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# Myriad pillars formed by intussusceptive angiogenesis as the basis of intravascular papillary endothelial hyperplasia (IPEH). IPEH is intussusceptive angiogenesis made a lesion

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**Summary.** Intussusceptive angiogenesis (IA) is the process by which pre-existing blood vessels split, expand and remodel through intravascular pillar formation. In previous works, we studied the morphologic characteristics of intravascular papillary endothelial hyperplasia (IPEH) and suggested the participation of IA in the histogenesis of the lesion. Our current goal is to demonstrate that myriad papillae in IPEH are in fact myriad pillars, the hallmarks of IA. For this purpose, specimens of 14 cases of IPEH were used for conventional histologic techniques, immunohistochemistry and immunofluorescence in confocal microscopy. The studies showed the following pillar characteristics: a) structural composition by an endothelial cell (EC) cover and a connective core, b) characteristic pillar image and its appearance and disappearance in whole-mounted and series of individual views in confocal microscopy (requirements for pillar identification), c) arrangement in masses, alignments and meshes, and d) formation from vein intimal ECs, which extend and originate loops that encircle vein wall components (interstitial tissue structures: ITSs) and fibrin. The encircling ECs form the pillar cover and the encircled ITSs or fibrin form the initial core. Intraluminal endothelial bridges also originate from the vessel wall and from the pillars (nascent and thin pillars). In conclusion, the formation of myriad pillars, predominantly in veins, is the basis of IPEH. This lesion may therefore be considered an excessive expression of IA: IA becomes a lesion.

**Key words:** Intussusceptive angiogenesis, Endothelial cells, Vein wall vascularization

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## Introduction

The two principal mechanisms of angiogenesis occur by sprouting and intussusception. Intussusceptive angiogenesis (IA) is the process by which pre-existing blood vessels split, expand and remodel through the intraluminal formation of tiny pillars (≤2.5 $\mu$m in diameter), large pillars (>2.5 $\mu$m in diameter) and folds. Pillars, the demonstration of which requires identification in 3D images, are therefore the principal indicator (hallmark) of IA. Sprouting and intussusception can be complementary mechanisms, with synergistic interaction (Djonov et al., 2000; Hlushchuk et al., 2011; Peebo et al., 2011; Konerding et al., 2012; Díaz-Flores et al., 2017a; Karthik et al., 2018).

In recent studies (Díaz-Flores et al., 2016, 2018a), we assessed the morphologic characteristics of intravascular papillary endothelial hyperplasia (IPEH), a term coined by Clearkin and Enzinger in 1976 and currently in use, although it has received several names since its initial description as 'hémangio-endothéliome végétant intravasculaire' by Masson in 1923. This lesion commonly occurs in dilated veins and must be differentiated from blood vessel tumours, principally from angiosarcoma (Clearkin and Enzinger, 1976; Kuo et al., 1976; Hashimoto et al., 1983; Pins et al., 1993). The primary finding in IPEH is the presence of

numerous papillae in the vein lumen. In our studies on IPEH, we hypothesized that endothelial cells (ECs) of the vein intima extend into the vessel wall and around fragments of fibrin, encircle and separate vein wall components or fibrin or both and originate papillae by a piecemeal mechanism possibly related to IA. Indeed, we suggest that papillae described in IPEH are similar to pillars described in IA. If this is the case, IPEH, a reactive process rather than a tumour, could be considered an exacerbated intussusceptive angiogenic response (presence of myriad pillars) and therefore an excellent substrate for future studies on the mechanisms of intussusception.

With the above in mind, the aim of this work is a) to study the characteristics of the so-called papillae in IPEH and whether they comply with requirements to be considered intussusceptive pillars and b) to explore pillar arrangement and the morphologic findings related to pillar formation.

## Materials and methods

### *Tissue samples*

We used samples from 14 cases of IPEH, 12 from a previous study (Díaz-Flores et al., 2016) to which we added two new cases. All the samples were obtained after searching the archives of Histology and Anatomical Pathology of the Departments of Basic Medical Sciences of La Laguna University, University Hospital, and Eurofins® Megalab-Hospiten Hospitals of the Canary Islands, for the period 2005-2019. Paraffin blocks were made from surgical specimens of 14 Caucasian patients: 6 males and 8 females, aged between 8 and 71 years. Ethical approval for this study was obtained from the Ethics Committee of La Laguna University (Comité de Ética de la Investigación y de Bienestar Animal, CEIBA2020-0376), including the dissociation of the samples from any information that could identify the patient. The authors therefore had no access to identifiable patient information.

### *Light microscopy*

Specimens for conventional light microscopy were fixed in a buffered neutral 4% formaldehyde solution, embedded in paraffin and cut into 3 μm-thick sections. Sections were stained with Haematoxylin and Eosin (H&E) or Trichrome staining (Roche, Basel, Switzerland. Ref. 6521908001).

### *Immunohistochemistry*

Histologic sections, 3 μm-thick, were 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 monoclonal mouse anti-human, clone QBEnd-10 (dilution 1:50), catalog No. IR632 and alpha-smooth muscle actin (αSMA) monoclonal mouse anti-human, clone 1A4 (dilution 1:50), catalog No. IR611. 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®. For external positive and negative controls, we used the cecal appendix, which contained positive and negative tissue components for the target antigens explored. For the double immunostaining, we used anti-CD34 antibody (diaminobenzidine, DAB, as chromogen) to highlight CD34+ ECs and anti-αSMA (aminoethyl-carbazole, AEC, substrate-chromogen) for anti-αSMA+ pericytes/smooth muscle cells.

