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From Cell Biology to Tissue Engineering

Intravascular papillary endothelial hyperplasia (IPEH). Evidence supporting a piecemeal mode of angiogenesis from vein endothelium, with vein wall neovascularization and papillary formation

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Summary. Intravascular papillary endothelial hyperplasia (IPEH) is a reactive process of questioned pathogenesis (primary proliferation of endothelial cells/ECs versus organizing thrombi). The aim of this study is to assess the organization of morphologic patterns, with precise location of neovascularization and papillary distribution in IPEH to clarify the role of the vein wall (mainly vein intimal ECs) in lesion development and papillary formation. We studied 12 cases of IPEH in skin and subcutaneous veins by serial histological sections and immunohistochemical procedures. In four well-structured cases (the remaining cases showed overlapping events), we found four principal histological patterns organized by zone: 1) invaginated vein wall zone with microvascular networks. The intraparietal microvessels presented CD34+ and CD31+ ECs arising from ECs of the vein intima, and αSMA+ pericyte-like cells originating from modified SMCs of the media layer. 2) Papillary zone, generally with myriad papillae, formed by ECs of intraparietal microvessel networks encircling vein wall components (parietal papillae). 3) Organizing thrombotic zone from microvascular networks of invaginated vein wall zone. 4) Unorganized thrombotic zone partially covered by ECs, also originating from vein intimal endothelium and arranged in a monolayer or encircling thrombotic fibrin (thrombotic papillae). In conclusion, the capacity of vein intimal ECs and those originating from them (in newly-formed microvessels in the vein itself and covering the unorganized thrombi) to encircle vein wall components or fibrin, and to form papillae (ECs form the cover and encircled components the core) supports a piecemeal mode of angiogenesis as a pathogenic basis of IPEH. This mechanism encompasses the two histogenetic hypotheses outlined above.

Key words: Angiogenesis, Endothelial cells, Vein wall vascularization, Trombus organization

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Introduction

Since the initial description as "hémangio-endothéliome végétant intravasculaire" by Masson, 1923, intravascular papillary endothelial hyperplasia (IPEH) (term coined by Clearkin and Enzinger, 1976) has received different names (Masson's tumour, Masson's pseudoangiosarcoma, Masson's intravascular hemangioendothelioma, papillary endothelioma, intravascular endothelial proliferation, intravascular angiomatosis, intravascular papillary endothelial hyperplasia, and "endovascularite proliférante thrombopoietique" (Henschen, 1932; Salyer and Salyer,

1975; Kuo et al., 1976; Cozzutto et al., 1979). IPEH is considered a reactive proliferation of the endothelial cells (ECs), which originate bundles of papillae with stromal support. IPEH commonly occurs in dilated venous spaces (Pins et al., 1993) and must be differentiated from blood vessel tumours, principally from angiosarcoma (Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kuo et al., 1976; Barr et al., 1978; Hashimoto et al., 1983). In IPEH, the phenomena of thrombus organization and venous stasis are frequently associated with EC proliferation. Two possibilities have been considered in IPEH pathogenesis: that it is an exuberant growth of organizing thrombi (since papillae can be observed focally in thrombi), as maintained by some authors (Salyer and Salyer, 1975; Clearkin and Enzinger, 1976), or that it is a primary proliferation of ECs followed by thrombosis, as hypothesized by Masson in his original description (Masson, 1923). Most authors consider that thrombosis plays an important role in the development of this process, based on the presence of focal findings of IPEH in organizing thrombi, and in ultrastructural and immunohistochemical characteristics of the lesion (Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kreutner et al., 1978; Cozzutto et al., 1979; Amérigo and Berry, 1980; Albrecht and Kahn, 1990; Steffee and Iskandar, 1996; Soares et al., 2008; Kim et al., 2013). However, the existence of cases without thrombosis and the possible occurrence of this process in cystic lymphangiomas indicate that the primary proliferation of ECs cannot be totally ruled out (Kuo et al., 1976). In any case, the basis for the unusual exuberant growth of ECs and the development of the peculiar papillary pattern in IPEH have not been clarified.

The object of this study was: a) to establish the zones with different morphologic patterns in IPEH, using serial histological sections and immunohistochemical procedures, and b) to assess the precise location, characteristics, and origin of newly formed microvessels in these zones, and their role in vein wall invagination and papillary structure formation, thereby contributing to a better understanding of IPEH histogenesis.

