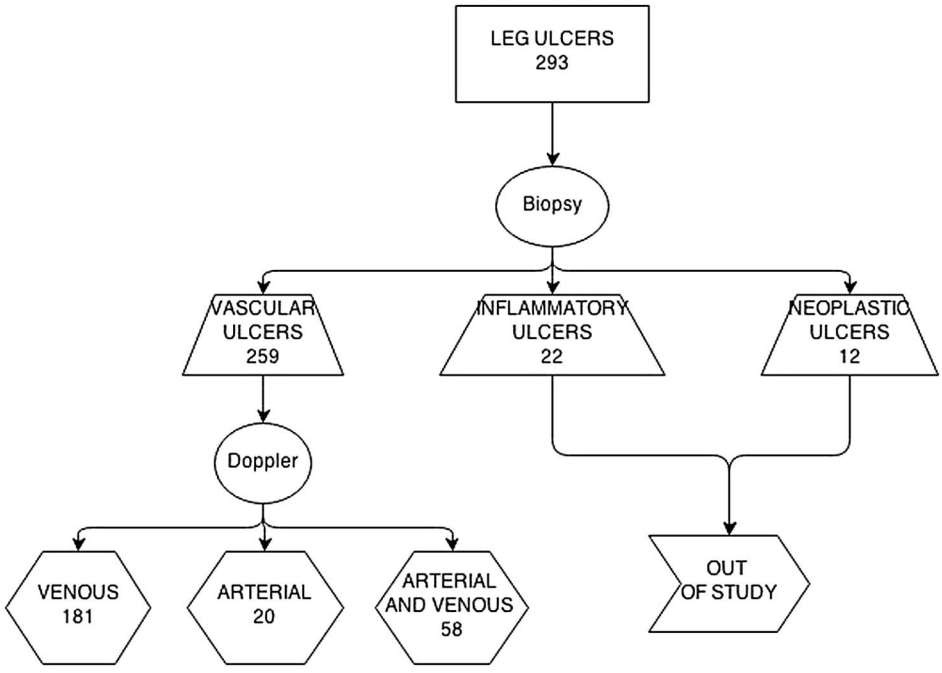

FIGURE 1. Flow chart with criteria for exclusion and inclusion.

TABLE 1. Demographic and Clinical Data for all Patients and per Groups

	Mean Age, yr	Sex	Site	Comorbidities	Duration of Ulcer	Size (Diameter)	Symptoms	Evidence of Lymphedema
Venous	65	M, 60	72 medial malleolus	103 arterial hypertension	From 6 mo up to 2 yr	Up to 15 cm	24 pain	13 evidence
		F, 121	83 lateral malleolus	99 artrosis			10 itch	168 no evidence
			9 distal tibia	59 renal insufficiency			147 no symptoms	
			15 calf	47 atrial fibrillation				
				43 hyperuricemia				
				20 aortic insufficiency				
				17 diabetes				
				13 neoplasia				
				12 mitral insufficiency				
				12 chronic hepatitis				
				7 Parkinson disease				
				18 other				
Arterial and venous	66	M, 19	22 medial malleolus	40 arterial hypertension	6 months up to 1 yr	Up to 10 cm	30 pain	10 evidence
		F, 39	20 lateral malleolus	25 diabetes			8 itch	48 no evidence
			12 distal tibia	21 artrosis			20 no symptoms	
			4 calf	19 renal insufficiency				
				17 atrial fibrillation				
				8 hyperuricemia				
				7 aortic insufficiency				
				6 mitral insufficiency				
				3 neoplasia				
				2 chronic hepatitis				
Arterial	70	M, 8	2 medial malleolus	15 arterial hypertension	9 mo	Up to 7 cm	18 pain	20 no evidence
		F, 12	0 lateral malleolus	12 renal insufficiency			2 no symptoms	
			13 distal tibia	8 diabetes				
			5 calf	5 aortic insufficiency				
				4 atrial fibrillation				
				2 mitral insufficiency				
				1 neoplasia				