### *Immunofluorescence in confocal microscopy*

For immunofluorescence, tissue sections (10 μm-thick) were obtained as described above. For antigen retrieval, sections were deparaffinized and boiled for 20 minutes in sodium citrate buffer 10 mM (pH 6), rinsed in Tris-buffered saline (TBS, pH 7.6, 0.05 M), and incubated with the following primary antibodies diluted in TBS overnight in a humid chamber at room temperature: mouse monoclonal anti-CD34, code no. IR63261 (ready-to-use), and rabbit polyclonal anti-collagen type I (1/100 dilution, code AB749P, Millipore). For double-immunofluorescence staining, sections were incubated with a mixture of monoclonal and polyclonal primary antibodies (mouse monoclonal anti-CD34 and rabbit polyclonal anti-collagen type I). The next day, the slides were rinsed in TBS and incubated for one hour at room temperature in the dark with the secondary biotinylated goat anti-rabbit IgG (H+L) (1:500, Code: 65-6140, Invitrogen, San Diego, CA, USA) and Alexa Fluor 488 goat anti-mouse IgG (H+L) antibody (1:500, Code: A11001, Invitrogen), followed by incubation with Streptavidin Cy3 conjugate (1:500, Code: SA1010, Invitrogen) for one hour at room temperature in the dark. Nuclei were detected by DAPI staining (Chemicon International, Temecula, CA, USA). Sections were washed in TBS and exposed to a saturated solution of Sudan black B (Merck, Barcelona, Spain) for 20 minutes to block autofluorescence. They were rinsed in TBS and cover-slipped with DABCO (1%) and glycerol-PBS (1:1). Negative controls were performed in the absence of primary antibodies. Fluorescence immunosignals were obtained using a Fluoview 1000 laser scanning confocal imaging system (Olympus Optical).

## Results

### *General characteristics of IPEH*

The lesions were always well circumscribed and confined to dilated vessels (Fig. 1A,B), in which their

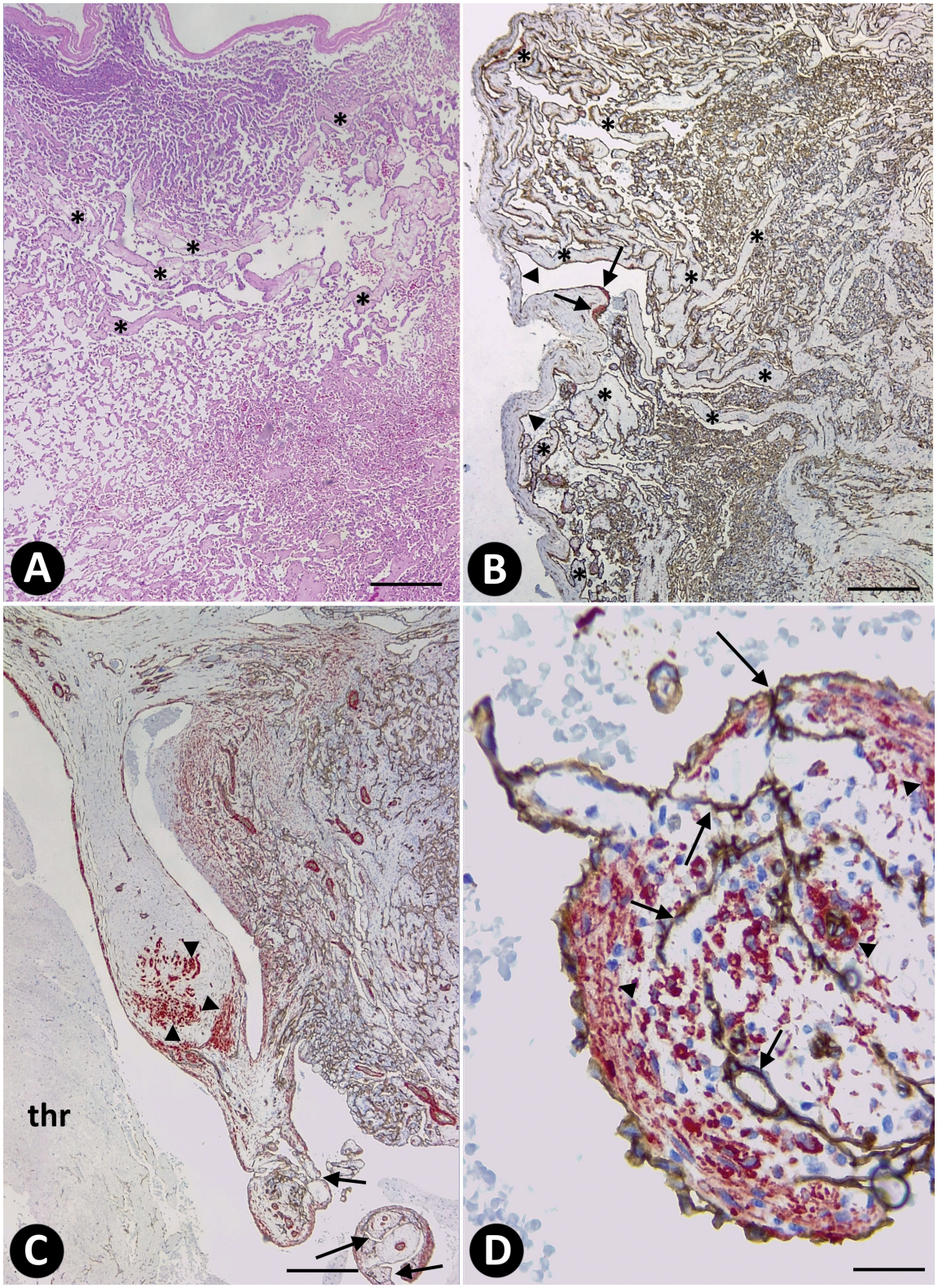


**Fig. 1. A, B.** General characteristics of intravascular papillary endothelial hyperplasia (IPEH). Panoramic views of vein portions affected by IPEH. Note that the lesions are confined to dilated veins whose walls are fibrotic, presenting isolated groups of αSMA+ cells (SMCs) (**B**, arrows) and in the internal layer CD34+ ECs (**B**, arrowheads). Folds, also covered by ECs, are observed arising from the vein wall (**A, B**, asterisks). Myriad pillars are present between the folds. **C, D.** Details of folds presenting a core with connective tissue and group of αSMA+ cells (arrowheads) and intra-fold extensions of vein covering ECs (arrows). An unorganized thrombus is observed in **C** (thr). A: H&E staining. B-D: Double-stained sections with anti-CD34 (brown) and anti-αSMA (red). Scale bars: A-C, 160 $\mu$m; D, 100 $\mu$m.

