

Diffuse Alveolar Damage in a Young Cat

Ryosuke KOBAYASHI¹⁾, Shigeki YAMANO²⁾, Katsuyuki TANAKA²⁾, Junichi KAMIIE³⁾ and Kinji SHIROTA^{1,3)*}

¹⁾Research Institute of Biosciences, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, ²⁾Kanie Animal Clinic, 4-164 Gakuto, Kaniecyou, Amagun, Aichi 497-0050 and ³⁾Laboratory of Veterinary Pathology, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan

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ABSTRACT. A 10-month-old cat was diagnosed with congenital subvalvular aortic stenosis. To resolve its hypoxia, oxygen therapy was administered a couple of times a week during two months. The oxygen partial pressure in the chamber was maintained between 30 and 35%, and the time for one procedure was 12–24 hr. The animal died due to severe respiratory failure. At necropsy, the lungs were voluminous and had a rubbery texture. Histologically, large type II pneumocytes with occasional atypia had diffusely proliferated within the lungs. Interstitial fibrosis was not observed, although some alveolar septa were thickened along with fibrinous exudates and neutrophilic infiltration. The histology of these lesions was consistent with diffuse alveolar damage (DAD), which might have been partially due to oxygen toxicity.

KEY WORDS: acute respiratory distress syndrome, diffuse alveolar damage, feline, interstitial pneumonia.

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Diffuse alveolar damage (DAD) reflects diffuse injury to pneumocytes and endothelial cells in alveolar septa. It is characterized by the formation of hyaline membranes (acute exudative phase), proliferation of type II pneumocytes (sub-acute proliferative phase), and interstitial fibrosis (chronic phase) in the lungs. For domestic animals, DAD has not been strictly defined, and this term is sometimes used as a synonym for interstitial pneumonia [1]. Experimentally induced DAD has been reported in pigs, dogs, and sheep [15] and many viruses with tropisms for pneumocytes can induce DAD [4, 6, 14]. In cats, DAD has been reported to arise after inhalation of nitrogen dioxide or due to infections with feline calicivirus [8], Avian H5N1 influenza virus [2, 7], and severe acute respiratory syndrome-coronavirus (SARS-CoV) [13].

In humans, DAD is the histological manifestation of acute lung injury and acute respiratory distress syndrome (ARDS), which are clinically characterized by sudden, fatal respiratory insufficiency in the absence of cardiac failure. It is known that DAD can arise due to a variety of causes, such as direct injury to the lung or systemic disorders like shock. In veterinary practice, ARDS has been mostly described in dogs [10, 11], but not in cats.

In this study, we describe DAD in a young cat that was characterized by predominant proliferation of type II pneumocytes.

A 10-month-old female domestic Japanese cat was brought to a veterinary hospital for a vaccination, and was found to have a cardiac murmur upon physical examination. On an ultrasonographic examination, cardiac disease was diagnosed as a severe grade of congenital subvalvular aortic stenosis. From five months after the first visit, pulmonary

edema often developed in the cat, and oxygen therapy using an Altas ICU station (TAIYO Electronics Co., Ltd., Tokyo, Japan) was administered a couple of times a week to resolve hypoxia. The oxygen partial pressure in the chamber was maintained between 30 and 35%, and the time for one procedure was 12–24 hr. Oxygen therapy had been frequently done during two months, but the cat's body conditions worsened and the animal died at the age of 17 months due to respiratory failure with pulmonary edema.

At necropsy, the subvalvular portion of the aortic valve showed severe stenosis with thickening of the wall and the left atrium was markedly dilated. The lungs were voluminous, rubbery, and showed mild congestion. There were a few hemorrhagic foci in the lungs (Fig. 1). Tissue samples of the heart and parts of the lungs were fixed in 10% formalin and sent to our laboratory for histological examination. These were routinely embedded in paraffin, cut at 4 μ m thicknesses, and stained with hematoxylin and eosin (HE). Masson's trichrome stain (MTC) and Watanabe's method for reticulin fibers were used on selected sections. For immunohistochemistry, mouse anti-cytokeratin clone AE1/AE3 (Dako, Copenhagen, Denmark; 1:100) and peroxidase-conjugated anti-mouse IgG [Histofine Simple Stain MAX-PO (M); Nichirei, Tokyo, Japan] were used as primary and secondary antibodies, respectively. For electron microscopy, small pieces of formalin fixed lung tissues were refixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were stained using uranyl acetate and lead citrate and were examined using a JOEL 1210 transmission electron microscope (JOEL, Tokyo, Japan).

Histological examination revealed that type II pneumocytes had diffusely proliferated in the lungs and alveolar spaces were obscure (Fig. 2). The proliferating pneumocytes were large and showed moderate atypia with a few mitotic figures (Fig. 3). Alveolar structures had not been

*CORRESPONDENCE TO: SHIROTA, K., Laboratory of Veterinary Pathology, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan.
e-mail: shirota@azabu-u.ac.jp

