Intrauterine Bronchiolitis Obliterans

Report of an Autopsy Case and Review of the Literature

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Summary. A case of newborn infant, born at 28 weeks gestational age, was incidentally diagnosed as bronchiolitis obliterans at autopsy by being recognized that the widespread bronchiolar stenosis by polypoid masses composed of cicatrical tissue, which was also proved by electron microscopic studies. Though bronchiolitis obliterans was observed in newborns, infants and children as well as in adults, the similar case of intrauterine bronchiolitis obliterans was reported only by Sir in 1962, as bronchiolitis obliterans connata. Because of nature and maturity of the lesion, it was considered that our case was effected by some causative agent two months or more prior to his birth.

Bronchiolitis obliterans was first described and recognized by Lange (1901), who differentiated it from overgrowth of fibrous tissue in alveoli such as organizing pneumonia. Thereafter it has been described in many human cases and in experimental conditions of animals. It has been observed in infants and early children, but intrauterine bronchiolitis obliterans cannot be found out in the literature except one case reported by Sir (1962).

Widespread bronchiolitis obliterans was incidentally noted in our autopsy case, who was clinically diagnosed as idiopathic respiratory distress syndrome and died on the 4th day after birth. In this paper the morphological features of this case are presented and nature of bronchiolitis obliterans will be discussed.

Report of a Case

The patient was a male infant born at 28 weeks gestational age, weighed 1160 gm at birth and was delivered from a 24 year-old mother of gravida 4 and para 1. There was no illness during the pregnancy. She didn't receive any medication during pregnancy.

She had vaginal bleeding at the 7th day prior to delivery. Therefore she was admitted to the University Hospital and was diagnosed as placenta praevia by the ultrasonic examination. But there were no abnormalities of pelvic examination. Maternal serologic tests for syphilis was negative. The labor was uneventfull except premature rupture of membranes. There were no abnormal findings of the embryonic adnexa.

The patient developed cyanosis at the peripheries just after birth. Apgar score was 7 at one minute after birth. He was immediately nursed in incubator, but general condition was gradually deteriorated. On the 3rd day of life, apneic attack began and occurred repeatedly thereafter. On the 4th day of life he died.

Mother was going well after delivery.

Necropsy Findings

(Autopsy No.: Kyushu University No. 16673)

Macroscopic Findings

The right lung weighed 14 gm. and the left 19 gm. Both were collapsed, intensely injected and diffusely consolidated. There were scattered areas of hemorrhage. A small quantity of bloody fluid was noted in the right intrapulmonary bronchi, but no blood in the pleural spaces. Cerebral hemorrhage accompanied with rupture into the lateral ventricle was recognized in striae terminalis of the left cerebral hemisphere.

Microscopic Findings

Several blocks of tissue were taken from each lobe of the lungs. Various stainings were applied to sections from both paraffin-embedded and frozen material.

The lungs were fairly developed. The hostological appearance showed incomplete expansion with intense congestion. Accumulation of immature granulocytes was scatteredly found in the edematous interstitium.

In the alveoli, inhalated squamous debris of amniotic fluid, desquamated alveolar epithelial cells and neutrophils were scatteredly found, but in mild degree. Pulmonary hemorrhage was also noted. Hyaline membrane was not observed in all sections. No septa were lined by metaplastic alveolar cells. No viral inclusion bodies were detected at all levels of the respiratory tract and in other organs. There was no proliferation of fibrous tissue in the alveolar septa as well as in the alveolar spaces.

In large and medium-sized bronchi, most frequent change was an increase in number of goblet mucus-secreting cells in the epithelium with pseudostratification. In the bronchial lumens seromucous exudate and desquamated epithelial cells were occasionally noted.

The most striking histological finding was partial obliteration or stenosis of the bronchioles, especially of the terminal bronchioles by the round or elongated polypoid masses (Figs. 1 and 2). The polypoid masses were fibrous connective tissue with hyalinization, containing a small number of fibroblasts (Fig. 3). Capillaries were found at the base of some polypoid masses. Almost all of these fibrous tissues were completely covered by a single layer of flattened epithelial cells, which continued to the epithelium of a remainder wall. Slight infiltration of chronic inflammatory cells was seen in the bronchioles. The projection of the polypoid masses into the lumens was varied in degree, from slightly elevated subepithelial focal scarring to the partial obliteration of the lumens which showed a narrow slit.

In other organs, there were no findings of chronic inflammatory processes. The brain showed immaturity, especially the persistence of the subependymal matrix. In the left cerebral hemisphere there was subependymal hemorrhage, which ruptured to the lateral ventricle. Thymus weighed 2 gm., in which cystic change of some Hussall's bodies, phagocytosis of nuclear debris by large histiocytic cells and depletion of thymocytes were noted. There were no remarkable changes in the lymph nodes. There was a nephrogenic zone in the kidneys. Extramedullary hematopoiesis was present in the liver and spleen as well as in the lungs.