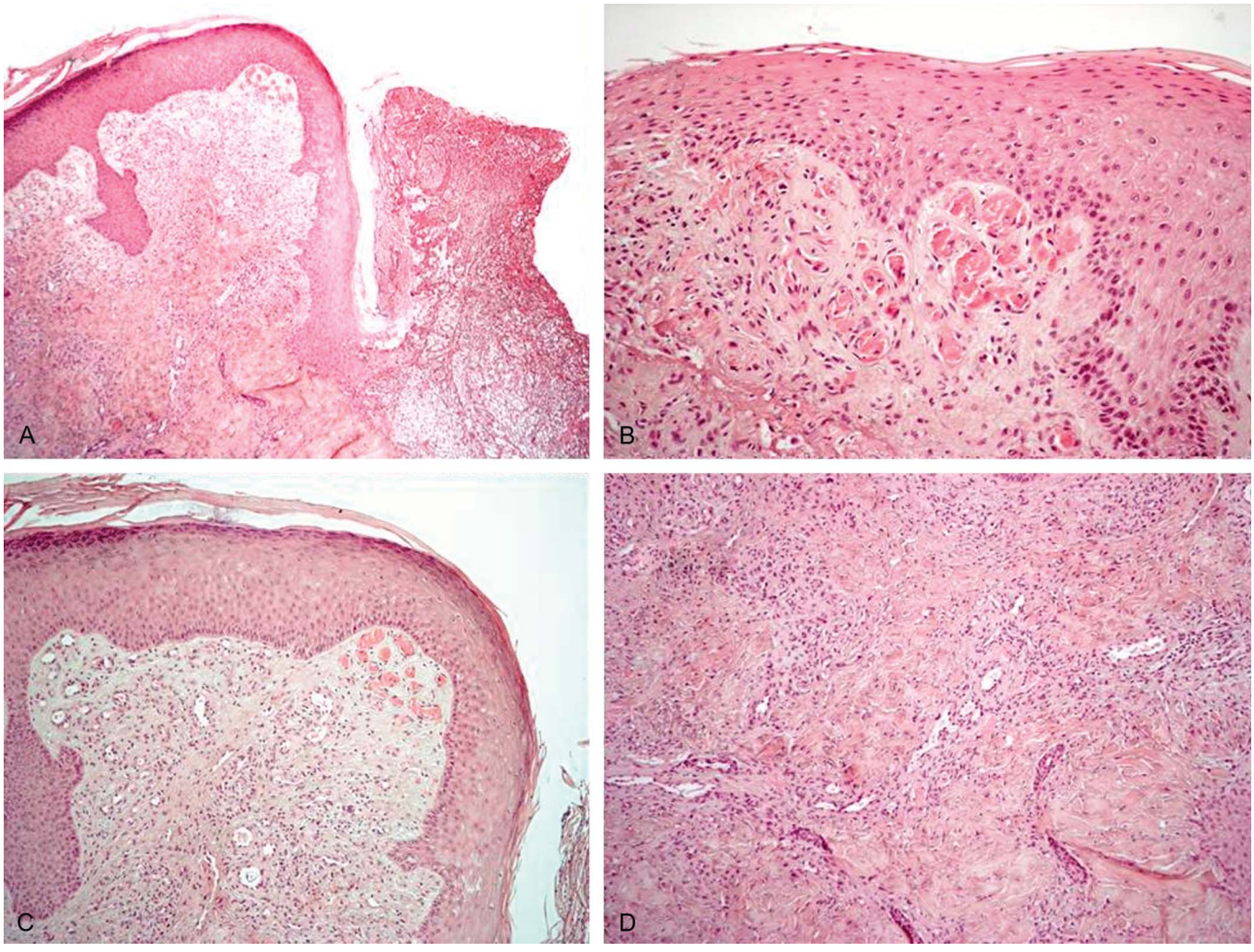

FIGURE 2. A–C, Histopathologic features of venous ulcers: ulcer and hyperplasia of the epidermis with an abrupt transition between the normal epidermis and the ulcer's area—"step sign" (original magnification H&E, ×2; ×10). D, Collagen bundles degeneration (original magnification H&E, ×20).

examination was performed to evaluate the patency of the arterial vessels.

