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Membranous Fibrosis of the Lung

Toshiaki MANABE, Yoshihiro KOBASHI and Masamitsu NAKAJIMA

Department of Human Pathology,
Kawasaki Medical School, Kurashiki 701-01, Japan

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ABSTRACT. Membranous fibrosis of the lung depicts a morphological feature of the fibrous tissue which covers alveolar duct walls. Membranous sheets of fibrous tissue usually bridge and obstruct the mouths of alveoli, and attach only at the tips of the septa; i.e., the alveolar duct walls, and often provoke a collapse of alveolar spaces. There seem to be two types of membranous fibrosis. The first type is, in fact, a fibrous replacement of pre-existing hyaline membrane, while the second is a *de novo* formation of membranous fibrous tissue which has little or no preceding hyaline membrane. We consider that both of these changes result from damage to the alveolar duct walls and may constitute forms of the fibrosing alveolar ductitis syndrome. Recognition of this type of fibrosis gives us a better understanding of the morphogenesis of so-called diffuse alveolar damage.

Key words : lung — fibrosis — DAD — alveolar ductitis

Pulmonary fibrosis is the end-stage of tissue injury in the lungs. It is usually non-specific and determination of its original cause may be difficult.[1] As described in detail in our previous communication,[2] the morphology of pulmonary fibrosis is usually divided into five patterns; interstitial fibrosis, intraluminal polypoid fibrosis, intraluminal diffuse fibrosis of complete type, intraluminal diffuse fibrosis of incomplete type and hyaline membrane incorporation. Recently, we realized that not all of the hyaline membranes are incorporated or fibrosed, and that some of the membranous fibrous tissue may be formed *de novo* without pre-existing hyaline membranes. Therefore, we began using the more generic and morphologic term of membranous fibrosis rather than hyaline membrane incorporation. To our eyes, there are two types of membranous fibrosis morphologically. The first type is the one which has previously been called hyaline membrane incorporation, in which pre-existing hyaline membranes are fibrosed to become membranous sheets of fibrous tissue, while the second type is characterized by the formation of fibrous tissue without the prior existence of hyaline membranes. In this communication, we describe the morphogenesis and pathogenesis of membranous fibrosis and discuss the spectrum of the alveolar ductitis syndrome in more detail.

MORPHOLOGY OF MEMBRANOUS FIBROSIS

Membranous fibrosis of the lung is a term that denotes a condition which is histologically characterized by the presence of membranous fibrous tissue

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sheets covering alveolar duct walls and bridging and obstructing alveolar mouths (Fig. 1). It is intraluminal in location. Although this fibrous tissue mainly exists in the alveolar duct, it may extend into respiratory bronchioles and, on rare occasion, may protrude into alveolar spaces when collapsed. Membranous fibrous tissue sheets usually attach to the tips of the septa; namely, the alveolar duct walls. In the early stage, they are loose and myxoid, while in the later stage they are densely fibrous with epithelial lining along the undersurface of the fibrous tissue (Fig. 2a, b). The oversurface of the fibrous tissue usually lacks epithelial coverage at any stage (Fig. 2b). The alveolar spaces may collapse but they usually remain as wide spaces or as slender slits.

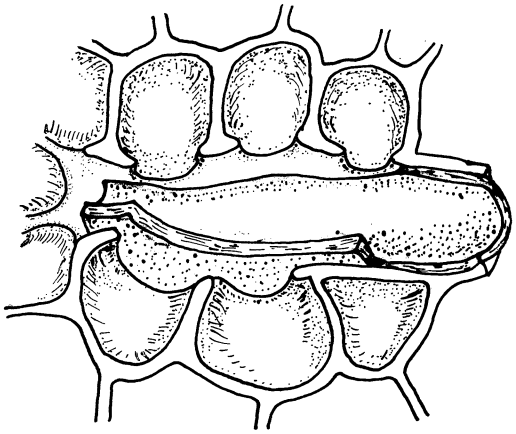

Fig. 1. Schematic diagram of membranous fibrosis. Note that a membranous fibrous sheet is in fact intraluminal in location.

