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MINIREVIEW

Changing Concepts of the Pulmonary Plexiform Lesion

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Summary

The plexiform lesion is the hallmark of plexogenic pulmonary arteriopathy, which accompanies severe primary pulmonary hypertension. Over the years, a wide variety of hypotheses have been offered to explain the pathogenesis of these glomoid structures. Most recently, the new techniques and concepts of molecular biology have been applied to the study of the plexiform lesion and have indicated that they are composed of phenotypically abnormal endothelial cells with different pathogenic origins in primary and secondary pulmonary hypertension. The new approaches and concepts have suggested new vistas for exploration.

Key words

Plexiform lesion • Plexogenic pulmonary arteriopathy • Primary pulmonary hypertension • Pulmonary giogenesis

Introduction

In 1973, the World Health Organization (WHO) convened a cluster of pathologists, cardiologists and physiologists, to review the understanding of primary (unexplained) pulmonary hypertension (Hatano and Strasser 1975). The major stimulus for the meeting was the 1967-1969 epidemic of unexplained pulmonary hypertension which was subsequently attributed to the ingestion of the appetite-depressant drug, aminorex (Gurtner, 1990). One outcome of the meeting was the recognition of a distinct constellation of lesions, so-called "plexogenic pulmonary arteriopathy" (Fig. 1), as the pathologic hallmark of primary pulmonary hypertension (Wagenvoort and Wagenvoort 1977, Loyd *et al.* 1988, Wagenvoort 1989). Moreover, pulmonary vasoconstriction was implicated as the common denominator in the pathogenesis of primary pulmonary hypertension.

Serious reservations have been expressed about this characterization. Thus, plexiform lesions are absent in approximately 30 % of patients who are diagnosed as having "plexogenic arteriopathy". Moreover, in instances where plexiform lesions cannot be found, only medial hypertrophy, or more often, a combination of medial hypertrophy and concentric laminar intimal fibrosis (CLIF), may be present (Pietra 1990). "Plexogenic arteriopathy" occurs not only in primary pulmonary hypertension but also in pulmonary hypertension due to congenital heart disease, appetite suppressants, AIDS, and schistosomiasis (Cool *et al.* 1997). Finally, the concept of vasoconstriction as the unique etiology of primary pulmonary hypertension has undergone revision as other etiologies and associations have been identified (Pietra 1990, Cool *et al.* 1997).

Despite these reservations, the designation "plexogenic pulmonary arteriopathy" has endured and the plexiform lesion continues to be its hallmark.

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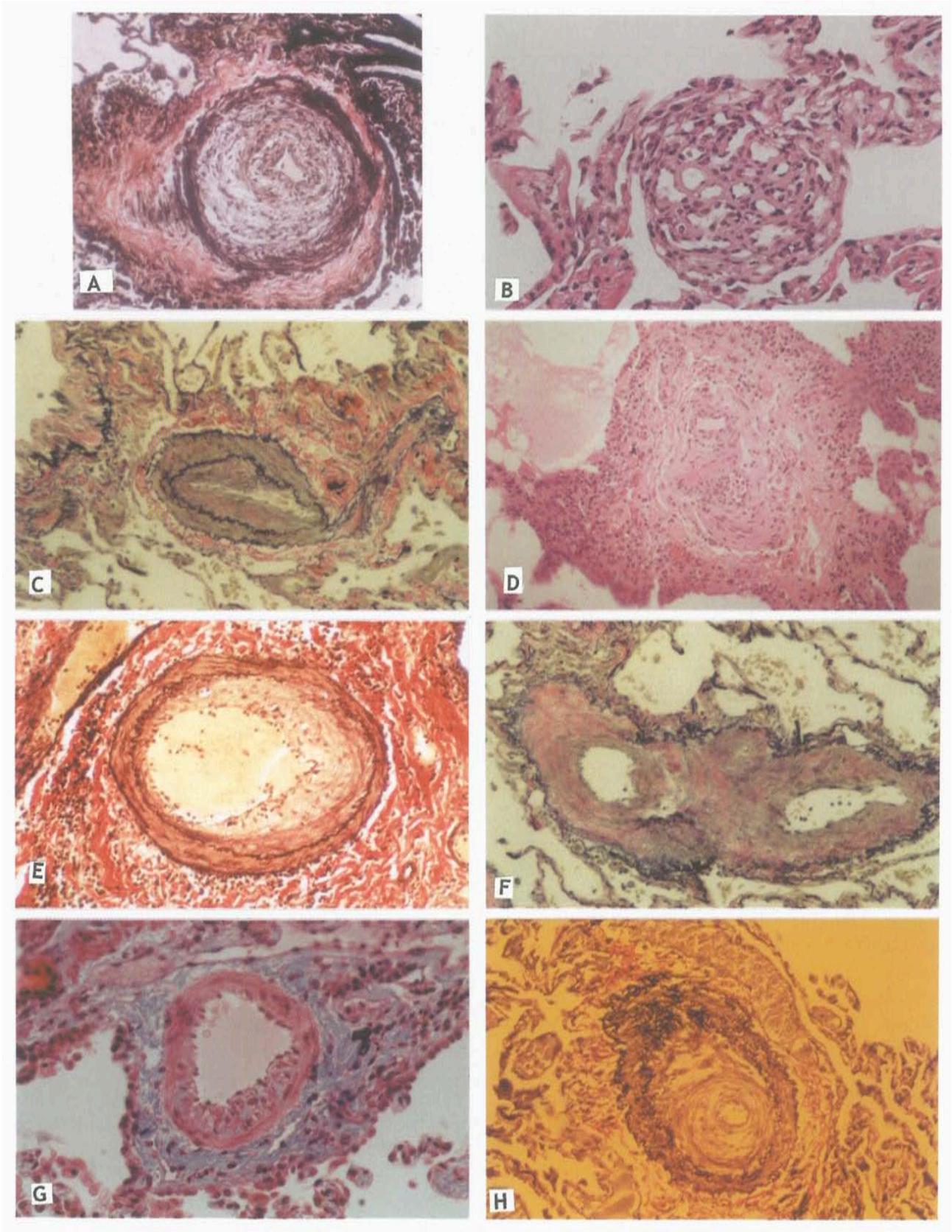

