CONGENITAL PULMONARY LYMPHANGIECTASIS

BY

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An analysis of the literature reveals scanty data on congenital pulmonary lymphangiectasis (Virchow, 1856; Klebs, 1889; Bredt, 1952). It would therefore appear to be a comparatively rare condition, yet an investigation of just over 451 consecutive necropsies on stillbirths and neonates, carried out in the Portsmouth area, revealed five cases. Reports of three of these have already been published (Laurence, 1955); the other two are Cases 4 and 5 of the present communication. Case 6 was examined at The Hospital for Sick Children, Great Ormond Street, Cases 7-9 were referred from Birmingham, and Case 10 from Toronto. Additional examples have been reported by Giammalvo (1955) and by Maidman and Barnett (1957). It therefore appears that the condition is not rare, but unrecognized, especially in its microscopic form.

Case Reports

Cases 1-3.—These have already been reported by Laurence (1955).

Case 4.—A male infant was born spontaneously at term, limp and blue, after a normal pregnancy. The cyanosis continued though he became more energetic. On the fourth day congenital heart disease was suspected, possibly a left-to-right shunt, as a soft apical systolic murmur could be heard. A radiograph of the chest (Fig. 1) was taken, which showed an enlarged heart and increased opacity of both lung fields with some mottling, suggestive of a diffuse cystic change. The child was placed in an oxygen tent but without any effect on the cyanosis. By the sixth day the liver had enlarged, and there was a gradual fall in temperature, with a concomitant rise in the pulse and respiration rates. His condition deteriorated. On the eighth day he died.

At necropsy the infant (weight 3.1 kg.) was well formed, but markedly cyanosed. Both lungs were considerably heavier than normal, and studded with small, fluid-containing vesicles throughout; some of those on the surface resembled very dilated lymphatic

FIG. 1.—A radiograph of Case 4 showing diffuse opacity and mottling of both lung fields, suggestive of a generalized cystic condition.

vessels. The parenchyma itself was congested and consolidated, and in places mucopurulent material could be expressed from the air passages. The hilar lymph nodes were normal and the pleural cavities dry. The heart was somewhat dilated, but otherwise the remaining systems showed no abnormalities to the naked eye.

Case 5.—A male infant, who progressed moderately well for a few days following a normal pregnancy and delivery, developed increasing cyanosis and vomited his feeds. Antibiotics settled the slight pyrexia (99.6° F.), but failed to improve the child's general condition. In spite of continuous oxygen the cyanosis increased. On the fifteenth day there was obvious congestive cardiac failure, which did not respond to digoxin, and he died on the thirtieth day of life.

At necropsy the infant, who weighed 3½ kg., was seen to be poorly nourished and markedly cyanosed.

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Bilateral serous pleural effusions were present (150 ml. in all). The lungs were abnormally firm and the subpleural lymphatics were prominent. The cut surface was pink and exuded abundant clear fluid. The gross appearances were thought to be those of pulmonary oedema and diffuse fibrosis. The heart (45 g.) showed moderate right ventricular dilatation and hypertrophy. The ductus arteriosus was only patent to a probe. A small serous pericardial effusion was present and the peritoneal cavity contained 200 ml. of ascitic fluid. The liver and spleen were large and congested.

Case 6.—This full-term male infant, in whom irregular heart sounds and meconium-stained liquor, suggesting foetal distress, were noted before breech delivery, was stillborn and the placenta was normal.

At necropsy at The Hospital for Sick Children the infant, who weighed only 2 lb. 10 oz., showed abnormalities of the eyes and arms and had a bilateral harelip and cleft palate.

Both lungs were hypoplastic and showed an exaggerated but fine lobular pattern with dilated subpleural lymphatic vessels, giving an appearance not unlike that of a liver with biliary cirrhosis. On cross-section, the parenchyma was unexpanded and divided into small lobules by numerous, irregular cysts measuring up to 1 mm. in diameter.