Material and methods

Tissue samples of IPEH

The archives of the Department of Anatomical Pathology of the University Hospital and of the Hospiten® Hospitals of the Canary Islands were searched for cases with diagnosis of IPEH in veins of dermis and subcutaneous tissue, and 12 cases showing a "pure" (primary) form of the Hashimoto classification (Hashimoto et al., 1983) were selected. After serial sections, four of the selected cases (with well-stratified, spatial histologic zones) were used for microphotograph compositions that enable the location of intravascular patterns of IPEH and their spatial interrelation with each other and with the wall and residual lumen of the affected vessel. Patients were Caucasian: 5 male and 7 female, aged 8 to 71 years. Protocols were performed in accordance with international ethical guidelines.

Light microscopy

Specimens for light microscopy were fixed in a buffered neutral 4% formaldehyde solution, embedded in paraffin, and cut into 4 μm-thick sections. Sections were stained with Haematoxylin and Eosin (H&E), Masson trichrome, Wilder's reticulin stain, and Orcein stain.

Immunohistochemistry

Three μm-thick sections were cut and attached to silanized slides. After pre-treatment for enhancement of labelling, the sections were blocked with 3% hydrogen peroxide and then incubated with primary antibodies (10-40 minutes). The primary antibodies (Dako, Glostrup, Denmark) used in this study were CD34 (dilution 1:50); CD31 (dilution 1:50); α-smooth muscle actin (αSMA) (dilution 1:50); desmin (dilution 1:50); h-caldesmon (dilution 1:50), and CD68 (dilution 1:50). The immunoreaction was developed in a solution of diaminobenzidine and the sections were then briefly counterstained with haematoxylin, dehydrated in ethanol series, cleared in xylene, and mounted in Eukitt®. Positive and negative controls were used. For the double immunostaining, we used anti-CD34 antibody (diaminobenzidine -DAB- as chromogen) to highlight CD34+ ECs and anti-αSMA or anti-CD68 (aminoethyl-carbazole -AEC- substrate-chromogen) for pericytes/smooth muscle cells (SMCs) and macrophages, respectively.

Results

Histopathologic characteristics of IPEH. Organization in zones with a different pattern

Myriad papillae and networks of microvessels were observed in all cases (n: 12) and thrombosis was observed in 11 of them. In four well-structured cases (the remaining cases showed overlapping events), the lesions were well circumscribed and confined to dilated veins, whose walls (with or without elastic fibres) showed unmodified and modified areas. Unmodified areas of the vein wall displayed ECs (CD34+ and CD31+) in the intima, SMCs (αSMA+, desmin+, h-caldesmon+) in the media, and stromal cells (CD34+, CD31-) in the adventitia (Figs. 1, 2). Modified areas of the vessel wall were thickened and generally appeared invaginated, forming folds (Figs. 1, 2), which were incorporated into several regions of the intraluminal lesion. These regions showed two types of surfaces oriented towards the vessel lumen: one endothelialized, either smooth or irregular with papillae (Figs. 1, 2), and the other of unorganized thrombi (Figs. 1, 2). In these

intravascular regions, four principal histological patterns were distributed in overlapping zones: 1) invaginated vein wall zone with microvascular networks, 2) papillary zone, 3) organized thrombotic zone, and 4) unorganized thrombotic zone (Figs. 1, 2). The invaginated vein wall zones of each region were attached to the vessel wall by stalks of variable length (Figs. 1 and 2), which showed invaginated structural components of the neighbouring unaffected vessel wall, that is, ECs (CD34+, CD31+) and SMCs (αSMA+, desmin+, h-caldesmon+) sandwiching a central zone with CD34+ stromal cells (Fig. 2D,E).

Invaginated vein wall zones with microvascular networks originating from vein intimal ECs

The thickened and invaginated vein wall zones presented numerous anastomosing vascular channels, which originated from intimal ECs and penetrated between the SMCs (αSMA+) of the media layer (Fig. 3A). Using double staining with CD34 and αSMA, the complex networks of vascular channels, with slit-like or well-defined lumens, showed ECs (CD34+) and perivascular cells (αSMA+) with a pericytic aspect (Fig. 3B). Perivascular cells and SMCs of the media layer of