Fig. 1. *Plexogenic pulmonary arteriopathy. The constellation of lesions is an assortment of obstructive and proliferative lesions of the small muscular pulmonary arteries. Panels B and D represent different stages in the maturation of plexiform lesions.*

The Plexiform Lesion: Changing Views of Pathogenesis

Until a few years ago, proposed etiologies and pathogenetic mechanisms for the plexiform lesion varied considerably. Among the hypotheses were congenital glomoid abnormalities (Moshcowitz *et al.* 1961), myofibroblastic and fibrillary-cell scarring (Smith *et al.* 1990), recanalization of thrombi (Bredt 1932, Harrison 1958), arteriovenous shunts (Kucsko 1953) and intense vasoconstriction accompanied by necrotizing arteritis and fibrinoid necrosis (Fishman 1975, Wagenvoort and Wagenvoort 1977, Yamaki and Wagenvoort 1985, Heath and Edwards 1958). Of this plethora of hypotheses, only the latter remains to this day as a plausible possibility. One important byproduct of these changing concepts concerning etiology is the appreciation of the plexiform lesion as a dynamic structure that can vary considerably in cellular composition and organization depending on its stage of maturation and differentiation (Tuder *et al.* 1998ab). This recognition takes into account that early lesions are cellular but that they become less so, and increasingly fibrotic, as they mature (Wagenvoort and Wagenvoort 1977). As a corollary, it seems reasonable to anticipate that the likelihood of reversing a plexiform lesion will depend on the stage and cellularity of the lesion (Yamaki and Wagenvoort 1985, Wagenvoort and Wagenvoort 1984).