In addition there were hypoplastic kidneys, a tentorial tear, a left diaphragmatic hernia, and multiple malformations of the heart. These included a mitral atresia, a ventricular septal defect, a hypoplastic left ventricle, and a bicuspid pulmonary valve.

A full-term, stillborn, female sib also had a harelip and cleft palate and weighed 4 lb. 10 oz. Foetal distress was noted for which no cause was found at necropsy. Unfortunately, no sections are available for examination. From the description, however, it might be possible that this case was also an example of pulmonary lymphangiectasis.

Case 7.—A female infant was born spontaneously after a normal pregnancy, but with the cord wound tightly round her neck. She had "white asphyxia," gave one long gasp and died without respiration ever having been established.

At necropsy the infant weighed 2.1 kg. "The bulky unexpanded lungs showed a network of very prominent lymphatic vessels under the pleural surfaces. In many areas, especially near the base and the free borders, numerous subpleural cysts containing clear, serous fluid were found. On the cut surface the parenchyma presented a spongy appearance with fluid-containing cysts extending throughout the lung, dividing the parenchyma into very distinct lobules" (Dr. H. Baar). The pleural cavity and hilar lymph nodes were normal.

The heart was markedly enlarged and showed aortic stenosis with patent intraventricular and interauricular septae and hypoplasia of the left ventricle and mitral valve. The ductus arteriosus was widely dilated. Apart from a tentorial tear and a subdural haematoma, there were no other significant findings.

Case 8.—A male infant was born spontaneously after a normal pregnancy. He immediately became deeply cyanosed and hypotonic, and, in spite of mucus aspiration, died six hours after delivery.

At necropsy he was seen to be a normally developed but markedly cyanosed child (weight 2.2 kg.). "The lungs were bulky and greyish-white with innumerable pinhead-sized subpleural cysts scattered all over the surface. Some of the cysts were collapsed, but the majority were filled with clear, serous fluid. The lungs were fairly well aerated, and fluid-filled cysts, which were irregular in shape and size (up to 2 mm. in diameter), could be seen with the naked eye throughout the parenchyma. They tended to give the lung an exaggerated lobular pattern" (Dr. H. Baar). The pleural cavities and tracheo-bronchial lymph nodes were normal.

There was marked enlargement of the heart, chiefly of the right atrium and ventricle. The left ventricle and atrium and aortic ostium were hypoplastic. A large auricular septal defect and patent ductus arteriosus were present. The only other positive finding was a large right-sided subdural haematoma.

Case 9.—A male infant was born spontaneously, weighing 2.3 kg. Meconium-stained liquor was seen before the head was fully crowned, though there had been no previous signs of foetal distress. The child cried well, but his breathing was irregular. Cyanosis became marked in spite of the usual resuscitative measures and continuous oxygen, and he died two hours after delivery.

At necropsy the lungs were "voluminous and extremely oedematous. To the naked eye it seemed as if a thin layer of ice enveloped the whole lung immediately underneath the pleura. Through this layer, the wide lung markings were obvious" (Dr. H. Baar). The pleural cavities each contained 10 ml. of clear, serous fluid. Apart from the congestion of the cerebral vessels, and a small rupture of the great vein of Galen, there were no other significant findings.

Case 10.—A full-term male infant became cyanosed and flaccid 10 minutes after an uneventful delivery. He was transferred within an hour to hospital, but was dead on arrival.

At necropsy 15 hours later, deep cyanosis and petechial haemorrhages of the skin were found. Venous congestion was generalized, and particularly severe in the lungs. Bilateral subpleural haemorrhages were present, but no other abnormal features were noted on naked-eye examination of the lungs.

The liver was also markedly congested, and there was a haemorrhage into the left adrenal gland. A small left tentorial tear was present.

