Intrapulmonary Bronchopulmonary Anastomoses and Plexiform Lesions in Idiopathic Pulmonary Arterial Hypertension

To the Editor:

Idiopathic pulmonary arterial hypertension (IPAH) is a rare and severe disease characterized by a progressive increase in pulmonary vascular resistance, right ventricular failure, and early death (1). The histopathology of IPAH includes marked medial, intimal, and adventitial thickening. Plexiform lesions, characterized by marked capillary proliferation, are pathognomonic of severe IPAH, are generally believed to be derived from pulmonary arteries (PAs), and may contribute to disease progression (2). Although IPAH is primarily a disease of the pulmonary circulation, many findings point to concomitant involvement of the bronchial circulation. Individuals with IPAH often show evidence of bronchial artery (BA) hypertrophy and prominent vasa vasorum (vasa) in the PA wall (3). These observations suggest active involvement of the bronchial circulation in the pathobiology of IPAH, which may also include involvement of preexisting intrapulmonary bronchopulmonary anastomotic pathways (IBAs). The anatomic basis of arterial and venous connections between the pulmonary and bronchial circulations has been extensively reported in humans (4). Prominent IBAs have recently been reported in diverse neonatal lung disorders, including alveolar capillary dysplasia (5), bronchopulmonary dysplasia (6), congenital diaphragmatic hernia (7), and meconium aspiration syndrome (8). Each of these developmental diseases is partly characterized by pathologically remodeled PAs with an abnormal lung microvasculature. As a result, prominent IBA could favor the shunting of blood away from the pulmonary bed through the IBA owing to high pulmonary capillary pressure, which may contribute to hypoxemia and disease progression.

In this study, we examined lung tissue from adult patients who died with severe IPAH to determine whether prominent IBAs are present in fatal IPAH and to further assess whether the bronchial circulation could contribute to the development of plexiform lesions. Lungs from five patients (three women; ages 22–51 yr) who died with severe IPAH were fixed for standard histology that included hematoxylin and eosin staining and immunostaining with CD31 and D2-40 to identify vascular and lymphatic endothelial cells, respectively. Serial sectioning of areas involved by plexiform and dilatation lesions were performed, and two computerized three-dimensional image reconstructions were done in two separate cases.

We found evidence of markedly dilated and congested bronchial circulation in each case (Figure 1A), and signs of peribronchiolar hemorrhage were observed (Figure 1A'). We also found widely patent connections between PAs and BAs (Figures 1B and 1C). Plexiform lesions were intimately associated and connected to the dilated and congested bronchial microvessels, including the vasa (Figures 1D–1F). Plexiform lesions appeared to be directly linked with bronchial veins (BVs) (Figures 1F and 1G). Some plexiform lesions were in very close proximity to open BA–PA anastomosis (Figures 1A and 1B). Plexiform and dilatation lesions appeared to be directly linked with pulmonary veins via dilated BVs (Figure 1G).

Our findings provide anatomical evidence of prominent IBA in patients with IPAH. The presence of striking intimal occlusion or narrowing of small PAs suggest that high resistance may favor increased regional blood flow toward an open IBA in lieu of providing downstream perfusion of alveolar capillaries for gas exchange. Because of increased hemodynamic stress through the bronchial circulation, we speculate that lung plexiform lesions in IPAH may be derived from bronchial microvessels and veins. In comparison with small PAs, BAs tend to have thicker media and smaller external diameter and do not accompany airways, as observed in these tissue samples. Ink injections or perhaps casting of bronchial circulation are possible additional tools for further confirmation of BAs for clear identification (5).

We further show that the vasa of PAs are directly linked with plexiform lesions. We used three-dimensional reconstruction to provide further evidence that plexiform lesions originate from BAs and connect with the bronchial microvessel or vasa surrounding the PA and connect with the bronchial microvessels around airways. We also show that plexiform lesions are located at the bronchiolar wall and are connected to the bronchial microvessel, providing additional evidence that plexiform lesions are potentially part of the bronchial circulation. We identified plexiform lesions between the airway and PAs, where the vessels of bronchial circulation normally reside. We found that pulmonary veins drain plexiform lesions and propose that plexiform lesions are connected proximally to bronchial microvessels. We further propose that the dilation lesions are distal to plexiform lesions and could potentially be pathologically dilated BVs, as previously suggested (9) (Figure 1H).