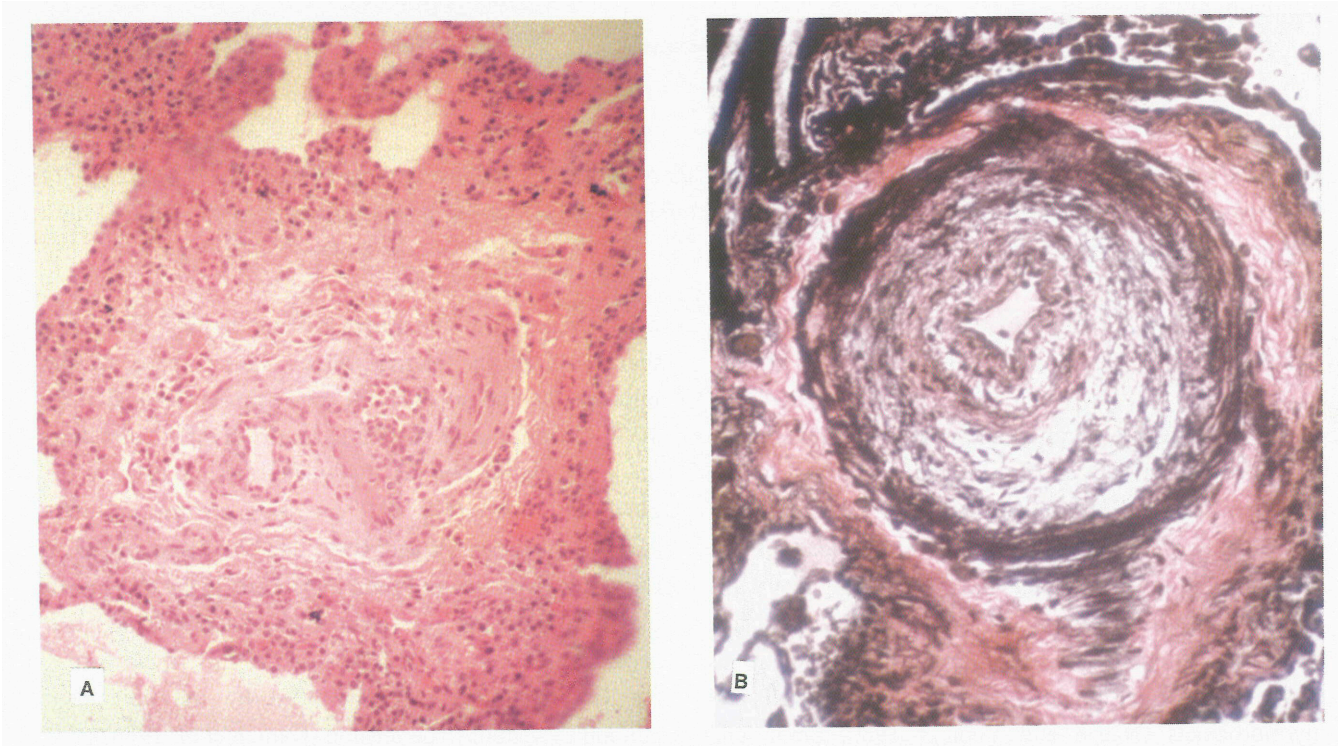

Fig. 2. *Plexiform lesion and concentric laminar intimal fibrosis. A. Mature cellular plexiform lesion. Contrast with Figure 1B. B. Concentric laminar intimal fibrosis (CLIF) close to the origin of a supernumerary artery from its parent vessel.*

Conventional Staining Techniques

By conventional histologic techniques, the plexiform lesion is a glomoid structure consisting of closely packed endothelial cells within a mucopolysaccharide matrix (Fig. 2) (Moshcowitz 1927, Heath and Edwards 1958, Pietra *et al.* 1989, Palevsky *et al.* 1989, Pietra and Ruttner 1987). Although the plexiform lesion can occur at various sites within the lung (Jamison and Michel, 1995), one distinctive presentation is within an aneurysmal dilatation of a small arterial branch close to its origin from the parent vessel (Fig. 3). The branch containing the plexiform lesion has been called a supernumerary artery and characteristically originates at right angles to the parent vessel. The muscle-elastic organization at the mouth of the supernumerary artery is richly innervated (Fillenz 1970) and its structure has been interpreted as suggestive of a baffle valve (Bunton *et al.* 1996).

When plexiform lesions occur in a supernumerary artery, concentric laminar intimal fibrosis (CLIF) is consistently found close to its origin (Fig. 3). Moreover, distal to the plexiform lesion is a constellation

of dilated vessels which make-up the so-called "dilatation" or "angiomatoid" lesions (Wagenvoort and Wagenvoort 1977, Pietra *et al.* 1989). This arrangement constitutes a "plexiform complex" which consists of CLIF, the plexiform lesion and the angiomatoid lesion (Fig. 3). Inflammatory cells are often found within, and at the perimeter of, the plexiform lesion (Chazova *et al.* 1995, Tuder *et al.* 1994).