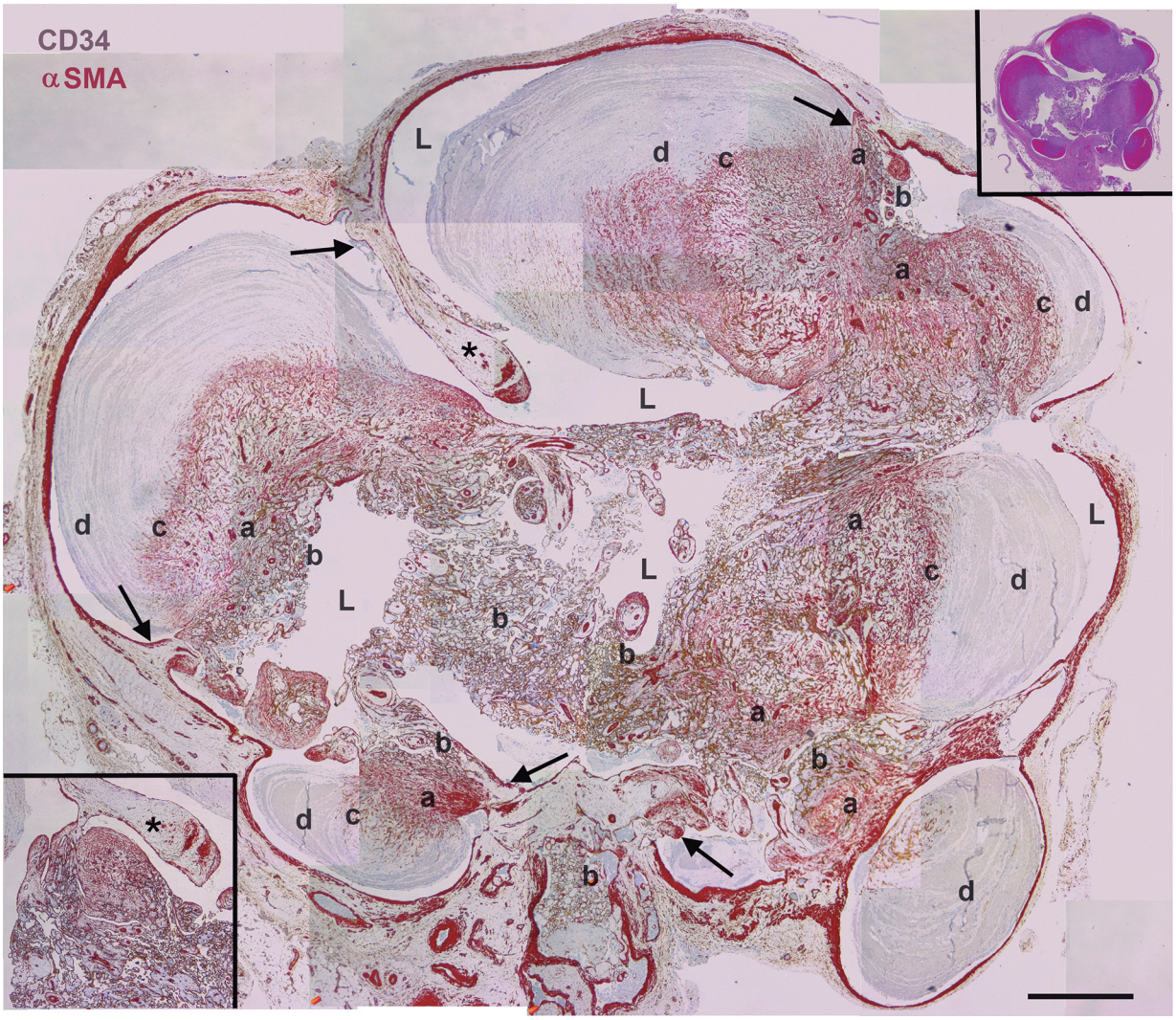

Fig. 1. Intravascular papillary endothelial hyperplasia (IPEH). Microphotograph composition of a histologic section double-stained with anti-CD34 (brown) and αSMA (red) (top insert: similar image of a histologic section stained with H&E). IPEH is confined to a dilated vein whose wall is partially affected, invaginated, and incorporated into several regions of the intraluminal lesion. Four zones are identified in each region according to morphologic pattern: 1) invaginated vein wall zone with microvascular networks (a), 2) papillary zone (b), 3) organized thrombotic zone (c), and 4) unorganized thrombotic zone (d). Note that each intraluminal region shows two types of surfaces oriented toward the vessel lumen (L): one endothelialized, smooth or with papillae, and the other formed by unorganized thrombi. The intraluminal lesion is joined to the vein wall by stalks (arrows). A stalk appears unconnected to the intraluminal lesion (asterisk), but in another of the serial sections (bottom insert), the connection is observed. L: vessel lumen. Bar: 1 mm.