walls showed an internal layer formed by ECs expressing CD34 (Fig. 1B), a medial layer with varying numbers of αSMA+ smooth muscle cells (SMCs), ranging from numerous to few and forming small isolated groups (Fig. 1B), and a generally fibrosed, external layer, with CD34+ stromal cells. The vessel walls presented numerous intraluminal folds, which varied in length and size (Fig. 1B). In the sections, the folds appeared as giant pillars (Fig. 1), were covered by CD34+ ECs (Fig. 1D), and showed a core formed by connective tissue and varying numbers of αSMA+ cells (Fig. 1B-C). The folds were frequently divided by intra-fold extensions of the covering ECs (Fig. 1C-D). Thrombi were generally present, with or without organization (Fig. 1C). Myriad pillars were located between the folds (Fig. 1A-C and Fig. 2A).

### *Size and structural characteristics of pillars*

Pillars varied from small (≤2.5 $\mu$m in diameter) to large (>2.5 $\mu$m in diameter) and giant (intraluminal folds of the vein wall) (Fig. 2A), and showed a cover and a core. The pillar cover is formed by ECs, which were CD34+ (Fig. 2B-D and Fig. 3A). Pillar cores contained packed collagen fibres (Fig. 3B-H) and some of them fibrin (Fig. 3D), αSMA+ cells (pericytes and/or vascular SMCs, or their processes) (Fig. 2B-C) and fibroblasts/myofibroblasts. In addition to these components, large pillars could contain other interstitial cells and blood vessels of varying size (Fig. 4A, insert). In confocal microscopy, collagen type I was demonstrated in the pillar core (Fig. 3E-H and Fig. 4B-K).

### *Identification of pillars and pillar arrangement*

In confocal microscopy, we observed the appearance and disappearance of pillars in series of individual views (Fig. 3E-G and Fig. 4C-K) and the characteristic pillar image in the whole-mount view (Fig. 3H and Fig. 4B). By this procedure, the pillars appeared forming meshes and pillar groups, which frequently acquired an arboriform aspect (Fig. 4B-K) (see below). Likewise, pillars that appeared isolated in 2D sections could be observed connected to other pillars in whole-mounted images.

Pillars in the irregular groups, meshes and alignments could form intravascular septa (Fig. 2 to Fig. 4) and were joined by contact of their covering ECs (Fig. 4A), core-to-core (Fig. 2B and Fig. 3A) and/or by thin pillars, which appeared transversely, obliquely or longitudinally sectioned (Fig. 2B-D, Fig. 3 and Fig. 4). The thin pillars were also observed joining several large pillars (Fig. 3A). Joined or divided pillars with secondary pillars were often seen, resembling segmented cactus and their cladodes (Fig. 4A).

### *Findings related to pillar formation and IPEH morphology*

In the venous wall and underlying zones, the main morphologic findings related to pillar formation in IPEH included a) extension of vein intimal ECs through the wall of the vein itself, giving rise to loops and subsequently large pillars and folds and b) EC extensions from the large pillars giving rise to nascent and thin pillars, which contact with other pillars.

In the first case in which loops participate (dissecting loops that originate pillars through a piecemeal process), each loop was formed by bilayers of intimal ECs, which emerge from two points of the vein (connecting segments) (Fig. 5A) and encircle a portion of the vascular wall (interstitial tissue structures: ITSs) (Fig. 5A). In some areas, extensions of intimal ECs were also seen surrounding fibrin fragments (see above) (Fig. 3D). ITSs, surrounded by the internal EC layer of the loops, projected into the vein lumen, originating intraluminal pillars (mainly large pillars) (Fig. 5B). The external EC layer of each loop lined the tissue from which the ITS was segregated. Although the large pillars appeared intraluminal, they remained partially connected to the vein wall (Fig. 5B). Regions of the vein wall with numerous loops were frequently seen surrounding ITSs (Fig. 5C). Pillar core content varied depending on the tissue component surrounded by the loop. Thus, it could show numerous vascular SMCs (Fig 5A) or fibrotic tissue (Fig. 5D). Folds (giant pillars) were also formed by ECs and SMCs/fibrotic tissue extending through the vein wall (Fig. 5E). EC extensions through giant and large pillars formed new pillars (secondary pillars by splitting) (Fig. 5F). Convergent loop lumens were seen forming complex loop systems, which appeared intercommunicated or separated by large or thin pillars in serial individual views in confocal microscopy (Fig. 5G-J). Simultaneously, EC filopodial ridges (nascent pillars) and very thin pillars, which originated from the large pillars or from the vein wall, interconnected large pillars (Fig. 5K and 5L). Finally, the aggregation of and increase in all previously exposed tissue components resulted in the characteristic image of IPEH (Fig. 5M).

## Discussion

In this work, we demonstrate that the papillae in IPEH meet the requirements for being considered intussusceptive pillars, which therefore supports the existence of an angiogenic intussusceptive mechanism in IPEH development. In addition, we confirm the morphological and immunohistochemical characteristics of the pillars. Finally, we report pillar arrangement and features related to pillar formation in IPEH.

