system, through which the venous flow of the upper half of the body drained into the inferior vena cava.

In the past, evaluation of collateral vessels was commonly performed by angiography and CT. Transcutaneous ultrasonography is not capable of demonstrating the collateral veins around the esophagus because of intervening bone and intrapulmonary air. However, in TE2DD, the distance between the transducer and these vessels is reduced, and there are fewer obstacles, and so, visualization is easier. Moreover, with TE2DD, both anatomic and hemodynamic information can be obtained simultaneously. If a facility for a fast Fourier transform were incorporated in the ultrasound scanner, a quantitative evaluation of flow would also be possible. Although there are some limitations such as the small field of view and the long learning period required for the operator to be able to recognize the anatomy and interpret the ultrasound images, TE2DD is an extremely useful method for the study of collaterals and other vessels in the vicinity of the esophagus.

REFERENCES

Epithelial Necrosis and Alveolar Collapse in the Pathogenesis of Usual Interstitial Pneumonia*

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We report ultrastructural evidence of epithelial necrosis and alveolar collapse in a patient with usual interstitial pneumonia (UIP). These changes were focal and confined to small areas characterized histologically by aggregates of interstitial fibroblasts embedded within a myxoid stroma (fibroblastic foci). Ultrastructurally, the denuded epithelial basal lamina in these areas showed deep infoldings into the interstitium, and the luminal surfaces of the resultant clefts often were re-epithelialized. These findings suggest that the fibroblastic foci commonly seen in UIP represent sites of acute lung injury, and that alveolar collapse following epithelial necrosis is an important mechanism of lung remodeling. In addition to new insights regarding the pathogenesis of fibrosis in UIP, these observations may have important implications for assessing prognosis and selecting treatment strategies. (Chest 1988; 94:1309-11)

The pathogenesis of interstitial fibrosis in usual interstitial pneumonia (UIP) has been the subject of extensive investigation. Several studies have suggested that UIP begins as alveolitis, and that fibrosis develops as a result of interstitial fibroblast proliferation and collagen deposition. Incorporation of intraluminal fibrosis into the interstitium has also been described as a mechanism of interstitial fibrosis. Recently, ultrastructural observations in patients with the acute form of interstitial pneumonia (Hamman-Rich disease, acute interstitial pneumonia) have shown that epithelial necrosis followed by collapse and apposition of alveolar walls is an important mechanism of parenchymal remodeling. We present evidence that this same mechanism

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also contributes to the formation of interstitial fibrosis in UIP.

CASE REPORT

A 68-year-old white man was referred to our institution for evaluation of increasing dyspnea. Physical examination revealed diffuse rales bilaterally and there was clubbing of his fingers and toes. A chest roentgenogram showed coarse reticular opacities throughout both lungs associated with moderate volume loss. He underwent thoracotomy with biopsy of the left upper lobe. The lung biopsy specimen was routinely processed for light and electron microscopy.

RESULTS

Light Microscopy

The lung showed typical histologic features of UIP characterized by a variegated low magnification appearance in which relatively normal lung alternated with zones of interstitial inflammation, fibrosis, and honeycomb change. The areas of interstitial fibrosis consisted mainly of end-stage, mature fibrosis with dense collagen deposition. There were also scattered small foci containing less mature fibrosis composed of aggregates of loosely clustered fibroblasts dispersed in a faintly basophilic, edematous-appearance matrix. Electron microscopy was performed on both the mature fibrotic areas and the fibroblastic foci.

Electron Microscopy

Ultrastructural examination in the fibroblastic foci showed patchy epithelial necrosis associated with denudation of basal lamina (Fig 1). In places, the alveolar septa were partially covered by cuboidal epithelial cells with surface microvilli and cytoplasmic lamellar bodies. Locally, the denuded epithelial basal lamina formed deep folds and clefts into alveolar septa, resulting in partial collapse of alveoli. Cuboidal epithelial cells often covered the luminal surface of these areas, resulting in permanent apposition of collapsed segments and incorporation of the invaginated basal lamina into the interstitium (Fig 2).