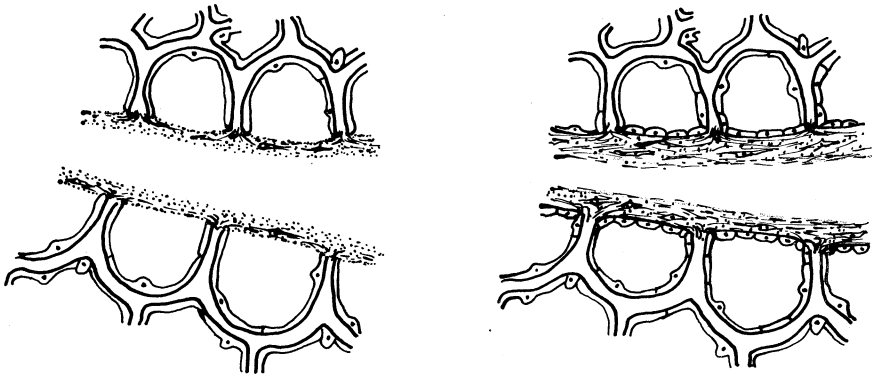

Fig. 2. This diagram shows the surface of membranous fibrous tissue. The membranous tissue is not epithelialized in its early stage of formation (a), but the undersurface of the fibrous tissue becomes lined by flat to plump cuboidal epithelial cells in its late stage (b). Alveolar spaces below this fibrous tissue may collapse.

MORPHOGENESIS AND PATHOGENESIS OF MEMBRANOUS FIBROSIS

From our study of lung fibrosis during the past five years, we have realized that two types of membranous fibrosis exist. The first type is actually fibrous replacement of hyaline membranes, such as shown in Fig. 3 and 4. This

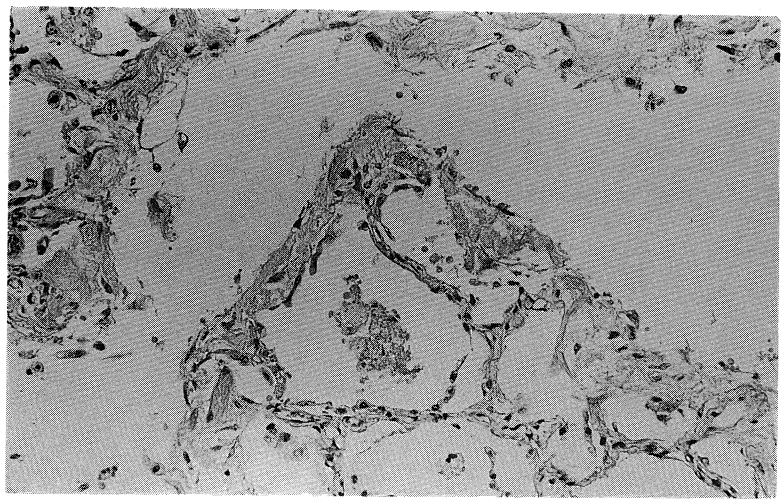

Fig. 3. Early stage of membranous fibrosis with some remnants of hyaline membrane