Thus, recruitment of IBAs in IPAH may contribute to intrapulmonary right-to-left shunt, give rise to plexiform lesions, and increase the risk for pulmonary hemorrhage or hemoptysis. Hemodynamic stress due to anastomoses between the bronchial and pulmonary circulations through IBAs may lead to increased congestion and subsequent vascular wall stretch in the bronchial circulation and expansion of the vasa, which may provide a pathway for progenitor and inflammatory cells to participate in pulmonary arterial remodeling (10).

In summary, we provide histologic evidence supporting a potential role of the bronchial circulation and IBA in the pathobiology of IPAH and propose that the bronchial circulation may further contribute to the development of plexiform and dilatation lesions in severe IPAH. ■

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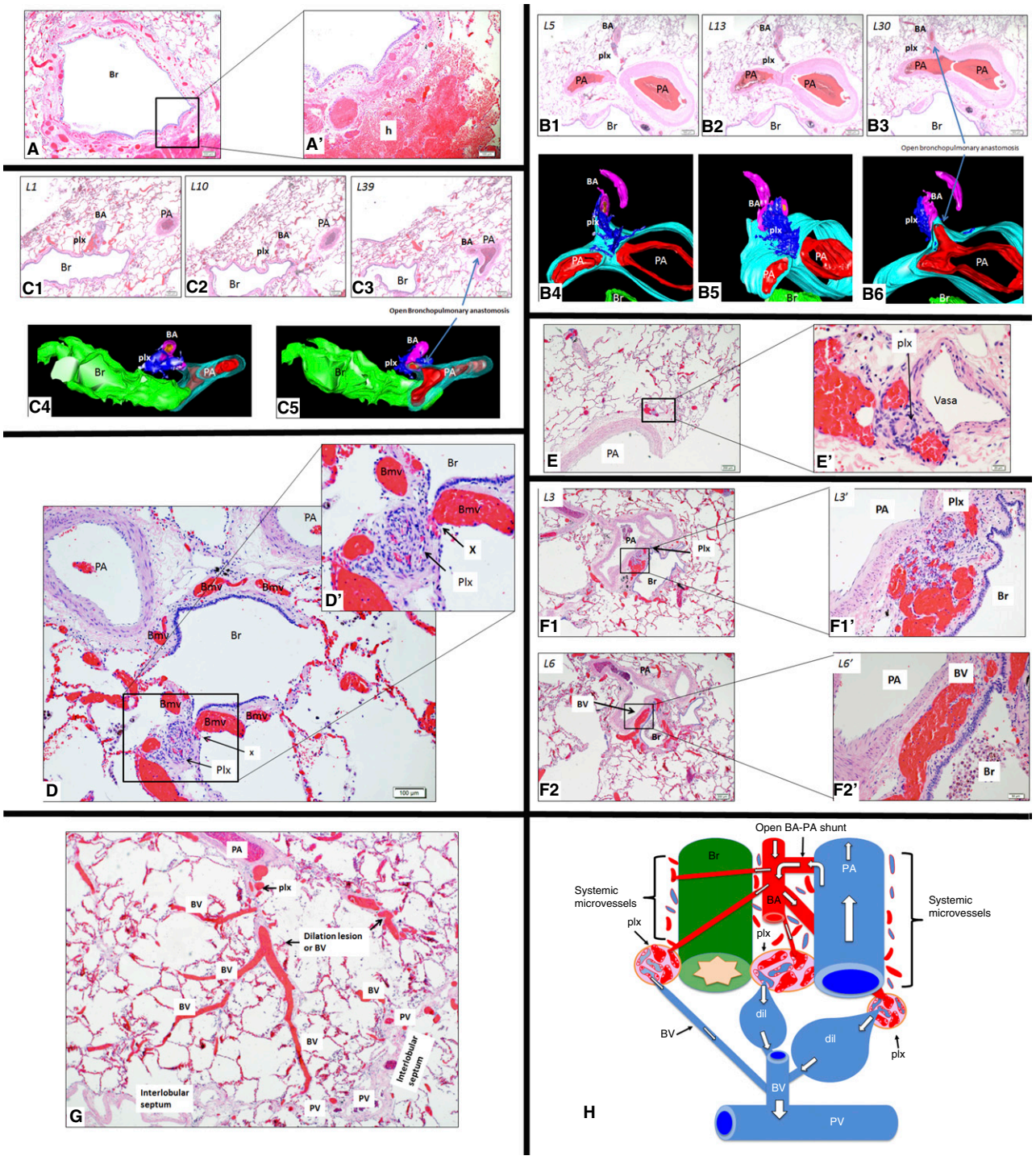