Fig. 1. Two polypoid masses are projecting into the lumens from one side of the walls of terminal bronchioles and are covered by flattened epithelial cells. These masses are composed of scar tissue containing a few fibroblasts. Slight infiltration of chronic inflammatory cells is found in the adjacent edematous interstitium. ×115 H and E
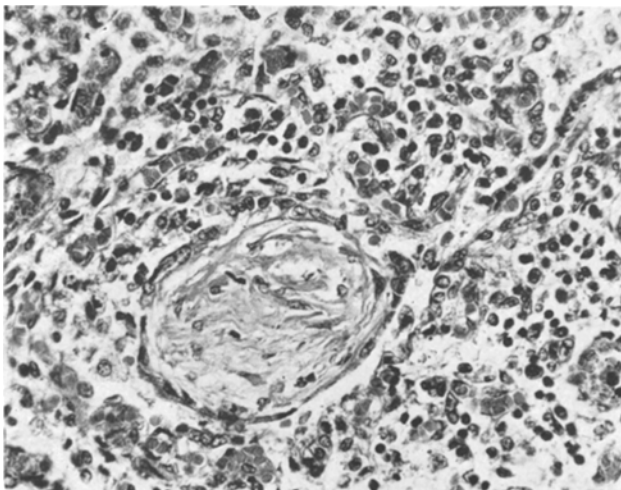

Fig. 2. Polypoid mass occupies the lumen of terminal bronchiole which is transversely cut. ×230 H and E

In addition, electron microscopic studies were done to certify that the polypoid masses were composed of scar tissue. Pulmonary tissue that had been fixed in 10% formalin solution was postfixed in 3% glutaraldehide and 1% osmium tetroxide buffered to pH 7.4 with 0.1 M cacodylate solution, dehydrated in a graded series of ethanol, embedded in Epon 812. Sections 1.0 μ in thickeness were stained with toluidin blue, and were studied by a light microscope. Ultrathin sections of suitable
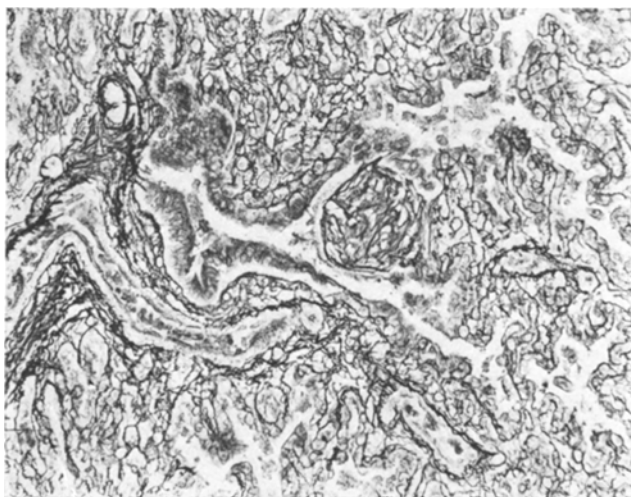
Fig. 3. A well-circumscribed scar tissue is noted at the diverging point of the terminal bronchioles. No fibrosis in other pulmonary interstitium. $\times 150$ Silver
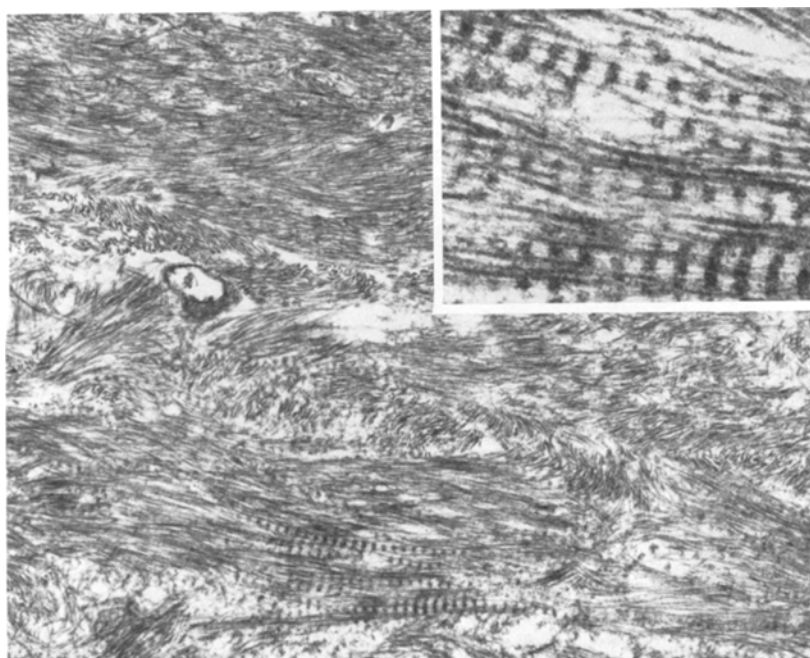

Fig. 4. Electron micrograph of polypoid mass showing accumulation of mature collagen fibers and a few fibrous long-spacing fibers. Inset shows fibrous long-spacing fibers with dense bands in regular periodicity of 900 Å. Uranyl acetate and lead citrate, $\times 15000$; inset, $\times 48000$

areas, in which were noted projecting polypoid masses, were stained with uranyl acetate and lead citrate and examined in an electron microscope. These masses were composed of a large number of collagenous fibers with regular periodicity of 640 Å

on the average and about 200 Å in diameter and arranged in bundles and in interlacing pattern. There were a few fibrous long-spacing fibers, which showed a periodicity of 800 Å to 900 Å with dense bands connected by fine filaments (Fig. 4). A small number of fibrous long-spacing fibers were also noted in the interstitial spaces of the alveolar septa. These electron microscopic findings proved that the polypoid masses were composed of nothing but scar tissue.