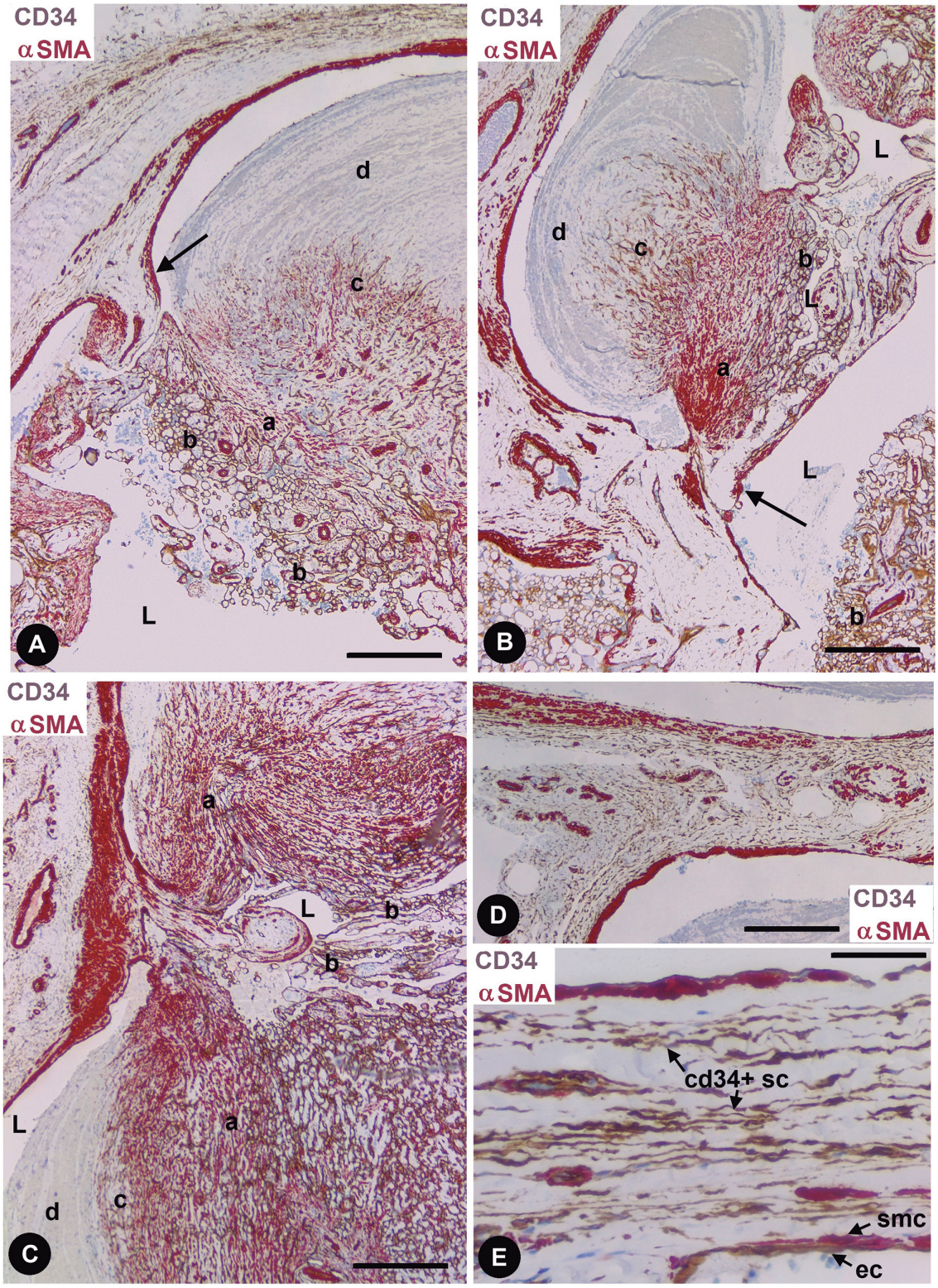

Fig. 2. A, B. The invaginated vein wall zone with microvascular networks (a), papillary zone (b), organized thrombotic zone (c), and unorganized thrombotic zone (d) are well identified under this magnification. **C.** A region showing a mirror image of the invaginated vein wall with microvascular networks (a). Note that these zones embrace narrow spaces of the lumen (L) with papillae (b). A thrombus (c and d) is observed in the surface opposite the zone with papillae. **D, E.** Detail of stalks formed by invaginated unaffected vein wall adjacent to the affected wall, in which ECs and SMCs (invaginated intima and media layer) sandwich a central zone with CD34+ stromal cells (cd34+ sc) (invaginated adventitia layer). Double-stained sections stained with anti-CD34 and anti-αSMA. Bars: A, B, C, 100 μm; D, 60 μm; E, 30 μm.