Doppler evaluation showed the presence of vascular hemodynamic impairment in 259 patients, as subsequently confirmed by 2 punch biopsies of 3 mm, performed on the bed and on the border of each ulcer, respectively. The specimens were fixed in 10% neutral-buffered formaldehyde, routinely processed and stained for hematoxylin and eosin, von Kossa, periodic acid-Schiff, and Pearls (Fig. 1).

Among the 34 patients who were excluded from our study because of their histological diagnosis, 22 patients resulted affected by ulcers deriving from inflammatory conditions (mainly vasculitis and pyoderma gangrenosum), and 12 patients resulted affected by neoplastic ulcers (10 ulcerated basal-cell carcinomas, 1 ulcerated porocarcinoma, and 1 patient affected by large-cell granular lymphocytic leukemia of the lower leg). All of the patients presenting neoplastic ulcers had been misdiagnosed on the basis of clinical presentation and previously treated as VLUs for at least 6 months by general physicians or other departments.[5]

A histological study of epidermal, dermal, and hypodermal features of all 259 vascular ulcers was performed, and these findings were compared with the hemodynamic data to evaluate the similarities and differences between ulcers of venous, venous and arterial, and arterial insufficiency origin. The data were collected in accordance with good medical practice guidelines in the aim to ensure accuracy and integrity.

OUTCOMES AND MEASUREMENTS

The primary objective of this study was the evaluation of potential correlations between hemodynamic impairments and VLU histopathologic features.

RESULTS

A total of 259 patients were evaluated (87 men and 172 women, with a male to female ratio of 1:1.9) with a mean