Electron microscopic examination in the areas of mature fibrosis showed a continuous layer of alveolar lining cells which were mainly type 2 pneumocytes. Neither epithelial necrosis nor denudation of the basal lamina was seen. Invaginated basal laminae were focally present. Sometimes they were contiguous with epithelial basal laminae, but frequently they appeared fragmented and discontinuous (Fig 3). The adjacent interstitium contained numerous collagen fibrils organized in broad sheets.

Discussion

The findings in our case suggest that epithelial necrosis and alveolar collapse are important in the pathogenesis of UIP. The epithelial necrosis is confined to small foci that are widely scattered and recognized histologically by the presence of loosely aggregated interstitial fibroblasts (fibroblastic foci). Similar areas can be found in most examples of UIP. Alveolar collapse also occurs in the fibroblastic foci and likely results from the epithelial necrosis. Ultrastructurally, alveolar

FIGURE 1. Electron micrograph of a fibroblastic focus showing denuded epithelial basal lamina (arrowheads). A fibroblast is interposed between a capillary (Cap) and the basal lamina. AS = air space. Original magnification: ×6,000.

FIGURE 2. Electron micrograph of a fibroblastic focus showing collapse of an alveolar septum, characterized by invagination of a segment of basal lamina (arrow) into the interstitium. A detached fragment of invaginated basal lamina is also present (arrowheads). The luminal surface has been re-epithelialized, causing the invaginated basal lamina to be permanently incorporated into the alveolar septum. AS = air space. Ep = epithelial cell, Cap = capillary. Original magnification: ×3,000.
collapse is characterized by invagination of the denuded epithelial basal lamina into alveolar septa with the formation of deep clefts. Re-epithelialization occurs over the luminal surface of the basal lamina in these areas, leaving collapsed segments permanently apposed and incorporated into the interstitium. This mechanism helps to explain several aspects of parenchymal remodelling in UIP, including interstitial thickening, honeycomb change and volume loss.

Our conclusions are based on examination of a single case, and, of course, additional cases will need to be studied to confirm them. However, the fact that the epithelial necrosis and alveolar collapse were localized to fibroblastic foci that are found in most cases of UIP suggests that these same changes occur in other cases. Additional study will likely require prospective evaluation since tissue specimens need to be sampled extensively to be sure that the fibroblastic foci are represented. The random sampling that is usually performed in retrospective ultrastructural studies can easily overlook these areas, and may explain the absence of alveolar collapse in the 17 cases examined ultrastructurally by Corrin et al.3

The presence of epithelial necrosis and alveolar collapse does not exclude the role of either interstitial collagen deposition or intraluminal fibrosis in the pathogenesis of UIP. Clearly, collagen deposition contributes to interstitial thickening as demonstrated ultrastructurally in the areas of mature fibrosis in our case. However, collagen deposition alone cannot explain the loss of lung volume and honeycomb change that occur during the course of UIP. A combination of alveolar collapse and collagen accumulation could explain these changes, however, and it is likely that these processes are complementary in the pathogenesis of UIP. Mural incorporation of intra-alveolar exudates and intraluminal fibrosis may also contribute to interstitial fibrosis.3 Although we did not identify mural incorporation in our case, this process is difficult to demonstrate ultrastructurally, and its absence may be related to sampling problems.

In addition to implications regarding the pathogenesis of UIP, the presence of fibroblastic foci might be important for other reasons. Since these areas likely represent the sites of acute lung injury in UIP, and since they are easily identified by light microscopy, they could be utilized as markers of disease activity. The presence and extent of fibroblastic foci may also be useful in predicting prognosis or response to therapy. The finding of epithelial necrosis and alveolar collapse may also have implications for choosing treatment strategies. Current therapy is aimed mainly at decreasing alveolitis or inhibiting fibroblast replication. Identification of modalities that could prevent either epithelial injury or alveolar collapse might also be important.

REFERENCES