Gross Appearances of the Lungs

Many features common to all or some of the cases are at once apparent. The lungs are usually bulky and inelastic, with pronounced lobulation. Prominent

FIG. 2.—The lungs of Case 8 showing very prominent subpleural lymphatic vessels and subpleural cysts.

FIG. 3.—The lungs of Case 7 with exaggerated lobular pattern and subpleural cysts, some of which are collapsed and appear as dark depressions under the surface.

subpleural lymphatic vessels form a dense network (Fig. 2), and in the majority of cases subpleural cysts can be seen with the naked eye. These may measure up to 3 mm. in diameter, and are transparent and glistening. They are filled with clear, colourless serous fluid, and their thin walls have a smooth inner surface. After fixation, these cysts tend to collapse, and they are then seen as darkish depressions under the pleura (Fig. 3).

Section of the lung of a typical case shows a parenchyma diffusely honeycombed with fluid-containing cysts of irregular shape and size, some of which may reach as much as 5 mm. in diameter (Fig. 4). The cysts near the hilum are elongated and often enlarged (Fig. 5). In addition there is a considerable increase in the fibrous tissue of the interlobular septa, which, together with the cystic spaces, gives the lungs their grossly exaggerated lobular pattern. In all the cases studied, both lungs were almost uniformly affected by the cystic changes.

Serous fluid, suggestive of pulmonary oedema, may ooze from the cysts when the fresh lung is cut, while the abundant interlobular fibrous tissue may simulate the appearance of pulmonary fibrosis. Indeed, these diagnoses were made in three cases on gross examination (Cases 1, 5, and 9), and one was mistaken for interstitial emphysema (Case 3). The condition was, however, correctly recognized in four others (Cases 4, 6, 7, and 8), whereas the abnormality passed unnoticed in only two cases (Cases 2 and 10) until sections of the lungs were examined microscopically.

Histology

The cysts are situated mostly in the connective tissue under the pleura and in the interlobular septa (Figs. 6 and 7), though collections of smaller spaces can be found within the lobules themselves. They are often closely related to bronchi and blood vessels, sometimes sharing a common wall (Fig. 8).

The cyst walls, rarely more than 10 μ in thickness, consist of a delicate network of elastic, collagen, and occasionally smooth muscle fibres (Fig. 9). They are lined by a single layer of flat endothelial cells, which in Case 2 is extensively desquamated and curled up in the centre of the space.

Faintly eosinophilic material or red blood cells may be present in the spaces, but more usually these appear completely empty. In Case 4, however, many cavities contain pus cells, infection presumably having spread from the neighbouring air passages and alveoli (Fig. 10).

The spatial arrangement of the cystic spaces within the lung was investigated. Serial sections, 10 μ thick, were cut and the preparations projected on to cellulose acetate sheeting by an Aldis projector fitted with a microscope attachment; the

FIG. 4.—The lung of Case 7 cut at right angles to the main vessels and bronchi. The cysts show as dark rounded spaces.

outlines of the spaces were drawn in Indian ink in consecutive sections in one area, and in every fifth section in other but larger fields. The tracings were superimposed accurately one upon another after lightly colouring the "lumina" (Fig. 11). From these it became evident that the spaces are part of an intricate network of intercommunicating channels. The individual channels themselves vary in width, not only from one another, but

also in different parts of the same channel. Thus, a space only $15\ \mu$ in diameter may be in direct continuity with a cystic dilatation 2 mm. in diameter. Further, the channels are constantly changing direction, and may double back upon themselves or take a spiral course. In the sections examined, none of the cysts appears to be without a communication with the remainder of the network, and so far no true valves have been found. Structures described as valves by Giammalvo (1955) and Maidman and Barnett (1957) were probably only folds in the channel wall.

The abundant connective tissue of the interlobular septa appears almost embryonic, and none of the cases shows thick collagen fibres of chronic inflammatory changes. In some instances, the lung parenchyma itself looks immature, resembling that of a seven-month foetus. Sometimes it is unexpanded, sometimes partially or well aerated, and in one case there is a terminal pneumonia. Alveoli may contain red blood cells

FIG. 5.—Lung of Case 7 cut in the plane of the main vessels and bronchi. The cysts appear as dark spaces which tend to be elongated towards the hilum.