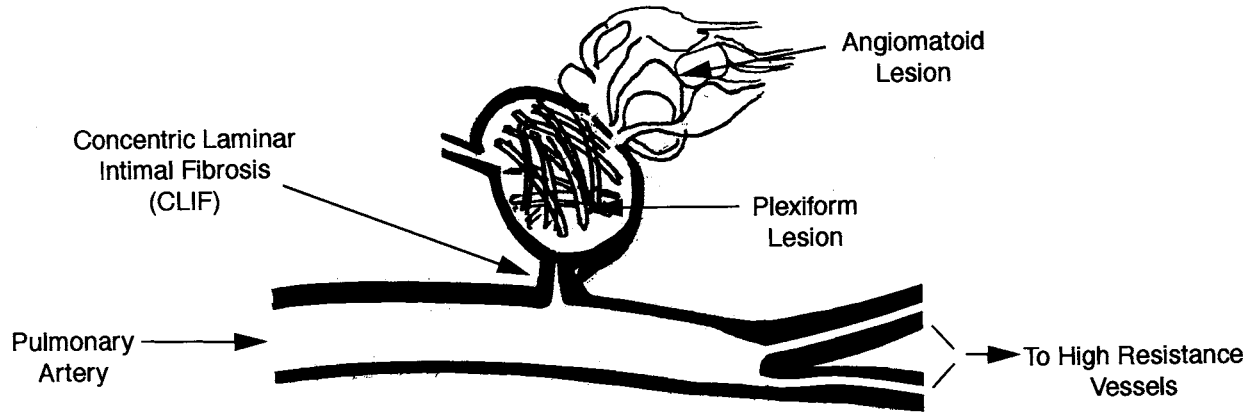

Fig. 3. *Architecture of the plexiform complex which consists of concentric laminar intimal fibrosis (CLIF) at origin of supernumerary artery, the plexiform lesion and the angiomatoid lesion. Modified after Moshcowitz et al. (1961), Naeye and Vennart (1960), and Kanjuh et al. (1964).*

The Cellular Composition of the Plexiform Lesion

Intimal proliferation and capillary channels have long been identified as characteristic features of the plexiform lesion (Heath and Edwards 1958, Wagenvoort 1959). However, since the early descriptions of the plexiform lesion, opinions have differed about the cellular nature of the intimal proliferation. As indicated previously, these have been designated variously as smooth muscle cells, endothelial cells, fibrillary cells and myofibroblasts (Naeye and Vennart 1960, Smith and Heath 1979, Wagenvoort and Wagenvoort 1977). Platelet thrombi are not uncommon. The recent observations of Tuder, Voelkel and Cool using molecular markers, have dispelled much of the ambiguity concerning the cellular composition of the plexiform lesion (Tuder *et al.* 1994, Cool *et al.* 1999). They have underscored that endothelial cells predominate and that muscle cells are lacking but have also recognized that as the lesions evolve, inflammatory cells, myofibroblasts and connective tissue elements may be intermingled (Tuder *et al.* 1994).

Etiology and Pathogenesis

The architecture of the plexiform complex (Fig. 3) is consistent with the hypothesis that a jet lesion, originating in the concentric laminar intimal fibrosis at the mouth of the branch vessel, causes injury to the opposite wall upon which the jet impinges (Kanjuh *et al.* 1964, Larrabee *et al.* 1949). In line with this reasoning is the interpretation that the angiomatoid lesion, distal to the plexiform lesion (Fig. 3), represents an area of post-stenotic dilatation (Wagenvoort and Wagenvoort 1977). Consistent with the jet-lesion hypothesis is the absence of plexiform lesions in pulmonary hypertension that accompanies mitral valvular disease: in this circumstance, the jet is pictured as minimized by the coincident pulmonary venous hypertension (Kanjuh *et al.* 1964).

However, although the jet-lesion hypothesis may account for the occurrence of plexiform lesions in supernumerary arteries, it cannot do so for lesions that occur elsewhere in the lung far removed from the area of concentric laminar intimal fibrosis. In these loci, plexiform lesions may be the result of necrotizing arteritis. Two lines of evidence are in favor of this hypothesis:

1) *Experimental*, i.e. the occurrence of pulmonary plexiform lesions in dogs and sheep after the surgical production of severe pulmonary hypertension and widespread necrotizing pulmonary arteritis by anastomosing a systemic artery to a restricted pulmonary vascular bed, i.e. to one lobe of the lung

(Harley *et al.* 1968, Saldãna *et al.* 1968, Schnader *et al.* 1996), and

2) *Clinical*, as indicated by successive observations in a patient with severe primary pulmonary hypertension: lung biopsy three months before autopsy revealed widespread necrotizing arteritis and interstitial pneumonia; autopsy three months later revealed widespread plexiform lesions (Palevsky *et al.* 1989).

Other associations between necrotizing pulmonary arteritis and plexiform lesions are even more circumstantial. Although it seems reasonable to attribute plentiful lesions in Eisenmenger's Syndrome to necrotizing pulmonary arteritis caused by exposure of the pulmonary circulation to systemic arterial blood pressures, less evident is why plexiform lesions are more frequent in pulmonary hypertension associated with scleroderma than with AIDS (Cool *et al.* 1997).

