Idiopathic Pulmonary Hemorrhage in a Mouse

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Remarkable accumulation of alveolar macrophages containing protein crystals (PCs) has been recognized in mice under variable conditions as follows; parasitic infections [2, 6, 11], grain dust exposure [1], pulmonary tumor [5], bronchopneumonia [10] as well as an inheritable pulmonary disease, known as an unusual pneumonia, of the motheaten (me/me) and viable motheaten (me^v/me^v) mice [7, 9]. In addition, quite rare occurrence of such a pulmonary lesion in mice without any other complications has been recognized among histologists [1]. However, histological description of the lesion has not been made. Recently, it has been shown that PCs in alveolar macrophages might be a hallmark of previous pulmonary hemorrhage in mice [6, 7]. The present note describes the histopathology and electron microscopy of a mouse spontaneously affected with the entity mentioned above.

The animal examined is a WBB6F₁ (WB-W/+ × C57BL/6J-W^v/+) female mouse, 6 weeks of age, raised in a commercial breeder and used for routine seromonitoring. At autopsy, the lungs were diffusely atelectatic with increased consistency.

Histologically, most of the alveoli had many alveolar macrophages containing PCs (positive with eosin and acid fuchsin, and negative with Perls' Prussian blue stain, periodic acid-Schiff reaction, Ralph's method for hemoglobin and Gmelin's reaction for hematoidin) and some iron-positive granules (Figs. 1 and 2), serous or fibrinous exudates and hyaline membrane-like structures. Those macrophages were bulged with PCs, or frequently fused each other, resulting in forming PC-rich multinucleated giant cells. Fresh hemorrhagic foci involving several neighboring alveoli were scattered with some erythrophagia by alveolar macrophages.

Alveolar walls were diffusely and remarkably thickened by increased prominence of capillary

basement membranes and proliferation of fibrous tissue including fibroblasts (Figs. 1 and 2). Double contour appearance or splitting of capillary loops with invasion of collagen fibers between alveolar capillary and epithelial basement membranes were frequent. Mononuclear cells were rare in the walls. Neutrophils were infiltrated in some alveoli filled with fibrinous substance, but those were quite rare within alveoli of other areas. Hemosiderin deposits were not seen in the alveolar walls, while they were marked in alveolar macrophages. Alveolar type II cells were markedly swollen, bulging into the spaces and slightly increased in number.

Several large intraluminal and fine intraepithelial PCs were seen in bronchioli with slightly increased mucous secretion.

Fig. 1. Accumulation of alveolar macrophages and multinucleated giant cells containing numerous PCs in the cytoplasm, and marked thickening of alveolar walls. Hematoxylin-eosin. ×400.

Fig. 2. Prominent capillary basement membranes. Cytoplasm of alveolar macrophages were smudged with iron-positive fine granules. Prussian blue-periodic acid-Schiff-hematoxylin. $\times 400$.

Electron-microscopically, large macrophages in the alveoli contained inclusions of rod-shaped PCs, coarse electron-dense granules, finely granular substances, and concentrically laminated features, each of which was bounded by single smooth-surfaced unit-membrane (Figs. 3 and 4). In the alveolar walls capillary basement membranes were remarkably and diffusely thickened, but no electron-dense deposits suggestive of immunoglobulin aggregates were recognized. Alveolar type II cells were bulged with increased laminated bodies. Cytoplasmic sheets of alveolar type I cells were partially ballooned and disrupted.

No significant lesions were detected in the kidneys and any other organs examined. No additional incidences were found in the colony, in which the present case was obtained.

Similar alveolar lesions have been known in the motheaten and viable motheaten mice [7, 9], which have varied immunological defects. There is little description of pulmonary interstitial lesions except for frequent cuffs of lymphoid cells around bronchi or blood vessels or both, and

Fig. 3. Electron-dense rods of PCs and finely granular substances (arrow heads) bounded by smooth-surfaced membranes in an alveolar macrophage. Nucleus (N). Mitochondrion (M). Uranyl acetate-lead nitrate. $\times 17,700$.

marked deposition of IgM around arterioles with mononuclear cell infiltrates. The cause of alveolar hemorrhages has not been referred in those mice. In human beings, three categories of diffuse pulmonary hemorrhage are classified on the basis of immunopathological studies [8]; one in which anti-basement membrane antibody is present (i.e., Goodpasture's syndrome), a second in which immune complexes are found (i.e., systemic lupus erythematosus), and a third in which neither can be demonstrated (i.e., idiopathic pulmonary hemorrhage: IPH). Although immunopathological examination was applied neither in alveolar walls nor in the renal glomeruli in the present case, the pathomorphological features representing chronically repeated episodes of intrapulmonary hemorrhage without vasculitis, inflammation, necrosis or granulomata were similar to those of IPH [8]. Diffuse thickening of the alveolar capillary basement membrane detected remarkably in the present case has been also found in human IPH [4]. The critical etiology of IPH is unknown, however, inherent

Fig. 4. An alveolar macrophage having PCs and laminated bodies, and thickening of capillary basement membrane without electron-dense deposits suggestive of immune complex in alveolar wall (upper half). Endothelial cell (E). Uranyl acetate-lead nitrate. $\times 4600$.

weakness of the pulmonary capillary basement membrane has been expected to account for the bleeding [3, 4]. Conversely, interstitial fibrosis and hyperplasia of the alveolar type II cells are regarded as nonspecific, secondary changes. In

mice type II cell abnormality and hyperplasia have been seen in the lungs with alveolar hemorrhage of apparently different etiology from the present case [9, 11].

In our case thickening of the capillary basement membrane was conspicuous without evidence of deposition of immune complex by electron-microscopical examination. These findings indicate that the primary change is a capillary bed injury by unknown cause as in IPH in man.

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要 約

マウスの特発性肺出血の1例(短報): 佐藤 宏・奈良間功²⁾・土谷 稔²⁾・板倉智敏¹⁾・大林正士(北海道大学獣医学部家畜寄生虫病学講座, ¹⁾比較病理学講座, ²⁾樹立生物科学技術研究所)多数の好酸性蛋白結晶をもつ肺泡マクロファージおよび多核巨細胞の肺胞内集簇と, 肺胞壁の肥厚を特徴とするマウス肺を, 組織学的ならびに電顕学的に観察した. この病態の原因として, 肺胞壁毛細血管基底膜の異常による肺胞内出血が示唆された. これはヒトの特発性肺出血 idiopathic pulmonary hemorrhage (hemosiderosis)に相当する特異なマウス肺病変と考えられた.