FIG. 6.—Lung of Case 2 to show distribution of lymphatic spaces and abundant interlobular connective tissue (haematoxylin and eosin $\times 16$).

FIG. 7.—Lung of Case 7 showing distribution of cysts in close relationship to blood vessels (haematoxylin and eosin $\times 10$).

FIG. 8.—Lung of Case 10 with subpleural spaces in an interlobular septum in close relationship to blood vessels (haematoxylin and eosin $\times 35$).

FIG. 6

FIG. 8

FIG. 7

FIG. 9

FIG. 10

FIG. 9.—A blood vessel running obliquely across the field with several lymphatic spaces in close relationship to it, and actually sharing a common wall (Weigert's elastic and Van Gieson's stain $\times 400$).

FIG. 10.—Left lung (Case 4) showing subpleural and septal cystic spaces containing pus cells (haematoxylin and eosin $\times 70$).

FIG. 11.—Reconstruction of 20 serial sections of 10μ thick, with the outline of the cystic spaces drawn in indian ink, and the lumina lightly shaded in. The pleura and main blood vessels are lightly indicated. The lymphatic spaces are part of a continuous network of vessels.

FIG. 11

and an occasional mononuclear cell. The bronchi generally have an intact epithelium. The hilar glands show no abnormality.

Discussion

The position of the cystic spaces in the normal distribution of lymphatics, as described by Miller (1947), their close relationship to blood vessels and bronchi, and their structures can leave little doubt that they must be derived from lymphatic vessels. These cystic spaces differ considerably from the cysts of bronchial origin, which are often air-filled, have a lining of bronchial or respiratory epithelium and are related to, if not in actual continuity with, the air passages. Occasionally, however, such air-filled cysts may be lined by flattened "endothelial" cells as in the cases of Flemming (1934) and Bowden (1948), but

careful search usually reveals groups of columnar or cubical cells, indicating the true nature of the cysts.

Congenital lymphangiectasis must be distinguished from a number of other conditions. At necropsy it could be mistaken for interstitial emphysema as happened in Case 3. In emphysema, however, the cystic spaces contain air, and under the microscope, although they may have an "endothelial" lining acquired from the connective tissue, neither their position and their relationship to other structures nor the structure of the wall is constant.

Care must be taken when airless lungs containing normal but dilated lymphatic vessels are examined, as they may occasionally have the honeycombed appearance of congenital lymphangiectasis. Closer examination will reveal that the vessels are fewer in number, constant in calibre, and run a straight course.

The rare intrapulmonary lymphangioma, though difficult to distinguish from lymphangiectasis, is recognized by its localized nature and its differing structure (Anderson, 1953). The case of Anspach and Wolman (1933) reported as pulmonary lymphangiectasis is almost certainly an example of one of these tumours.

Finally, the condition has to be differentiated from the cases in which pulmonary lymphatic cysts are part of a generalized lymphatic disorder throughout the body, such as those of Mann and France (1955) and McKendry, Lindsay, and Gerstein (1957). In congenital cystic pulmonary lymphangiectasis the cysts seem to be strictly confined to the lung.

As the condition appears to be found only in stillbirths and neonates, it can be assumed to be congenital. The only case reported in an older subject (Bredt, 1952, Case 2) is more likely to be one of bronchial cystic disease with the cysts having the endothelial-like lining referred to earlier. No blockage of the veins or lymphatic vessels has yet been seen to suggest secondary lymphangiectasis, while chylothorax, lymphorrhagia, and inflammatory reaction of the connective tissue amongst other features (Roujeau, Delarue, and Depierre, 1950) were not present in the cases examined.