3D observation of the characteristic image of pillars and their appearance and disappearance in successive serial views is required to accurately demonstrate these structures (Burri and Tarek, 1990; Burri, 1992; Djonov et al., 2000, 2002, 2003; Burri and Djonov, 2002; Burri et al., 2004; De Spiegelaraere et al., 2012; Logothetidou et al., 2018). The procedure for meeting these requirements generally involves vascular corrosion casting using scanning electron microscopy (recognition

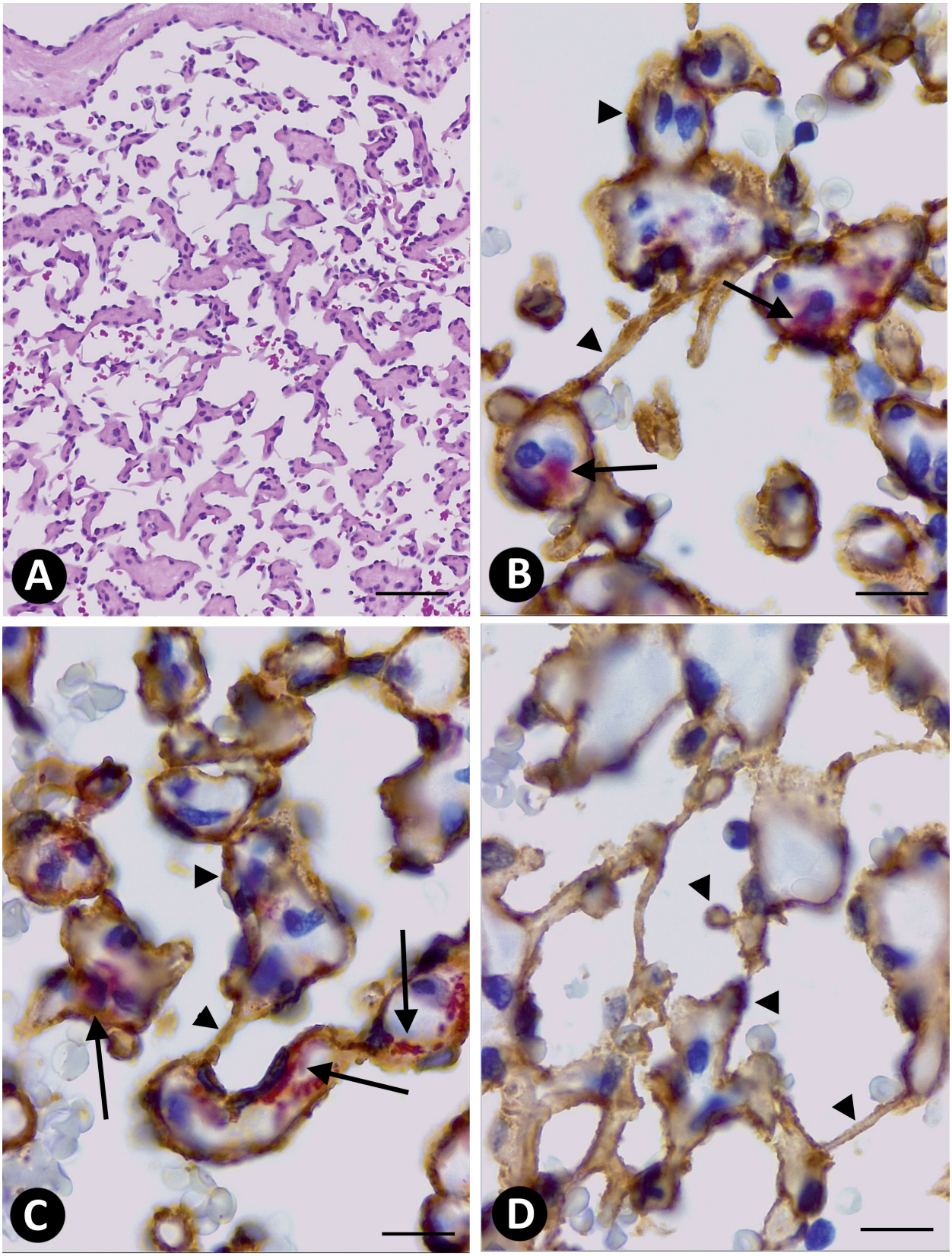


**Fig. 2.** Numerous pillars of varying size are observed in sections stained with H&E **(A)** and double immunostained with anti-CD34 (brown) and anti-αSMA (red) **(B-D)**. Pillars show a cover formed by CD34+ ECs (**B-D**, arrowheads) and a core in which αSMA+ cells or their processes can be seen (**B-C**, arrows). Note thin pillars joining larger pillars and together forming networks **(B-D)**. Scale bars: A, 100 $\mu$m; B,C, 10 $\mu$m; D, 15 $\mu$m.