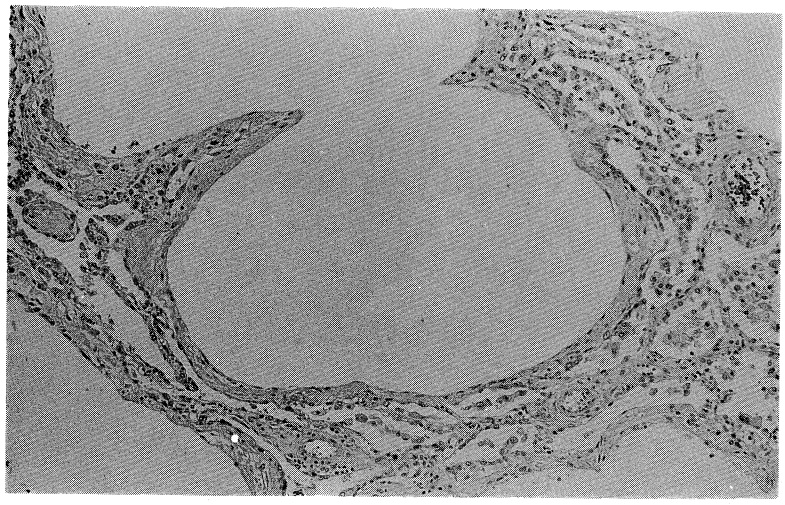

Fig. 4. Late stage of membranous fibrosis

probably represents an end-stage form of mild diffuse alveolar damage which mainly involves alveolar ducts and usually manifests itself clinically as the adult respiratory distress syndrome. Morphogenesis of the fibrosis of this type has been described in detail.[3] Alveolar duct spaces surrounded by membranous fibrous tissue are widely distended to form a honeycomb structure. In the initial stage of fibrosis, fibrous tissue is usually loose in appearance. Remaining hyaline membranes with eosinophilic tincture are partially and fragmentarily visible, and are usually present along the side of the alveolar spaces (Fig. 3). In the late stage, no remnant of eosinophilic hyaline membranes is discernible and they are completely replaced by fibrous tissue (Fig. 4). The honeycombed walls are composed of collapsed alveolar walls which still retain slit-like spaces

inside (Fig. 5). The collapsed alveolar walls are sometimes normal in thickness and appearance but are also sometimes thickened with fibrous tissue. The second type of membranous fibrosis is composed solely of membranous fibrous tissue, and no remaining fragments of the hyaline membranes are seen even in its early stage (Fig. 6). The cellularity varies according to its stage. In either type of fibrosis, fibrous tissue sheets always show a connection with the alveolar duct walls, suggesting that fibrosis results from damage to the alveolar duct walls.