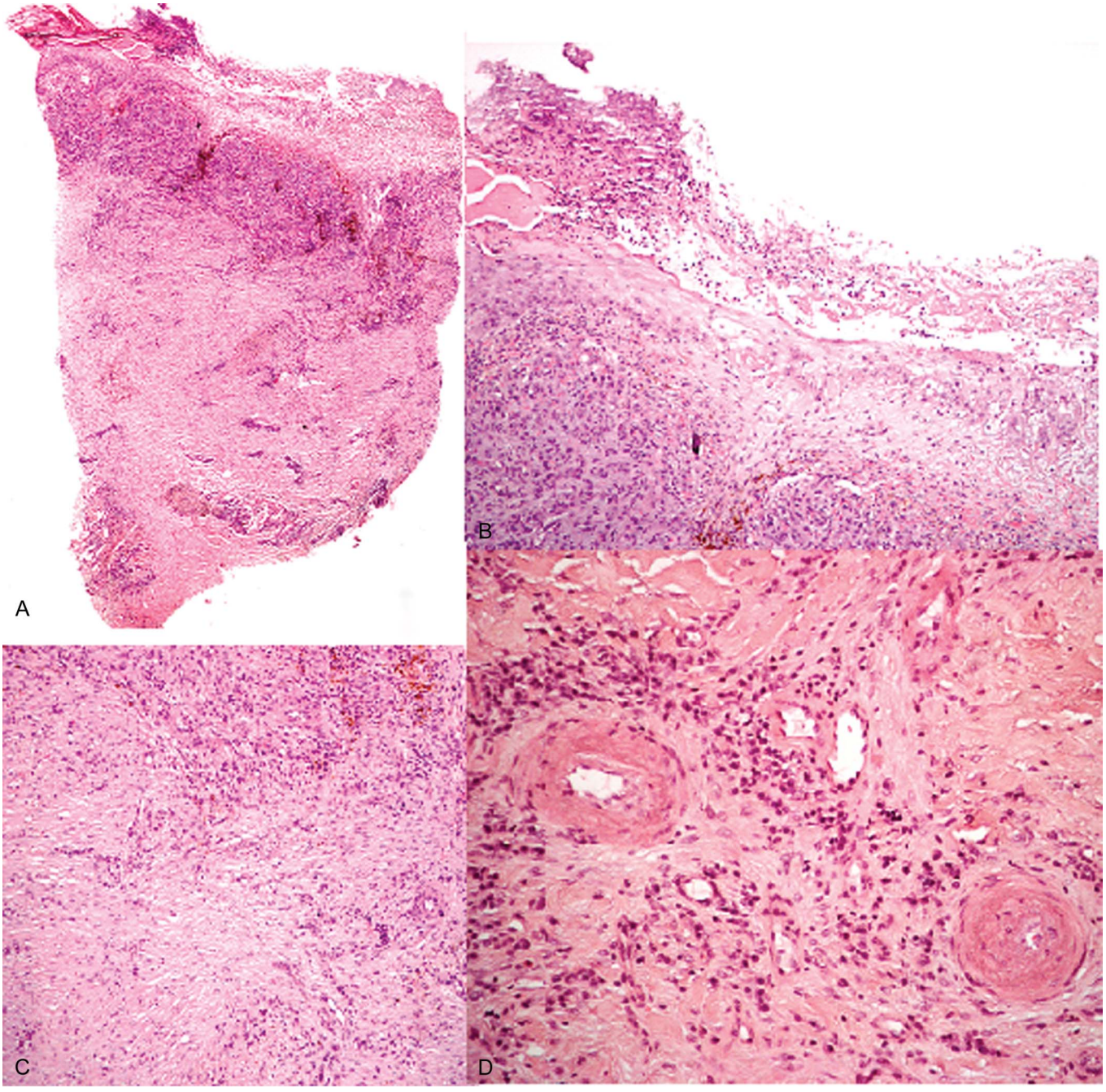

FIGURE 3. A and B, Histopathologic features of an arterial ulcer: progressive thinning and necrosis of the epidermis and the superficial dermis (original magnification H&E, 2×; ×10). C and D, Collagen bundles orientation and intraluminal thrombus (original magnification H&E, ×20; ×40).

age of 67 years (range, 54–98 years). Of these, 181 (69.9%) patients were affected by venous insufficiency, 58 (22.4%) by arterial and venous insufficiency, and 20 (7.7%) by arterial insufficiency (Table 1).

The histological examination of specimens obtained from both the border and the bed of each ulcer, interestingly, revealed significant differences in the ulcers of different pathogenic origin. Epidermal alterations are more assessable in biopsies taken from the ulcers' borders, whereas dermal and subcutaneous changes are mostly visible in biopsies from the ulcer beds.

Ulcers with a predominant venous impairment showed spongiosis in 80% of the cases, a marked epidermal hyperplasia in 77.3% of the cases, and an abrupt transition from normal epidermis toward ulcerated area in more than half of the patients (56.3%); thus, we suggest the term "step sign"

(Figs. 2A–C) for this feature. Ulcers with a predominant arterial impairment showed a progressive epidermal necrosis in 95% of the cases, with a tapering epidermal thinning in 90% of the patients (Figs. 3A, B).

The dermal changes in long-standing venous ulcers mainly consisted of diffuse edema (96.7%), granulation tissue (93.4%), fibrin (90.6%), hemosiderophages (87.8%), and collagen-bundle degeneration (81.2%) with fibrosis (77.9%) (Fig. 2D). These findings are different from those observed in arterial ulcers, where a significant presence of intraluminal thrombi of dermal vessels (95%) and dermal sclerosis (80%), sometimes with hyalinized aspects whereas the presence of granulation tissue (60%) and fibrin (25%) (Figs. 3C, D) was found only some cases.

It is worth noting that how the ulcers of venous and arterial origin showed histological features somewhere in between those of the purely venous and the purely arterial ulcers, with a predominance of the pathological features of the venous ulcers. In fact, the epidermis showed the same marked hyperplasia (77.2%) as the venous ulcers, a mild spongiosis (43.1%), whereas a mild tapering epidermal thinning was present only in 34.5%. Edema (60.3%), granulation tissue (70.7%), hemosiderophages (43.1%), and collagen-bundle degeneration (56.9%) with fibrosis (63.8%) are less common than in pure venous ulcers, whereas some pure arterial ulcer characteristics are also slightly expressed, such as the presence of intraluminal thrombi (50%) and a lower content of fibrin (25.8%).