Discussion

In this case, the histopathological findings in the lungs are characterized by: (1) bronchioles, especially terminal bronchioles, were partially obliterated or stenosed by polypoid plugs of cicatrical tissue arising from these walls, which were accompanied with slight infiltration of chronic inflammatory cells; (2) neonatal pneumonia in mild degree; and (3) atelectasis with marked congestion and patchy hemorrhage.

The first lesion is equivalent to that reported by other authors as bronchiolitis obliterans (Hart, Mayer, 1928; Giese, 1960; Spencer, 1968; Millard, 1971).

The time when this case was effected by some causative agent cannot be accurately estimated, but it is certain that this lesion was developed during intrauterine life because of nature and maturity of the lesion. Becroft (1971) described four cases of bronchiolitis obliterans in early children, who were diagnosed at necropsy and by the surgical specimens of the pneumonectomized lung, at intervals of two months and three years after acute adenovirus type 21 infection. The terminal bronchioles of three cases, dissected two months after acute illnesses, were obliterated by vascular fibrous tissue with sparse infiltration of chronic inflammatory cells and those of another case pneumonectomized three years after acute illnesses were completely obliterated or replaced by radiating fibrous scar tissue. Moran and Hellstrom (1958) studied experimentally the pathogenesis of bronchiolitis obliterans in rabbits. Animals killed one or two months after the exposure to nitrogen oxide presented well-defined bronchiolitis obliterans composed of fibrous granulation tissue.

The polypoid masses of our case consisted of hyalinized connective tissue containing a few fibroblasts. Therefore it is considered that our case was affected by some causative agent two months or more prior to birth.

In our case, it is also made certain by electron microscopic studies that the polypoid masses are composed of scar tissue. Moreover, it is interesting that a few fibrous long-spacing fibers of collagen are found in the polypoid scar tissue as well as in the interstitial spaces of the alveolar septa (Banfield, Lee, 1973).

Our case shows neither bronchiectatic nor emphysematous lesions, which have been discussed in relation to bronchiolitis obliterans as sequelae of initial lower respiratory inflammation (Mclean, 1958; Culiner, 1963; Anderson, Strickland, 1971; Becroft, 1971).

It is considered that bronchiolitis obliterans is a sequela of ulcerative or necrotizing bronchiolitis caused by various etiologies. Obliteration of the bronchioles by the projecting polypoid masses seems to be resulted from organization of fibrinous or highly proteinaceous exudate (Hart, Mayer, 1928; Moran, Hellstrom, 1958; Giese, 1960; Spencer, 1968; Becroft, 1971).

Bronchiolitis obliterans in general could be roughly divided into three categories: (1) following inhalation of irritant or damaging gases in adult cases, including fume of nitrogen dioxide (McAdams, 1955; Lowry, Schuman, 1956) ammonia (Edens, 1906), sulfuric acid (Edens, 1906) and others (LaDue, 1941); (2) occurrence after respiratory infections usually in infants and young children, especially influenza (Winternitz, 1920), measles (Hart, 1904), adenovirus infection (Nezelof, Meyer, Dalloz *et al.*, 1970; Becroft, 1971) and others; and (3) in conditions of unknown origin with incidious onset. Reports of each cases following aspiration of foreign body (Wegelin, 1908), inhalation burn (Perez-Guerra, Walsh, Sagel, 1971) or oxygen therapy (Anderson, Strickland, 1971) were also found.

In 1962, Sir reported a similar case of newborn infant to ours. In both lungs was recognized neonatal pneumonia with bronchiolitis obliterans. Fibrosis and chronic inflammatory infiltrate were also noted in the alveolar septa. He suggested that its etiology was an infection of amniotic fluid, especially of viral origin, because of repeated vaginal bleeding and late disturbances of pregnancy with pain of lower abdomen and knees after traumatic accident at 2 months prior to delivery.

The etiology of our case is unclear, as no maternal illnesses were noticed during pregnancy, and virological, bacteriological and other pathogenic examinations of this patient and his mother were not almost done.

Intrauterine bronchiolitis obliterans might result from fetal respiratory infection of some viruses through placenta or amniotic fluid. Low incidence of this disease in the intrauterine and neonatal period might be due to the characteristics of immunological environments and the mode of contact with causative agents during the intrauterine and neonatal life.

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