Figure 1. (*A*) The bronchial vasculature is overloaded because of shunted blood via an open intrapulmonary bronchopulmonary anastomotic pathway (IBA). Bronchial vessels are markedly congested around a bronchiole (Br) (magnification ×4). (*A'*) High magnification shows a hemorrhage (h). (*B*) A plexiform lesion (plx) is connected to the bronchial circulation and is in close proximity to an open bronchial artery (BA)–pulmonary artery (PA) anastomotic connection. Hematoxylin and eosin (H&E) sections (*B1–B3*) show that the plx bridges the BA and the wall of a large PA (*L5–13*). Deeper sections (*L30*) and three-dimensional images (*B4–B6*) show that the same BA connects to a large PA and forms an open BA–PA anastomosis. Three-dimensional images show that the plx is connected to the BA and to the vasa vasorum (vasa) of the PA (magnification ×2). (*C*) A plx is connected to the bronchial circulation and is in close proximity to an open BA–PA anastomotic connection as shown by H&E images (*C1–C3*). The plx bridges the BA and the microvessels within the wall of a larger (Br) (*L1–10*). Deeper section (*L39*) and three-dimensional images (*C4* and *C5*) show that the same BA connects to a larger PA via an open BA–PA anastomosis. Three-dimensional images show that the plx bridges the BA and the microvessels of the airway (Br) (magnification ×2). (*D*) A plx is connected (*X*) with dilated and congested bronchial microcirculation (Bmv). (*D'*) High magnification shows open connections between bronchial

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Figure 1. (Continued). microvessels and the plx (magnification ×10). (*E*) A plx develops on the vasa of a large PA (magnification ×4). (*E'*) High magnification confirms that the plx is intimately associated with the vasa. (*F*) A plx is located between a large PA and Br where the bronchial microvessels are normally located (*F1/L3*) (magnification ×4). (*F1'*) Higher magnification confirms that the plx is located where the systemic microvessels naturally reside. Deeper sections (*F2/L6*) show that the same plx in *F1* becomes a dilated bronchial vein (BV), as confirmed by a high-magnification image (*F2'*). (*G*) A plx is located at the site of vasa of a large PA that connects to a dilation lesion or dilated and congested BV that is eventually drained by a pulmonary vein (PV) that normally resides within the interlobular septum. (*H*) Prominent IBAs are present in distal lungs with idiopathic pulmonary arterial hypertension. The BA has an open connection with PA and blood shunts from the PA to the BA (*white arrows* depict blood postulated flow directions). Systemic microvessels surrounding the PA (vasa), and Brs (peribronchial microvessels) are supplied by the BA and drained by the BV, respectively. Because of the markedly increased shear stress due to shunted blood exerted on bronchial microvessels, a plx develops at the sites where systemic microvessels originally reside. Dilatation lesions (dil) are distal to the plx and represent blood overload and a dilated BV that is drained by the PV.

Positive ^{18}Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Predicts Preinvasive Endobronchial Lesion Progression to Invasive Cancer

To the Editor:

Central airway invasive squamous carcinoma develops from preinvasive dysplasia and carcinoma *in situ* (CIS) epithelial lesions (1). The natural history of preinvasive airway disease is variable, with a proportion progressing to invasive cancer and as much as 40% regressing to normal histology (2). This unpredictability creates difficulty in developing recommendations for the diagnosis, follow-up, and treatment of the disease (3).

Autofluorescence bronchoscopic (AFB) identification and regular surveillance biopsy of these lesions allow a strategy to intervene at the earliest stages of invasive cancer formation (4); however, a noninvasive imaging biomarker to detect malignant potential could assist the clinician in their decision to treat precancerous tracheal and bronchial lesions with potentially radical approaches.

Computed tomography (CT) lacks sensitivity and specificity in identifying premalignant peripheral bronchial lesions (5). Although ^{18}fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET) is the current gold standard imaging modality for staging patients with lung cancer and monitoring treatment response (6), its role in patients with preinvasive airway lesions has yet to be investigated.

We therefore investigated the novel use of ^{18}F-FDG-PET/CT as part of a surveillance program for patients with preinvasive lesions (CIS and high-, moderate-, and low-grade dysplasia). Over the course of 11 years, 44 patients (30 men; median age, 68 years) with preinvasive endobronchial lesions identified using AFB, underwent ^{18}F-FDG-PET/CT examination within 6 weeks from the AFB examination. The protocol also included AFB follow-up and

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