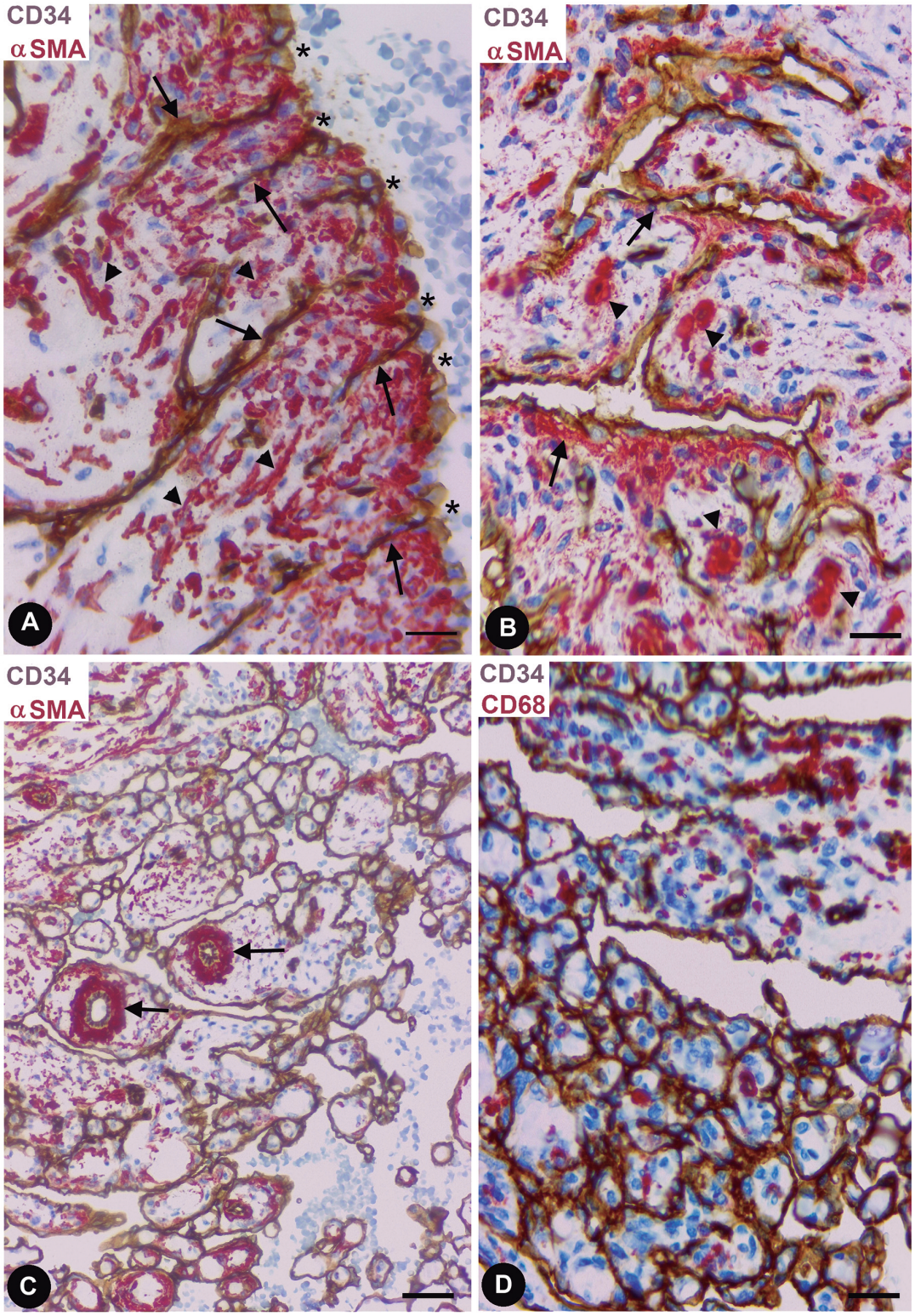

Fig. 3 A, B. Invaginated vein wall zones with microvascular networks. Note numerous vascular channels arising from the intima vein ECs (A, asterisks) penetrating the media layer (**A**, arrows) and originating complex networks **(B)**. Observe αSMA+ cells (red) of the media layer adopting a pericytic aspect around the vascular channel ECs (brown) of the complex networks. Between the microvessel networks (arrows), αSMA+ SMCs of the media layer (arrowheads) are present **(B)**. Note variable expression of αSMA in the cells between the microvessels. **C, D.** Papillary zone of IPEH. Papillae show covers formed by CD34+ endothelial cells (brown) and cores with variable cell and vascular components: acellular, with αSMA+ cells (**C**, red), with central vessels, some with thick walls (**C**, arrows) and with some CD68+ macrophages (**D**, red). A, B and C: Double staining with anti-CD34 and anti-αSMA. D: Double staining with anti-CD34 and anti-CD68. Bars: 30 μm.