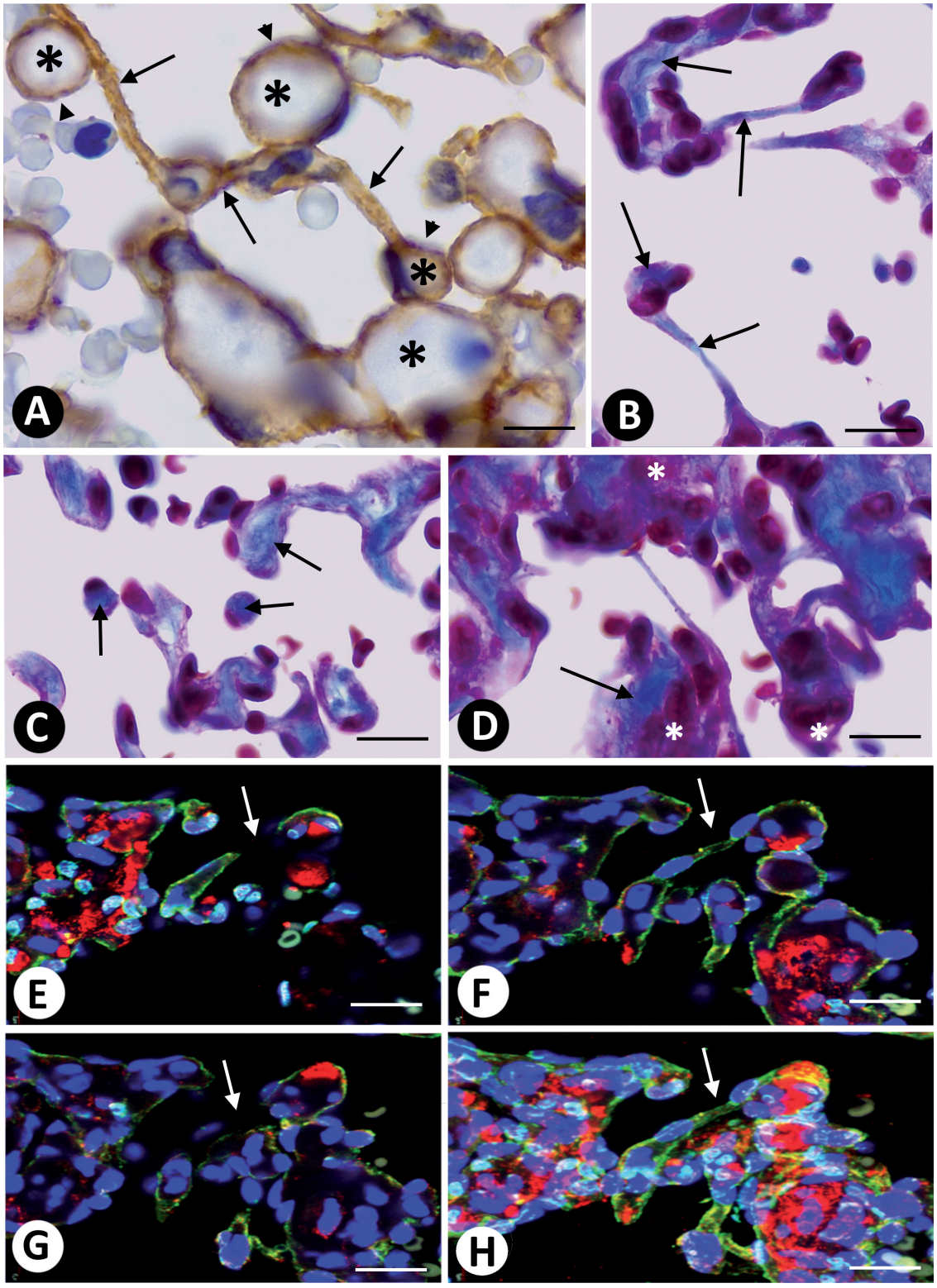


**Fig. 3. A.** A thin pillar (arrows) is observed joining several larger pillars (asterisks). Note CD34+ ECs forming the cover of pillars (arrowheads). **B-D.** Blue-stained collagen is seen in the core of large and thin pillars (arrows). Observe in **D** the presence of red-stained fibrin (white asterisks) associated with collagen (arrow) in some pillar cores. **E-H.** Collagen I (red) in the core of pillars and ECs (green) in the cover of pillars in confocal microscopy. Demonstration of the appearance and disappearance of a thin pillar in individual views (**E-G**, arrows) and its image in a whole-mount view (**H**, arrow). A: Double immunostaining with anti-CD34 (brown) and anti-αSMA (red). B-D: Masson trichrome staining. E-H: Pillars observed in confocal microscopy in individual **(E-G)** and whole-mount view **(H)** of a section (10 $\mu$m) immunostained with anti-CD34 (brown) and anti-collagen I (red). Scale bars: A, 10 $\mu$m; B-H, 15 $\mu$m.