On the contrary, it is much more likely to be a primary developmental anomaly similar to the lymphangiectasis in the limbs of newborn infants where neither hypertrophy of the vessel walls nor the tissue reaction is seen (Allen, Barker, and Hines, 1946). The occurrence of other major congenital malformations in over half the known

cases is additional evidence in favour of this view.

A possible explanation of this anomaly has been suggested earlier (Laurence, 1955). The lymphatics, which grow into the lung bud about the ninth week of intrauterine life, have formed by the fourteenth week large trunks in the connective tissue septa, which divide the parenchyma into distinct lobules. Normally this lobulation becomes indistinct after about the twentieth week as connective tissue diminishes and the lymphatics become much narrower (Maximow and Bloom, 1942). It is suggested that pulmonary lymphangiectasis represents a continued growth of the lungs, with the tissue elements maintaining the proportions observed at 16 weeks. This seems to be the only satisfactory explanation for the unusual histological appearances.

Giammalvo (1955) maintains that cystic dilatation of the lymphatics results from failure or delay in the linkage of isolated lymphatic spaces. If this were so, cysts would be more likely to be confined to the peripheral portions of the lungs where fusion would occur last. This distribution was not evident nor were the spaces found to be isolated cysts in the numerous serial sections studied and reconstructed, but were shown to form a network of intercommunicating channels. Injection methods could establish this point, but so far there has been no opportunity, as the lungs have been fixed or extensively cut beforehand.

Progressive cyanosis accompanying the cystic condition is not difficult to explain. Of the cases described, three were accompanied by congenital heart disease, and two, or possibly three others, by intracranial haemorrhage. In the remaining three, where cyanosis must have been largely of pulmonary origin, there was little venous or bronchial obstruction from the grossly enlarged but undistended lymphatic channels, as in some cases of interstitial emphysema (Macklin and Macklin, 1944). It is also unlikely that the volume of the cysts produced poor aeration of the lung by taking up the available thoracic space. The bulky interlobular connective tissue and the cystic lymphatic vessels probably increased the resistance to lung expansion, while the inelasticity of the lungs decreased the pumping action from the respiratory excursions on the pulmonary circulation (Maidman and Barnett, 1957). This would explain the cardiac changes sometimes noted. In addition, the parenchyma in several instances was immature. Taken together, these factors could explain the progressive cyanosis and the rapid clinical deterioration.

Summary

A further seven cases of congenital cystic pulmonary lymphangiectasis are added to the three previously described in 1955 and the five others reported in the literature. Evidence is produced to show that the condition is a diffuse but irregular dilatation of the pulmonary lymphatic vessels. This form of pulmonary cystic disease is differentiated from other similar conditions.

It is suggested that this is a true developmental malformation and the possible pathogenesis is discussed. Probable reasons for the accompanying cyanosis are given. The evidence indicates that this malformation is more common than the few reported cases would suggest.

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Addendum

Since submitting the above paper, three further cases have appeared.

Case 11.—A 10 lb. male infant was cyanosed from birth. Resuscitation was without avail and he died after 20 hours. At necropsy the lungs showed gross interstitial emphysema, and the brain an intraventricular haemorrhage.

Case 12.—An 8 lb. 8 oz. male infant cyanosed from birth died at 27 hours. Necropsy revealed multiple malformations, especially of the heart. Bulky lungs and a tentorial tear were found.

Case 13.—A 6 lb. male infant cyanosed from birth died at nine hours. At necropsy the lungs showed naked eye lymphangiectasis.

In Case 11 the pulmonary lymphangiectasis was obscured by superimposed emphysema (possibly resulting from the efforts at resuscitation), but the underlying cystic condition was evident on microscopy. Case 12 also was a microscopic diagnosis, while in Case 13 the cysts were obvious at necropsy.

These additional cases were found by Dr. N. E. France, of the Queen Elizabeth Hospital for Children, Hackney, in a series of 249 perinatal necropsies. They support the contention that the condition is not uncommon.