Adding complexity to plexogenic arteriopathy

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In PAH, a wide range of abnormal pulmonary vascular manifestations exist, all arising from the endothelium http://ow.ly/IWH2305bXpQ

In a landmark paper in the field of pulmonary hypertension research, Donald Heath and Jesse Edwards, in 1958, described the pulmonary vascular pathology that accompanies severe forms of pulmonary hypertension [1]. Examining lung tissue samples from patients with pulmonary hypertension associated with congenital heart disease and patients with primary pulmonary hypertension (now called idiopathic pulmonary arterial hypertension (PAH)), they distinguished six grades of severity and introduced the term "plexiform lesions". Ever since, the plexiform lesions have been a subject of interest and of frequently contentious debates [2–5]. To touch on just a few of the unresolved issues and questions: why do these lesions form? How many of these lesions are present in a patient's lung and are they haemodynamically important? What are the cellular components and the cell(s) of origin? A few investigators continue to be bored by these questions and have concluded that these complex vascular lesions are important mostly as an entertainment to a handful of pathologists.

We believe that these signature lesions of severe forms of PAH are indeed very interesting. Firstly, they are unique to the lung and they can teach us about fundamental principles of vascular biology; for example, the first "law" of vascular biology that the endothelium must be a monolayer [6]. In the plexiform lesions, endothelial cells pile up and the law of the monolayer is broken. This fact opened the gates to further research that has led to the formulation of pathobiological hypotheses and concepts such as endothelial cell injury giving rise to the proliferation of apoptosis-resistant, phenotypically altered, lumen-obliterating cells: "misguided angiogenesis" and "wound healing gone awry" [7]. Indeed, these complex vascular lesions have taught us many lessons and their investigation has greatly enriched our knowledge of the spectrum of cellular responses of the lung circulation to chronic stress. Secondly, plexiform lesions are a hallmark of irreversible and generally very difficult to treat pulmonary vascular syndromes. This is certainly true in PAH and perhaps also in chronic thromboembolic pulmonary hypertension (CTEPH), where some authors have reported that the presence of plexiform lesions is associated with pulmonary hypertension that persists after thromboendarteriectomy [8] (while others have argued that plexiform lesions do not exist in CTEPH [9]). Thirdly, the concept that lumen-obliterating lesions, other than plexiform lesions, are indeed haemodynamically important has led to the search for animal models that present such lesions and are irresponsive to vasodilator treatment. These models are "two hit" models; for example, monocrotaline, the endothelial cell toxic alkaloid, plus high shear stress induced by pneumonectomy as described by Okada *et al.* [10], or the combination of the vascular endothelial growth factor (VEGF) receptor blocker Sugen 5416 plus chronic hypoxia [11]. Animal models that present with pulmonary vascular lumen obliteration and are not spontaneously reversible have been accepted as models for preclinical drug trials.

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Against this background, the article by Ghigna *et al.* [12] in this issue of the *European Respiratory Journal* is of great interest, because the authors report, in addition to the plexiform lesion, the presence in PAH of another typical vascular lesion: a relatively large vascular structure connecting the pulmonary arterial, bronchial and pulmonary venous vasculature. The authors describe such lesions as "singular millimetric fibro-vascular lesions", abbreviated SiMFis, and relate their presence to the occurrence of haemoptysis. Additionally, the authors provide quantitative data that distinguish the lung vascular pathology of patients with *BMPR2* mutations from that found in PAH patients not carrying such mutations [12]. In this histological study carried out on tissues derived after lung transplantation, *BMPR2* mutation carriers showed more bronchial arterial hypertrophy, along with more pronounced venous remodelling and greater presence of SiMFis. Prior to transplantation, *BMPR2* patients in the cohort had presented more often with episodes of haemoptysis, while other clinical (*e.g.* haemodynamic severity and New York Heart Association functional class) and histological (*e.g.* presence of plexiform lesions and perivascular inflammation) features were comparable between mutation carriers and noncarriers.

Anastomotic connections between the bronchial and pulmonary circulations are known to exist in the normal lung, and it was suggested previously that these anastomoses become functionally more important in CTEPH [13] and in PAH [14]. While in the latter paper, it was debated that plexiform lesions are perhaps the result of the development of anastomoses, the data from Ghigna *et al.* [12] seem to suggest that plexiform lesions and SiMFis occur independently. However, ultimate proof that plexiform lesions and SiMFis are unrelated would have to come from more extensive stereological studies of the PAH lung. A clear mechanistic answer to the question of how SiMFis arise is currently lacking, but a possible explanation could be VEGF-driven bronchial angiogenesis, which may have resulted from stabilisation of hypoxia inducible factor-1α due to local tissue ischaemia or perivascular inflammation. The connection between plexogenic vascular remodelling and the bronchial circulation is also intriguing from an experimental standpoint: it is well known that mice not only lack a bronchial circulation, but are also less prone to develop occlusive vascular remodelling in response to stimuli that generate PAH-like disease in rats [15].

Ghigna *et al.* [12] confirm a previously reported greater frequency of bronchial arterial hypertrophy and haemoptysis in *BMPR2* mutation positive patients [16]. The authors also demonstrate an association between *BMPR2* mutation status and the presence of SiMFis. Given the current state of understanding of *BMPR2* signalling, there is little reason to hypothesise that *BMPR2* mutations *per se*, through a yet unknown molecular mechanism, would lead to the formation of anastomoses and haemoptysis. The difference between mutated and idiopathic PAH patients was not categorical but rather quantitative. SiMFis and haemoptysis did occur in *BMPR2* mutation negative patients, albeit less frequently. The clinical data of the studied patients do not suggest more severe disease in *BMPR2* mutation carriers, but generally speaking, haemodynamic compromise and disease progression tend to be more severe in *BMPR2* mutation carriers [17]. Obviously, patients did not all undergo haemodynamic assessment right before the lung transplant, so *BMPR2* mutation carriers may have had more severe disease, which perhaps explained a greater frequency of SiMFis and haemoptysis.

The article by Ghigna *et al.* [12] is also remarkable from another point of view. The authors report lung transplantation in a number of patients in functional class II. Moreover, transplantation was carried out in a number of patients who were treated with a single oral drug. In these patients, transplantation was driven by the occurrence of severe haemoptysis. These cases demonstrate that haemoptysis is a life-threatening complication in PAH, which can necessitate transplantation despite the availability of medical treatment and bronchial arterial embolisation.

In conclusion, the complexity of plexogenic arteriopathy in pulmonary hypertension has become a little more complex with the recognition of bronchial hypertrophy and increased occurrence of bronchial–pulmonary anastomoses in PAH. Important questions that remain to be answered are not only whether *BMPR2* mutations indeed play a role in the development of these anastomoses, but also whether there is more overlap between conditions such as CTEPH, PAH pulmonary veno-occlusive disease and hereditary haemorrhagic telangiectasia-associated pulmonary vascular disease than currently appreciated, and whether the term "precapillary" pulmonary hypertension is still appropriate for patients with plexogenic arteriopathy. An overarching concept is perhaps emerging: there is a wide spectrum of abnormal pulmonary vascular manifestations that includes anastomoses, plexiform lesions, venous abnormalities and even sarcomatous changes in thromboendarteriectomy tissue samples [18], and they all may originate from the pulmonary vascular endothelium.

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