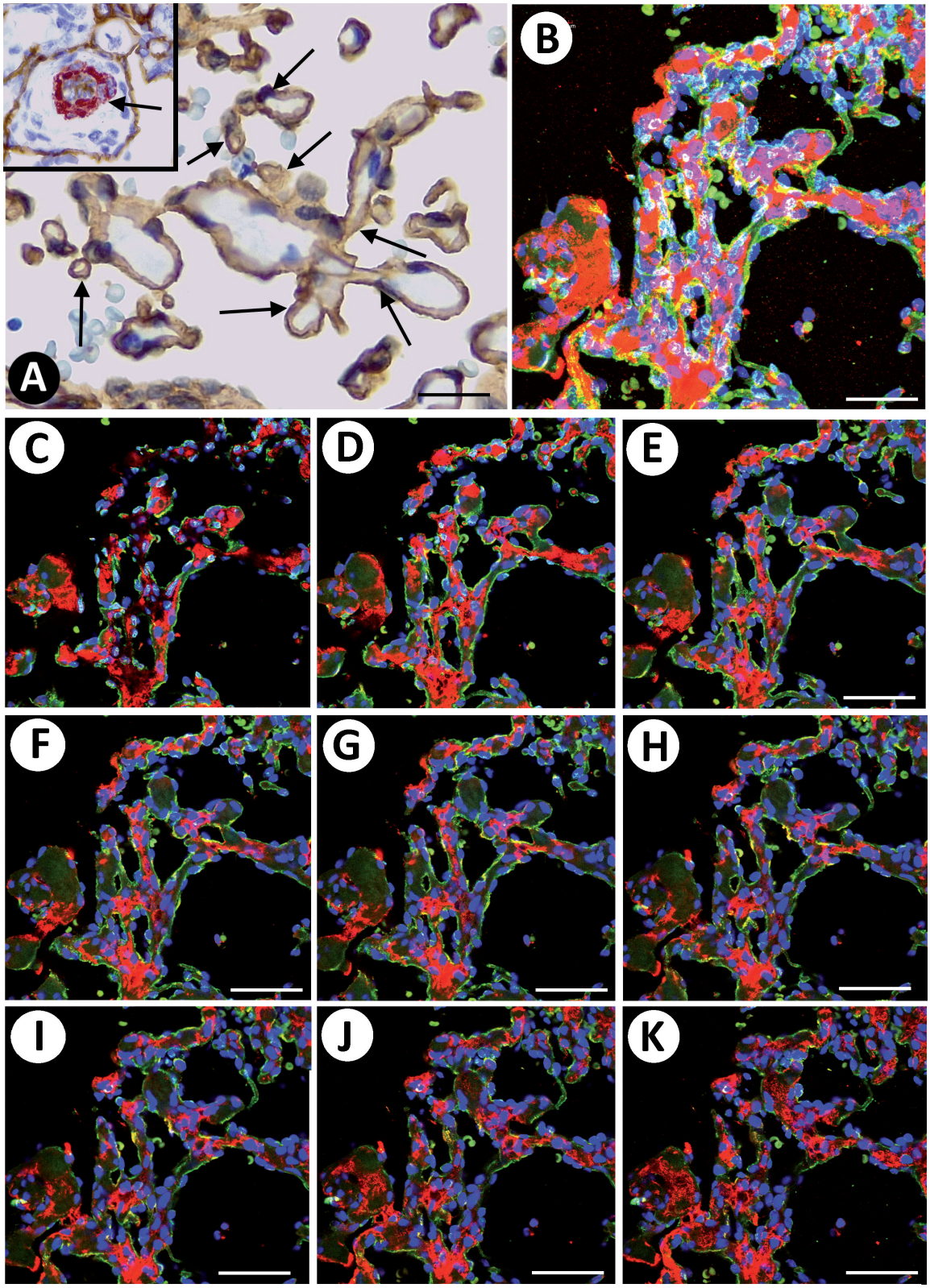


**Fig. 4. A.** Secondary pillars (arrows) are observed resembling segmented cactus with rounded cladodes. Insert of **A.** Presence of a vessel (arrow) in the core of a large pillar. **B-K.** Arborized form of a group of pillars observed in a whole-mount view **(B)** and in individual views **(C-K)** in confocal microscopy. Note the appearance and disappearance of several pillars in individual views in some of these pillars in the whole-mounted view. A and insert: Double-stained sections with anti-CD34 (brown) and anti-αSMA (red). B-K: Sections (10 $\mu$m) in confocal microscopy immunostained with anti-CD34 (brown) and anti-collagen I (red). Scale bars: A, 20 $\mu$m; B-K, 15 $\mu$m.