the veins were also h-caldesmon+ (some weakly) and occasionally desmin+.

Papillary zones (Intravascular papillae from vein wall with neovascularization)

The vascular channels in the vein wall originating from the intimal ECs and encircling components of the vein wall formed papillae (parietal papillae), which protruded into the vessel lumen. Therefore, papillae had a central stromal core and a cover formed by plump ECs, which expressed CD34 (Fig. 3C,D) and CD31. The components of the papilla core depend on media and adventitia thickness and on the extension and depth of microvessel penetration in the vessel wall. Thus, five types of papillae were observed in non-thrombotic zones, depending on cell and microvessel core content: acellular, αSMA+ cells, vascular structures, inflammatory cells (lymphocytes, macrophages, and eosinophils), and combinations (Fig. 3C,D). Most papillae were small and had an acellular core. The papillae with αSMA+ cells were larger, and double staining with CD34 and αSMA revealed that these cells frequently formed a subendothelial layer in the papillary core and/or were arranged around the ECs of the intrapapillary microvascular structures (sometimes originating thick layers) (Fig. 3C). The macrophages (Fig. 3D), lymphocytes, and eosinophils varied in number, depending on the papillae, but were generally scarce. Successive series of secondary papillae were observed over the primary papillae and were arranged in clusters (Fig. 3C,D).

Organized thrombotic zones

The organized thrombotic zones, located adjacent to the invaginated vein wall zones (Fig. 4A), showed numerous vascular buds emerging from the vascular channel networks of this adjacent zone (Figs. 4A,B). Double staining with CD34 and CD68 highlighted abundant macrophages between the vascular buds (Fig. 4C).

Unorganized thrombotic zones (Intravascular papillae formation from endothelialized thrombotic surfaces)

Finally, the unorganized thrombotic zones, forming a cap over the organized thrombotic zones and partially filling the vein lumen, showed a free surface, whose contour was sometimes partly covered by a monolayer of CD34+ (Fig. 4D) and CD31+ ECs. Thrombotic papillae (covered by endothelium and with a core formed by fibrin), originated by ingrowing ECs from the monolayer that covered the thrombus, were also observed in these unorganized thrombotic zones (Fig. 4E).

Discussion

In IPEH, several authors have described organized and unorganized thrombi, papilla fronds, and complex networks of thin-walled vascular channels (Masson, 1923; Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kuo et al., 1976; Barr et al., 1978; Kreutner et al., 1978; Cozzutto et al., 1979; Amérigo and Berry, 1980; Hashimoto et al., 1983; Albrecht and Kahn, 1990; Pins et al., 1993; Steffee and Iskandar, 1996; Akhtar et al., 2005; Soares et al., 2008; Akdur et al., 2013; Bologna-Molina et al., 2010; Kim et al., 2013). These components of IPEH generally overlap, making it difficult to establish their stratification, and the relationship between them and with the vein wall. Using serial histological sections and immunohistochemical procedures, we selected sections in four cases, in which early findings with zones expressing four morphologic patterns (invaginated vein wall zone with microvessel networks; papillary zone; organized thrombotic zone; and unorganized thrombotic zone) were well organized in several regions. The zonal organization and relationships of these patterns, the microvessel network origin and distribution, and the comparison of the results with previous studies on vein wall neovascularization by our group and other authors suggest reasons to explain the following: a) the role of vein intimal ECs in forming microvessel networks in the vein wall itself and covering free surfaces of unorganized thrombi, b) the intravascular lesion formation and its attachment to the vein wall and c) the mechanism of papillary development.