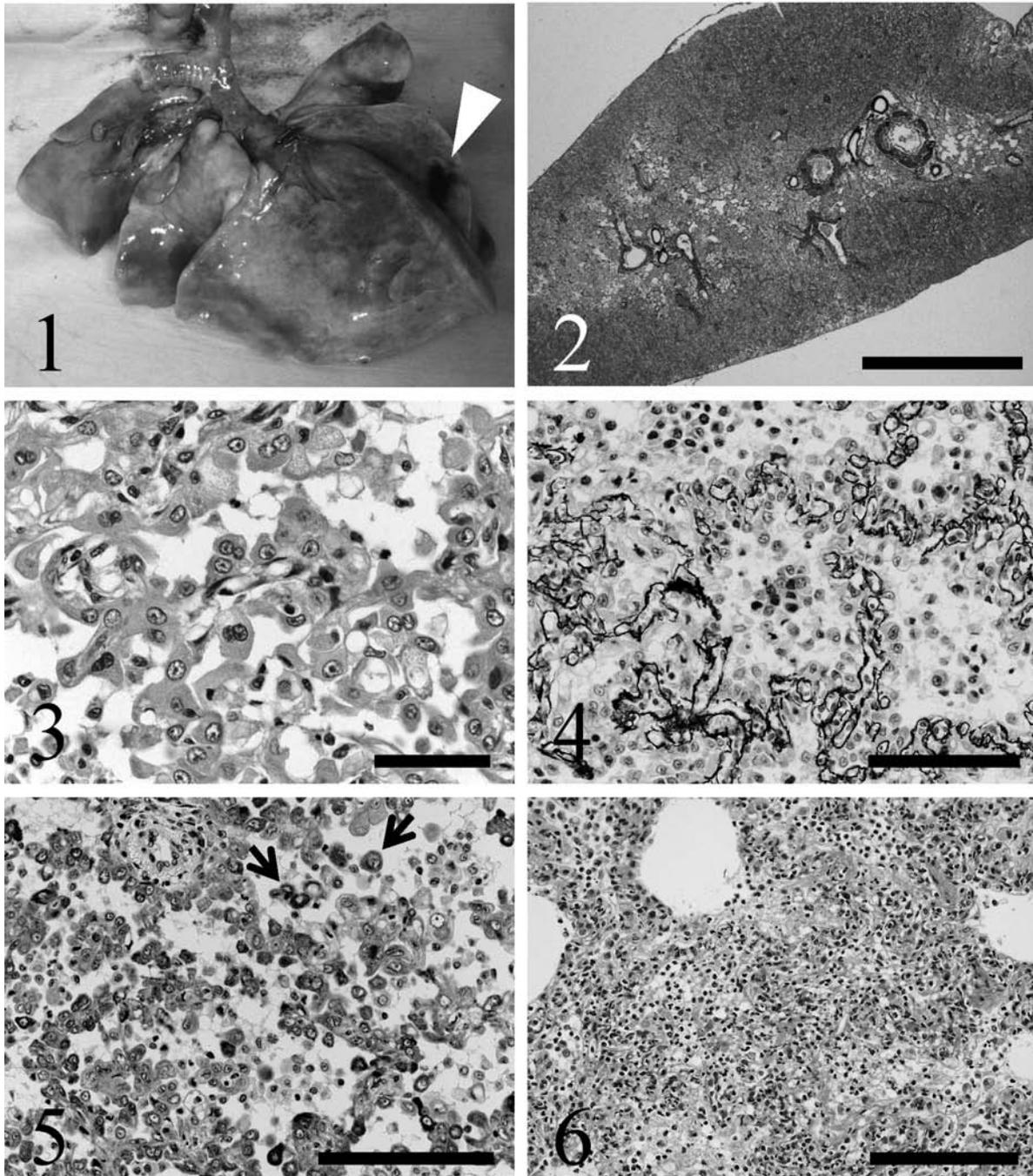


Fig. 1. Gross appearance of the lung. The lung was voluminous and had a rubbery texture. A few hemorrhagic foci were observed (arrow head).

Fig. 2. Overview of the distribution of lesions. Alveolar spaces were obscure. MTC. Bar=4 mm.

Fig. 3. High-power view of the alveolar spaces with proliferating type II pneumocytes. These cells were swollen and some showed moderate atypia. HE. Bar=50 μ m.

Fig. 4. Alveolar structure was well preserved in a lesion with proliferation. Watanabe's method for reticulin fibers. Bar=100 μ m.

Fig. 5. Alveolar spaces were filled with large cells, some of which were positive for cytokeratin (arrows). Bar=120 μ m.

Fig. 6. Alveolar septa were thickened along with fibrinous exudates and neutrophilic infiltration. HE. Bar=150 μ m.

destroyed and were well-preserved (Fig. 4). Goblet cells were not seen in any of the lesions. The alveolar spaces were filled with a number of macrophages and sloughed pneumocytes (Fig. 5). Some alveolar septa were thickened along with fibrinous exudates and neutrophilic infiltration (Fig. 6); however, hyaline membrane and interstitial fibrosis were not observed. On examination with the electron microscopy, no infectious agents were seen in any of the epithelial cells. In the heart, severe endocardial fibrosis was found in the constricted area.

The clinical and pathological findings suggested that the lung lesions in this case corresponded with those seen with DAD. The lesions had features of the subacute proliferative and acute exudative phases of DAD, but not the chronic fibrosing phase. Hyaline membrane as one of the discriminative histological findings of DAD was not observed in the present case. The fibrinous materials lining the alveolar walls are formed by increasing capillary permeability and cellular exudation [3]. The appearance frequency of the characteristic pulmonary lesions in DAD might be different among animal species, and previous report suggested that hyaline membrane could be formed by alveolar damage in cats [9]. In this case, we thought that mild concentration of oxygen which used in the therapy didn't induce intense endothelial cell injury resulting in hyaline membrane formation.

Oxygen toxicity may directly affect pneumocytes and capillary endothelial cells via the generation of reactive oxygen species, and the inhalation of highly concentrated oxygen induces lung injury and ARDS [12]. There are limited data on the sensitivity of cats to oxygen [3]. In dogs, oxygen concentrations lower than 50% generally do not induce lung injury [5]. Additionally, juvenile animals generally exhibit a higher resistance to oxygen toxicity than do adults [3]. Thus, it seems likely that oxygen toxicity was not the only cause of DAD in this cat, and there might have been some underlying predisposing factors. However, it was not possible to identify any systemic disorders that might have contributed to DAD, such as cardiogenic shock or acute pancreatitis.

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