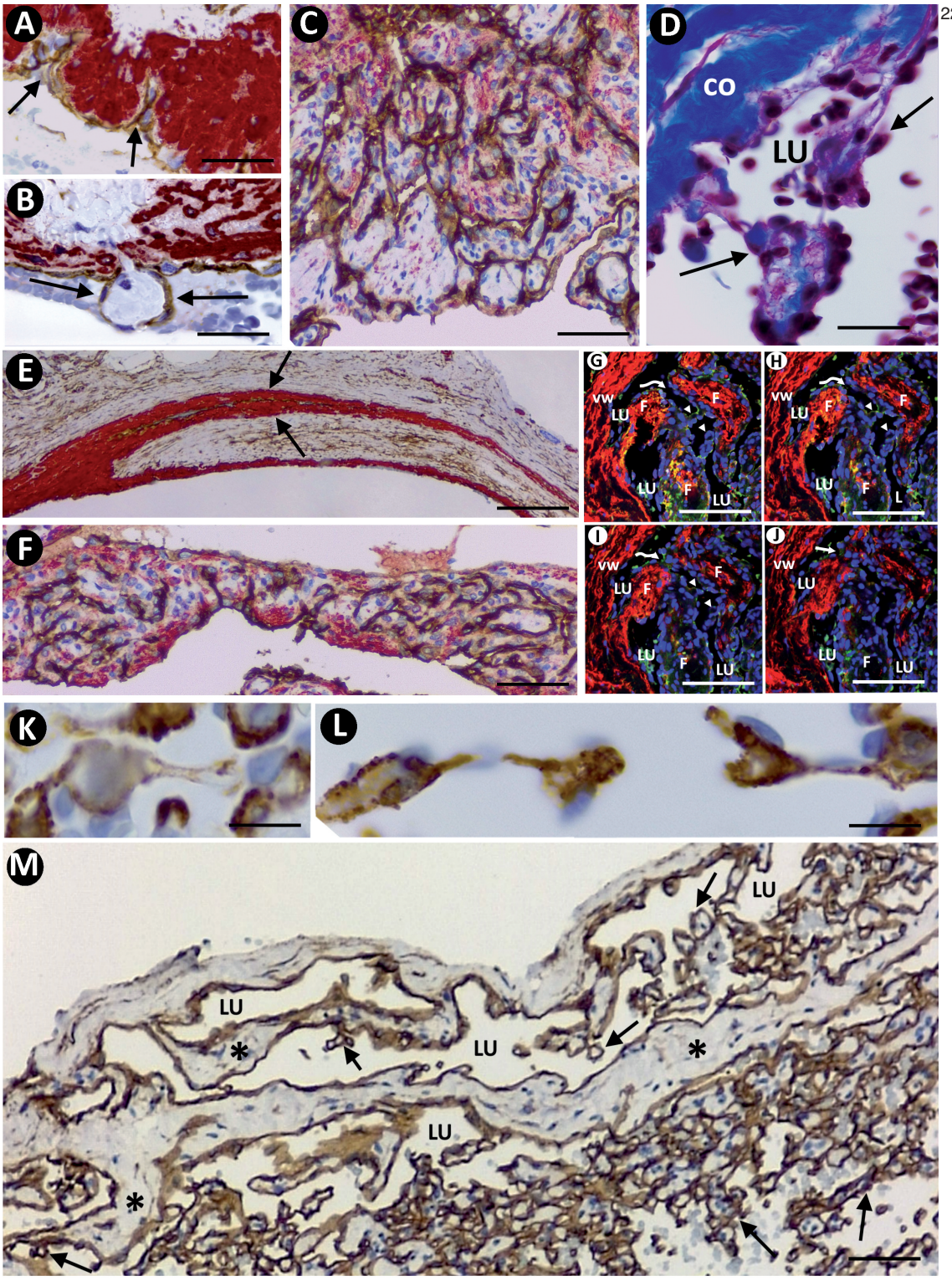


**Fig. 5.** Morphologic findings related to formation of pillars and folds in IPEH. **A.** Extension of vein intimal ECs (arrows) through the vein wall starting the formation of a loop. Note that the encircled components of the media layer (smooth muscle cells, SMCs) form a core or ITS. **B.** Intraluminal projection from the vein wall forming a pillar (arrows), in which encircling ECs and a core (ITS) with scarce cells is seen. **C.** Numerous extensions of vein intimal ECs surrounding components of the media layer (ITSs). **D.** Pillars (arrows), formed from a fibrotic vein layer (blue-stained collagen: CO; distended lumen of a loop: LU). Note that the pillars are partially connected to the vein wall. **E.** Initial stage of formation of large fold (giant pillars) from the vein wall, with an intraparietal extension of the vein endothelium and SMCs (arrows). **F.** Evolved stage of a large fold with separation from the venous wall and presence of numerous EC invaginations. **G-J.** Individual views in a section (10 $\mu$m) in confocal microscopy immunostained with anti-CD34 and anti-collagen I. Depending on the individual views, dilated lumens of loops in the vein wall appear intercommunicated or separated by large (arrow) or thin (arrowheads) pillars, thereby forming complex loops. **K, L.** Nascent pillars formed between other pillars. **M.** Large luminal spaces (LU) formed by dilated complex loops, delimited by folds (asterisks) separated from the vein wall and with numerous varying size pillars (arrows). Note the loose and dense association of the intraluminal pillars. A, B, C, E and F: Double immunostained sections with anti-CD34 (brown) and anti-αSMA (red). D: Stained with Masson trichrome (blue). G-I: sections (10 $\mu$m) in confocal microscopy immunostained with anti-CD34 and anti-collagen I. K-M: Immunostained with anti-CD34 (brown). Scale bars: A-C, E, 100 $\mu$m; D, 60 $\mu$m; F, 80 $\mu$m; G-J, 15 $\mu$m; K-L, 10 $\mu$m; M, 80 $\mu$m.

of holes) (Caduff et al., 1986) but is difficult to undertake in a lesion like IPEH in humans. Given this difficulty, we used thick tissue sections (10 $\mu$m), immunostained with markers for ECs, vascular mural cells and collagen, observed in confocal microscopy, obtaining serial individual views and images in whole-mount views. By this procedure, in structures denominated papillae by pathologists, we demonstrated the characteristic image of pillars and their appearance and disappearance. This demonstration was carried out in meshes and arboriform structures in the lesion.

Papillae also showed structural characteristics of

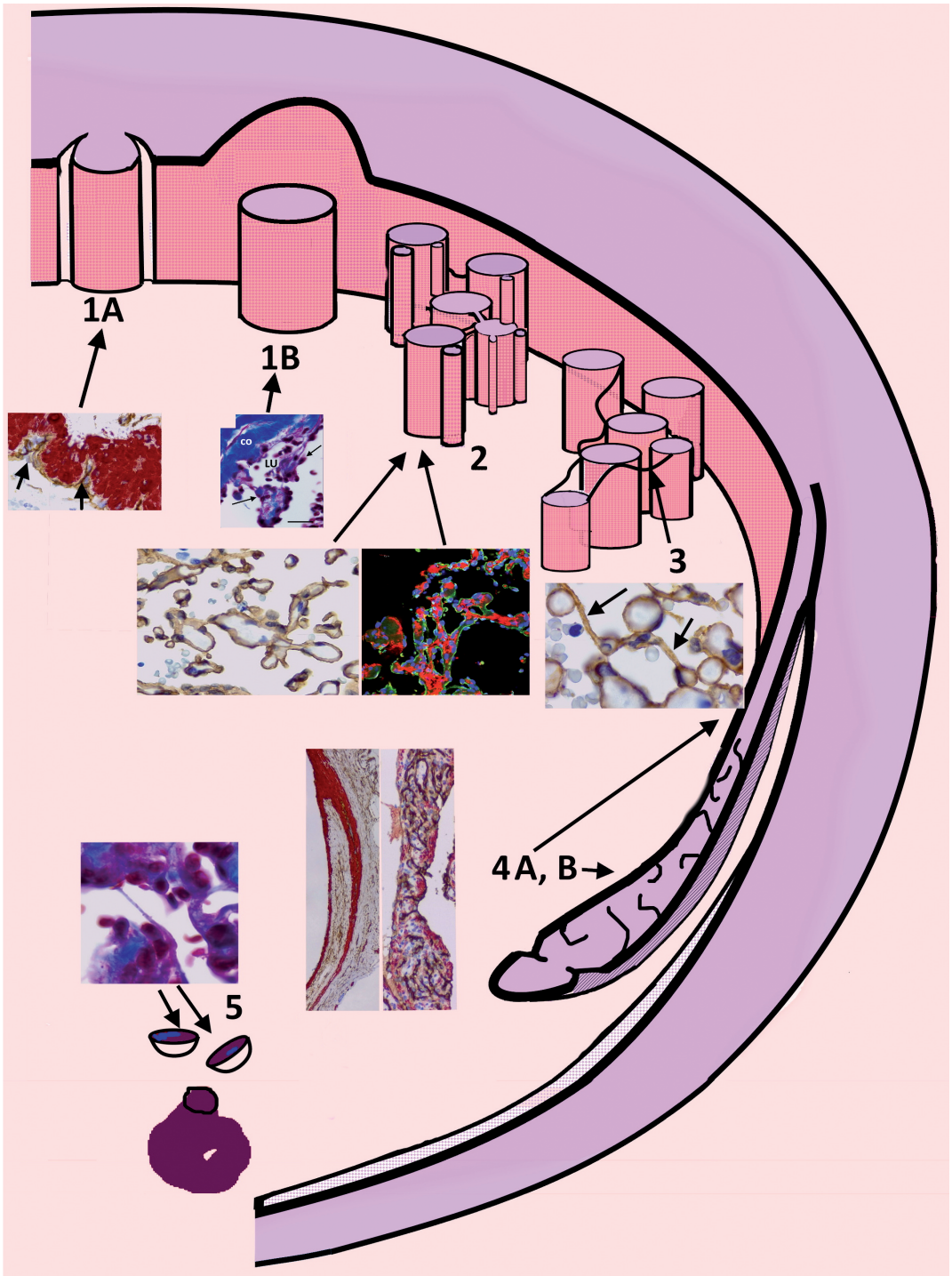


**Fig. 6.** Schematic representation of the main mechanisms of pillar and fold formation in IPEH. **1.** Pillar formation by loops. Extensions of intimal ECs in the wall of a blood vessel originate loops that encircle ITSs (**1A**). The inner layer of each loop (forming the pillar cover) and the ITS (forming the pillar core) are pushed to the vessel lumen when the loop lumen is open (**1B**). In some areas the pillar core remains in continuity with the vessel wall, especially at pillar ends (not shown in diagram). **2.** Pillar formation by pillar splitting. New pillars can be formed by the same procedure outlined for other pillars. **3.** Pillar formation by endothelial bridges. Endothelial bridges between the vein wall and pillars or between pillars originate nascent and thin pillars by a procedure that resembles transcapillary pillar formation. **4.** Giant pillar formation from folds of the vessel wall. Mechanisms 1, 2 and 3 also arise from the folds (giant pillars). **5.** Pillar formation by extension of ECs around fragments of fibrin.