Role of vein intimal ECs in forming microvessel networks in the vein wall itself and covering free surfaces of unorganized thrombi

An important finding in IPEH is the presence of vascular channels originating from vein intimal ECs, forming microvascular networks in the vein wall itself. Previous studies by our group demonstrated similar neovascularization in vein walls after perivenous administration of several substances, including PGE2 (Díaz-Flores et al., 1994a, 2011). In these conditions, the participation of intimal ECs in the origin of the microvessels in the vein wall was clearly demonstrated (sequential steps, in which migration of intimal ECs toward the media layer is the first event, followed by formation of intraparietal microvascular networks) (Díaz-Flores et al., 1994a, 2011). These findings are reactive in nature, as occurs in IPEH (Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kuo et al., 1976), and not specific (Díaz-Flores et al., 1994a, 2011). Moreover, the unorganized thrombotic zones partially filled the vein lumen, and some of their free thrombotic surfaces were also endothelialized from the vein intimal endothelium.

Intravascular lesion formation and attachment to the vein wall

Interestingly, in IPEH, the vein wall is focally affected (in patches), with invagination and fold

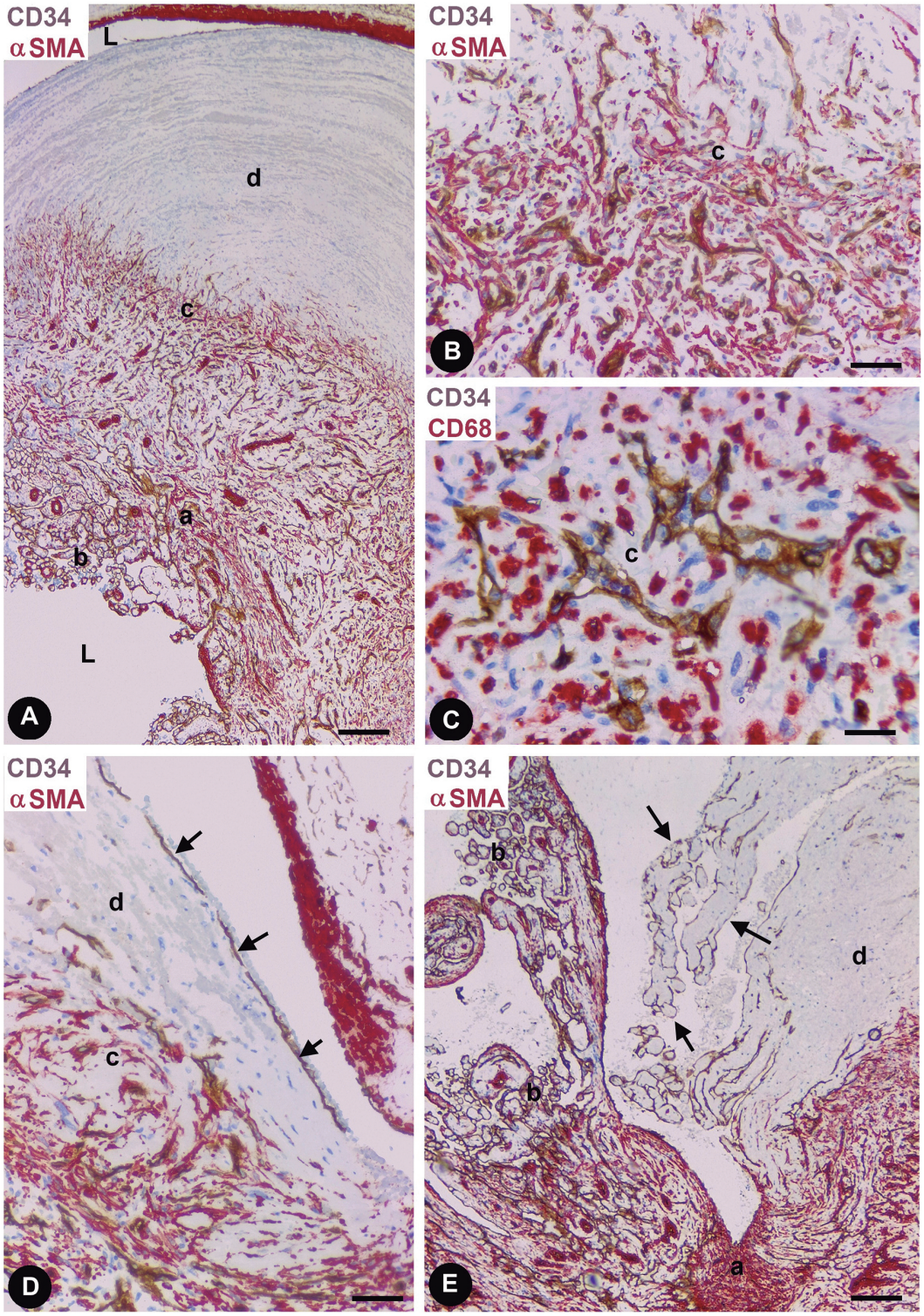

Fig. 4. Characteristics of thrombotic zones in IPEH. **A.** A thrombus (with and without organizing zones, c and d, respectively) is observed adjacent to the invaginated vein wall zone with microvascular networks (a). Note the papillary zone (b) in the opposite side. **B.** Organizing zone of the thrombus (c) with vascular buds showing CD34+ ECs. The buds at the bottom of the image also present αSMA+ pericytic-like cells, while at the top (in the border with unorganized thrombus), some of them only show ECs. **C.** In the organizing thrombotic zone, numerous CD68+ macrophages (red) are observed between vascular channels with CD34+ endothelial cells (brown). **D.** Observe a monolayer of CD34+ ECs that partially covers the luminal surface of the unorganized thrombotic zone (arrows). **E.** Formation of papillae in an unorganized thrombotic zone (arrows) originating from the ECs that cover its luminal surface. A, B, D and E: Double staining with anti-CD34 and anti-αSMA. C: Double staining with anti-CD34 and anti-CD68. Bars: A, E, 80 μ; B, D, 40 μm; C, 20 μm.

formation. In these folds, as in experimental conditions, most SMCs of the vein wall acquire pericyte-like characteristics (Díaz-Flores et al., 2009a) and form a subendothelial layer around the ECs of the growing vascular channels. The microvessel networks that parcelled the vein wall probably weaken its structure and, together with negative vein pressure, may facilitate wall invagination and fold formation. These invaginated vein wall zones with microvessel networks provide intraluminal support to other zones. On patch invagination, the neighbouring unaffected vessel wall (with normal cell components in the intima, media, and adventitia - Díaz-Flores et al., 2014) converges to form stalks.