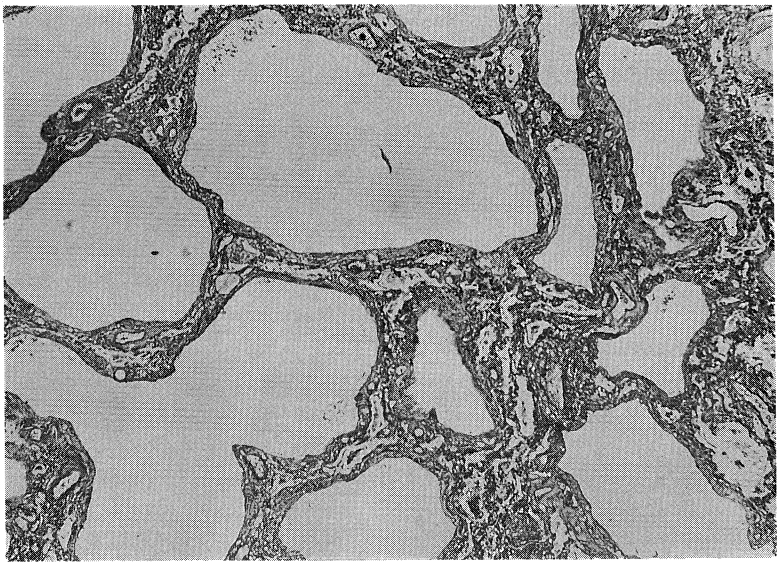

Fig. 5. Late stage of membranous fibrosis, forming honeycomb structure

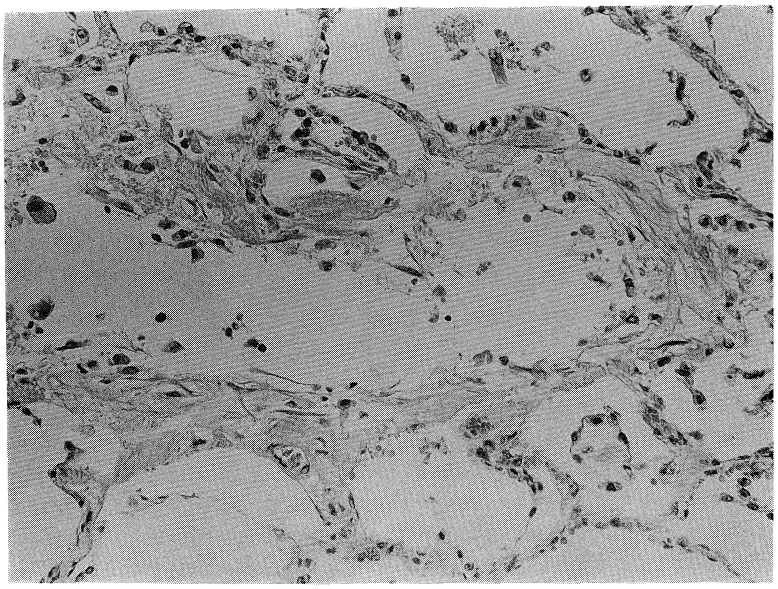

Fig. 6. Early stage of membranous fibrosis without hyaline membrane remnants

In contrast to the tissue of intraluminal polypoid fibrosis,[4] the fibrous tissue of membranous fibrosis never protrudes into alveolar duct spaces as a tissue mass, but instead covers and occludes the lumen of the alveolar mouths as a membrous tissue sheet. From our experience, this type of fibrosis occurs in the chronic form of idiopathic pulmonary fibrosis, in acute interstitial pneumonia of Katzenstein, in shock lungs, in the adult respiratory distress syndrome (ARDS) and in paraquat lungs as well as in association with some forms of bronchiolitis obliterans-organizing pneumonia (BOOP). The fibrosis of this type, therefore, is not specific to a certain disease. The implications of positive-pressure mechanical ventilation, especially with the use of positive end-expiratory pressure (PEEP), in the development of this membranous form of fibrous tissue is still speculative.

FURTHER CONSIDERATIONS ON ALVEOLAR DUCTITIS SYNDROME

As is the case in intraluminal polypoid fibrosis, we consider that membranous fibrosis represents a form of reaction patterns seen in the so-called alveolar ductitis syndrome. In its exudative phase, damage to the alveolar duct walls may cause the development of hyaline membrane (exudative or fibrinous alveolar ductitis), which in its later stage is organized by fibrous tissue. Therefore, the later stage may be referred to as fibrosed or organized alveolar ductitis. In contrast, there are some conditions where the fibrosing process develops *de novo*. This change may be designated as fibrosing alveolar ductitis, membranous type. Fibrosing alveolar ductitis of membranous type and that of the polypoid type seen in cases of BOOP are both caused by injuries to the alveolar ducts. These types of fibrosis are also seen in cases of bronchiolitis obliterans and interstitial pneumonia (BIP) or organized diffuse alveolar damage (organized DAD). The sites of damage in these diseases seem to be the same but the reactions induced thereby may differ. What causes such differences? As yet, we do not know.

According to the descriptions given by some authors,[5,6,7] there are two forms of DAD. The mild form of DAD involves alveolar duct walls and causes the development of hyaline membrane along the alveolar ducts, and therefore, as we pointed out, it is, in reality, a form of alveolar ductitis. The other form of DAD is a diffuse or severe form and indeed involves the alveolar walls. Because in these cases an alveolar wall is diffusely damaged and lesions are present diffusely and bilaterally in the lungs, this is literally diffuse alveolar damage. This type of alveolar damage may ensue with intraluminal diffuse fibrosis in its late stage. The existence of two forms of DAD may, therefore, indicate a difference in their etiology. The former, with the involvement of alveolar duct walls alone, may suggest the entrance of an inciting agent or agents through airways, whereas the latter, with diffuse involvement of the alveolar walls, may be due to either the vascular spread of causative agents or the extensive spread of toxic agents through airways. We consider that these two morphological changes should be separated in terms of their pathogenesis since they may represent different disease entities. Some hyaline membranes are fibrosed to develop membranous fibrous sheets under certain conditions. However, membranous fibrosis may develop *de novo*

and in such cases membranous fibrous tissues may sometimes be seen in association with intraluminal polypoid fibrosis. These two fibrosing processes; namely, membranous and intraluminal polypoid fibrosis, may be related to each other in the sense that they may develop after alveolar duct injuries. Therefore, it may be conceivable that the same or at least a similar pathogenetic mechanism is operative in their development. Furthermore, as has been discussed elsewhere,[8] damage of the alveolar duct walls may evoke both intraluminal and interstitial fibrosing processes at the same time. The formation of an abscess wall may be a good example of this phenomenon. We would also like to emphasize here that in some cases of BIP and acute interstitial pneumonia, unknown inciting agents may damage the alveolar duct walls and cause intraluminal polypoid, membranous, and interstitial fibrosis simultaneously.

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