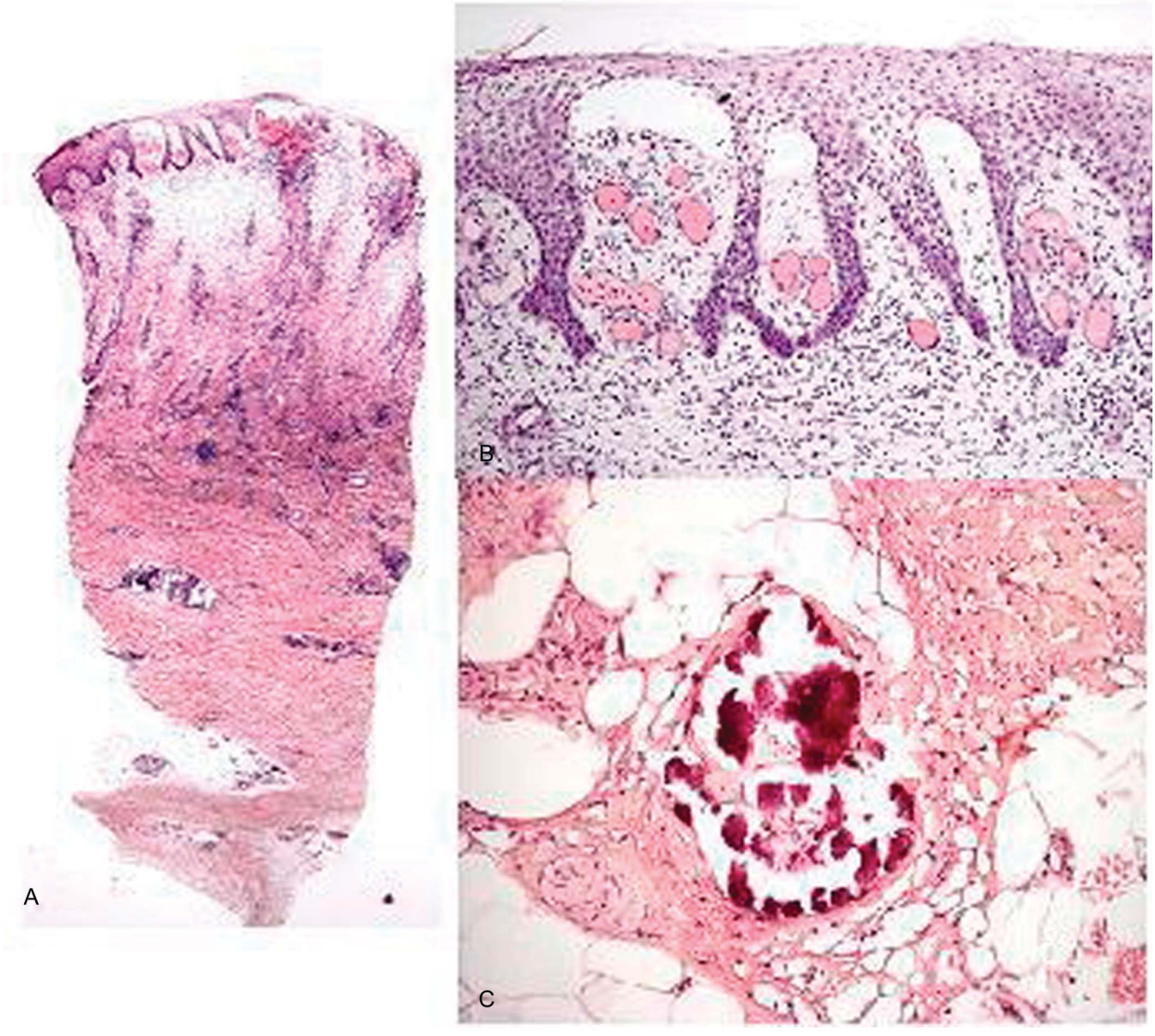

FIGURE 4. A and B, Ectatic lymph vessels in the papillary dermis of a long-standing chronic venous ulcer (original magnification H&E, ×2; ×10). C, Intraluminal calcium deposits (original magnification H&E, ×40).

Ectatic lymph vessels were observed in the dermis of 27 venous and arterial ulcers and in 89 cases of pure venous ulcers. A variable degree of phlebolymphedema has been also observed in both reticular and papillary dermis in 10 cases of venous and arterial ulcers and in 13 cases of pure venous ulcers. Ectatic lymph vessels were commonly seen as a result of a lymph circulation impairment because of the stasis dermatitis in advanced venous disease (Fig. 4) (Table 2).