Mechanisms of papillary formation

Vein intimal ECs and those originating from them (in newly-formed vessels in the vein itself and covering unorganized thrombi) also intervene in the mechanism of papilla formation. Thus, ECs encircle vein wall or thrombus components (parcelling the vein wall or thrombi), giving rise to isolated, apparently free papillae (parietal and thrombotic papillae, respectively) by a piecemeal mode of angiogenesis, by which ECs form the cover and encircled components the core. Likewise, the components of the core of parietal papillae may vary, depending on the depth of microvessel penetration in the vein wall (penetration is scant when papillae with little stromal support are formed). Moreover, by this mode of piecemeal angiogenesis, successive series of secondary papillae can form over the primary papillae, originating myriad papillae. The piecemeal angiogenic mechanism of vascular network with papillae formation described herein combines findings of sprouting and intussusceptive angiogenesis (Díaz-Flores et al., 1994b; Patan, 2000, Patan et al., 2001; Burri et al., 2004). Likewise, anastomosing vascular channels in the invaginated vein wall also contribute to thrombus organization in a non-papillary fashion (organized thrombotic zones) with some characteristics of repair through granulation tissue (proliferation of small blood vessels and macrophages recruitment) (Díaz-Flores et al., 2009b).

Another question is whether this response occurs as an unusual repair in a previous thrombus (Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kumar et al., 2004; Murugaraj et al., 2010; Shih et al., 2012; Akdur et al., 2013; Guledgud et al., 2014), or a primary proliferation of ECs followed by thrombosis and organization (Masson, 1923), at least in some instances (Kuo et al., 1976). Our observations support a pathogenesis of IPEH based on the inherent ability of activated veins to develop numerous microvessel networks in their own walls (Díaz-Flores et al., 1994a, 1994b, 2011) or in thrombi from their intimal ECs, forming invaginated vein wall zones and papillae. Given its characteristics, we consider the term "piecemeal mode of angiogenesis" appropriate for this process. This mechanism encompasses the two aforementioned possibilities of IPEH formation (Masson, 1923; Salyer and Salyer, 1975; Clearkin and Enzinger, 1976; Kumar et al., 2004; Murugaraj et al., 2010; Shih et al., 2012; Akdur et al., 2013; Guledgud et al., 2014) and may explain the onset of the lesion by thrombosis (Steffee and Iskandar, 1996), the absence of thrombosis in some lesions (Kuo et al., 1976), multiplicity and occasional recurrence (Cozzutto et al., 1979; Avellino et al., 1999), and occurrence in lymphangiomas (Kuo et al., 1976). Further studies are needed to accurately identify the agents (which may include thrombosis) that trigger the peculiar exuberant EC response in IPEH.

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