pillars (Caduff et al., 1986; Burri and Tarek, 1990; Burri, 1992; Djonov et al., 2000, 2002, 2003; Patan et al., 2001a,b; Burri and Djonov, 2002; Kurz et al., 2003; Burri et al., 2004; Patan, 2008; Makanya et al., 2009; Konerding et al., 2010, 2012; Paku et al., 2011; De Spiegelaere et al., 2012; Ribatti and Djonov, 2012; Ackermann et al., 2013, 2014; Mentzer and Konerding, 2014; Föhst et al., 2015; Díaz-Flores et al., 2017a,b; Hlushchuk et al., 2017), with the presence of a cover formed by ECs and a core with connective tissue. Thus, pillar cores (≤ 2.5 $\mu$m in diameter) contain collagen material, whereas larger pillars (> 2.5 $\mu$m in diameter) contain a core with more collagen, interstitial cells (mural vascular cells, myofibroblasts or migrating cells) and on occasion blood vessels. In recent studies, we demonstrated the presence of pillars with a similar structure in different processes of lymphatic vessels and in the sinuses of developing lymph nodes (Díaz-Flores et al., 2019a,b,c).

In vessels in which intussusception occurs, pillars can form meshes and alignments. In IPEH, the expression of these phenomena is greater, depending on the high number of pillars occupying the intravascular lesion and forming intricate masses. The presence of foci in which pillars are arranged more loosely has enabled us to examine pillar contacts, including contacts by covering ECs, core-to-core and primarily contacts established between large pillars through nascent and thin pillars. In addition, the predominance of irregular meshes and dense groups, alternating with focal linear arrangements of these papillary structures, now identified as pillars, lends an IPEH morphology to most of the lesion and a sinusoidal hemangioma-like aspect in occasional foci (Díaz-Flores et al., 2018a). Likewise, this varying arrangement of the pillars that leads to zonal differences in lesion morphology suggests a possible morphogenic action of IA in vessel tumours and pseudotumours. Linearly arranged pillars in IPEH forming intravascular septa show a similar aspect to those previously described in dilated hemorrhoidal veins in hemorrhoidal disease (Díaz-Flores et al., 2018b). Curiously, the initial description of IPEH by Masson (1923) was undertaken in a hemorrhoidal vein.

As far as the formation facts of the pillars are concerned (Fig. 6), the presence of vein intimal ECs originating loops that encircle vein wall components (ITSs) supports pillar formation by these loops, which give rise to pillars/papillae when the encircling ECs and the encircled ITSs are transported to the vein lumen. For a similar process in an experimental model, we have used the denomination 'piecemeal mechanism' (Díaz-Flores et al., 2017a,b). The vein intimal ECs can also surround fragments of thrombotic fibrin in IPEH (thrombosis is a common finding in IPEH). Therefore, pillars in IPEH are formed by a mechanism, which depends on loops in the vessel wall arising from extensions of the intimal ECs (Patan et al., 2001a,b) (parietal pillars) or on a simple extension of ECs around fibrin fragments (thrombotic pillars). New pillars can be formed by the same procedure from other pillars (splitting mechanism). Likewise, the formation of endothelial bridges (nascent and thin pillars) between the vein wall and pillars or between pillars resembles classic transcapillary pillar formation (Burri and Djonov, 2002; Burri et al., 2002). By this mechanism endothelial bridging occurs with endothelial intercellular junction reorganization and EC bilayer formation, followed by perforation of the EC bilayer and transport of collagen bundles into this perforation, in which processes of myofibroblasts and pericytes can also penetrate (Burri and Tarek, 1990; Burri, 1992; Djonov et al., 2000, 2002, 2003; Patan et al., 2001a,b; Burri and Djonov, 2002; Burri et al., 2004; Paku et al., 2011). The suction and subsequent transport of collagen bundles in nascent pillars involves a pulling force exerted by the actin cytoskeleton of ECs (Paku et al., 2011).

In IPEH, vein thrombosis, among other possible factors, can induce blood flow changes and the formation of numerous pillars, which can also facilitate flow changes, determining a vicious circle that influences the development of new pillars with different patterns in the lesion. Indeed, the formation of pillars is linked to hemodynamic conditions (Djonov et al., 2002; Turhan et al., 2008; Filipovic et al., 2009; Miele et al., 2009; Tsuda et al., 2009; Lee et al., 2011; Ackermann et al., 2013; Föhst et al., 2015), including the influence of intraluminal flow fields (Turhan et al., 2008; Tsuda et al., 2009; Lee et al., 2011; Ackermann et al., 2013). Likewise, hemodynamic changes can modify EC behaviour as occurs by down regulation of angiopoietin 2 (Tressel et al., 2007). VEGF expression correlates with thrombus remodelling in IPEH (Kim et al., 2013), and the therapeutic overexpression of VEGF in skeletal muscle (in a limited amount of extracellular matrix) blocks the formation of a gradient to induce sprouting angiogenesis (Gianni-Barrera et al., 2013). Therefore, in these conditions VEGF induces intussusception rather than sprouting angiogenesis. A similar mechanism could occur in the limited vascular space in which IPEH develops.

In conclusion, IA is the basis of IPEH, in which the formation of intraluminal pillars (principally intravenous) is markedly excessive, and the lesion adopts a papillary pattern. Therefore, IPEH may be considered as IA becomes a lesion. Likewise, given the high expression of intussusceptive phenomena (myriad pillars), IPEH is an appropriate substrate for future studies on IA mechanisms.

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