Calcium deposits were randomly distributed in the dermis of long-standing ulcers (lasting more than 2 years), irrespective of the underlying hemodynamic condition. All the ulcers, regardless of the time of onset, demonstrated an absence of skin appendages and of changes in the subcutaneous fat.

DISCUSSION

VLUs are a common medical problem and their treatment has a significant socioeconomic impact. Recent years have seen an increase in the attention being given to this pathology and in the number of new studies being published on the topic. Treatment and recurrences of venous ulcers seem to be the focus of most of the studies because of the high prevalence of this particular pathology.[2,4–9]

The clinical characteristics and risk factors of venous ulcers[2,10] have been reported by some authors, whereas others have presented treatment guidelines for arterial ulcers.[11,12] Fernandez et al[13] report that lymphatic dysfunction might play a role in the pathogenesis of chronic venous insufficiency.

TABLE 2. Main Histopathologic Findings

	Venous Ulcers (181)	Arterial Ulcers (20)	Arterial and Venous (58)
Epidermis			
Marked hyperplasia	77.3% (140/181)		72.4% (42/58)
Progressive epidermis thinning		90% (18/20)	34.5% (20/58)
Abrupt transition toward the ulcerated area	56.3% (102/181)		
Spongiosis	80.1% (145/181)		43.1% (25/58)
Necrosis		95% (19/20)	
Dermis			
Edema	96.7% (175/181)		60.3% (35/58)
Ectatic lymph vessels	49.2% (89/181)		46.5% (27/58)
Granulation tissue	93.4% (169/181)	60% (12/20)	70.7% (41/58)
Fibrin	90.6% (164/181)	25% (5/20)	25.8% (15/58)
Intraluminal thrombus		95% (19/20)	50% (29/58)
Hemosiderophages	87.8% (159/181)		43.1% (25/58)
Fibrosis	77.9% (141/181)		63.8% (37/58)
Sclerosis		80% (16/20)	
Collagen bundles degeneration	81.2% (147/181)		56.9% (33/58)
Intraluminal calcium deposits	15.5% (28)		10.3% (6/58)

The overall histological feature of ulceration is the loss of the entire epidermis and of at least part of the dermis, which rarely extends to the subcutaneous tissue. The ulcerative process destroys the normal pattern of collagen bundles in the dermis inevitably healing with a scar.

In this article, we described not only the most common histopathologic features in patients affected by VLUs of different hemodynamic origin but also some characteristic features frequently observed in each patient group.

The main histopathologic findings in venous and arterial and venous ulcers are epidermal hyperplasia, diffuse dermal edema, and collagen-bundle degeneration, whereas ulcers caused by arterial obstruction mostly present with necrotic and/or thinned epidermis and intraluminal thrombi within the dermal vessels.

Ulcers with venous and arterial and venous impairment showed evidence of phlebolymphedema (8.9% of all cases). Ruocco et al in 2012 well described the pathogenetic mechanism of the onset of phlebolymphedema as a result of chronic venous insufficiency. As a matter of fact, venous hypertension causes an increase of capillary filtration, which is initially well compensated by an increased lymph load. However, in long-standing ulcers, the transport capacity resulted saturated (ectatic lymph vessels are observed at histopathologic examination), thus leading to a lymph load fail and to an accumulation of interstitial fluid. In these cases, venous together with lymphatic insufficiency condition cause a progressive swelling of soft tissues, the so-called phlebolymphedema.[14] However, in our study, no features of phlebolymphedema were detected in the arterial ulcer group, and only in 23 total cases in the groups with chronic venous and arterial impairment. Thus, we suggest that in our study, chronic venous insufficiency represents the major pathophysiological mechanism of phlebolymphedema.[15,16]

Several authors[17–20] have already underlined the importance of skin biopsies in determining the etiology of leg ulcers, with the aim of excluding occasional cases of malignancies presenting as leg ulcers, and of better understanding, the etiopathogenetic mechanisms.

In our opinion, histopathologic and hemodynamic data correlation could provide the basis for future analysis of leg ulcers pathogenesis and may improve treatment protocols. We should underline that this observational study represents a single-institute experience and that larger series are needed to confirm our observations.

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