An entirely different view of the etiology and pathogenesis of the plexiform lesion has resulted from the use of molecular markers (Tuder *et al.* 1994, Voelkel *et al.* 1998, Cool *et al.* 1997). According to this view, the plexiform lesion is the result of „misguided angiogenesis", a disregulated proliferation of phenotypically-altered endothelial cells. Moreover, the „misguided" endothelium is pictured as a source of cytokines and growth factors, a source and attractant of inflammatory mediators, a promoter of coagulation and imbalanced with respect to vasoconstrictors and vasodilators.

Not all „misguided" endothelium is comprised of the same genetic material. Indeed, a different genetic composition is postulated for the plexiform lesions of primary and secondary pulmonary hypertension. Thus, in primary, as well as in AIDS or anorexigenic pulmonary hypertension, the plexogenic lesions have been shown to be monoclonal, presumably the consequence of an acquired somatic mutation that promotes autonomous growth of a stem cell-like endothelial cell in the vascular wall. The proliferative behavior of the "stem cell" entails vasculogenesis and angiogenesis and resembles that of stem cells in familial adenomatous polyposis and Kaposi's sarcoma. In contrast, the endothelial cells that comprise the plexiform lesions of secondary pulmonary hypertension are polyclonal, reflecting multi-cellular endothelial proliferation in response to exogenous stimuli, such as hemodynamic stress or viral infection (Lee *et al.* 1998, Tuder *et al.* 1998ab).

The studies involving immunochemical markers have also indicated that the plexiform lesion and CLIF are similar in cellular composition and that the two lesions are related, both temporally and etiologically (Cool *et al.* 1999). However, although plexiform lesions do occur independently of CLIF, the converse is not true: CLIF is invariably associated with plexiform lesions, an observation that supports the "jet lesion" hypothesis.

Although the concept of "misguided angiogenesis" affords a fresh approach to the pathogenesis of pulmonary hypertension, one that is firmly grounded in recent developments in systemic vascular biology, molecular biology, angiogenesis, vasculogenesis and cancer biology (Fearon *et al.* 1987, Folkman 1997, Kinzler and Vogelstein 1998), not all are convinced of the durability of the conceptual superstructure that has been built on this strong foundation. For example, Michel (1998), in keeping with more traditional views, regards the plexiform lesion and endothelial dysfunction as part of a repair reaction to severe vascular damage, e.g. following necrotizing arteritis (Wagenvoort and Wagenvoort 1977, Saldãna *et al.* 1968). Moreover, while acknowledging that the formation of new vessels is an essential part of a proliferative process, he is not convinced that angiogenesis is the instigator of the proliferative response. Finally, drawing upon observations on the monoclonality of smooth muscle cells in the atherosclerotic plaque, he questions the use of endothelial monoclonality as a marker of either angiogenesis or neoplasia (Benditt and Benditt 1973, Schwartz *et al.* 1995, Michel 1998, Collins 1997).

Unsettled Questions

One purpose of this presentation was to highlight some unsettled questions about the etiology and pathogenesis of the plexiform complex: the plexiform lesion, CLIF, and the „dilatation (angiomatoid) lesion". Although the newer techniques seem to have settled the predominant cell type in both the plexiform lesion and CLIF, only sporadic attention has as yet been paid to other cells that infiltrate the lesions as they evolve, to the inflammatory cells that are found within, and in the vicinity of, the plexiform lesion, or to the cytokines and growth factors that may contribute to the evolution of the lesions (Fishman *et al.* 1998).

In providing fresh insights into etiology and pathogenesis, the techniques of molecular biology have posed as many stimulating new questions as they have answered. Paramount among these are the nature of the hypothetical stem cell for monoclonality and the relationship of genetic predisposition of endothelial cells

to the proliferative responses of primary and secondary categories of severe pulmonary hypertension. The natural history of the plexiform lesion and the plexiform complex remains to be written. How to account for the diversity of the pulmonary vascular lesions in plexogenic arteriopathy? What is the relationship of angiogenesis/ vasculogenesis to the proliferative process that characterizes the plexiform lesion? The role played by necrotizing arteritis as the initiator of the plexiform lesion is unsettled. Also puzzling is the relationship, if any, between the proliferative response of the plexiform lesion and pulmonary capillary humangiomatosis, a benign neoplasm (Tron *et al.* 1986, Wagenvoort 1978).

Many other related questions come to mind. Nonetheless, the plexiform lesion stands not only as a landmark among the vascular lesions that accompany severe pulmonary hypertension but also as a weather vane for the exploration of the pathogenesis of the obstructive and proliferative pulmonary vascular lesions that characterize plexogenic arteriopathy.

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