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Primary diffuse tracheobronchial amyloidosis

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The case is reported of a woman who died at the age of 36 years from obstructive respiratory failure due to diffuse tracheobronchial amyloidosis which had caused symptoms for six years. When first seen her symptoms of wheezing cough and mucopurulent sputum sometimes streaked with blood were of recent onset, but on bronchogram and bronchoscopy her disease was already widespread. Appearances at bronchography were interpreted as malformation and at bronchoscopy as tracheobronchitis, possibly tuberculous. Bronchoscopic biopsy was necessary to make the diagnosis of amyloidosis. The amyloid gave the usual staining reactions with an apple-green birefringence in polarized light following staining with Congo red. At necropsy an extensive histological survey proved that the amyloid was confined to the trachea and main stem bronchi. There was no associated disease, no family history, and no upset in plasma proteins.

Primary tracheobronchial amyloidosis is a rare condition although many cases go unrecorded (Spencer, 1968). The following clinicopathological report is recorded because of the early age of onset, the short clinical history associated with extensive tracheobronchial deposits, and the widespread tracheobronchial amyloidosis at necropsy despite the absence of deposits in any other tissue.

CASE REPORT

CLINICAL HISTORY B.S., a 31-year-old childless housewife, was first admitted to the Austin Hospital in August 1964, because of a 'wheezy chest' which had not responded to penicillin. She had never smoked.

Born in Germany, she had had pneumonia as a child but a chest radiograph in 1944 had been normal. She came to Australia in 1951 and apart from tonsillitis in 1961 had been entirely free from respiratory symptoms until April 1964, when she developed an upper respiratory tract infection with fever, wheezing, and a cough with mocupurulent sputum occasionally streaked with blood. A short course of penicillin resolved her fever but a dry unproductive cough and an obvious respiratory wheeze persisted. In late July 1964 a chest radiograph showed a shadow in the right upper zone resembling an azygos lobe. A bronchogram showed gross bronchial deformity thought to be a malformation (Fig. 1).

On admission on 26 August 1964 an inspiratory wheeze was obvious and the left jugular vein was distended to 2 cm above the clavicle. Bronchoscopy on 29 August showed heaped up inflamed mucosa narrowing the tracheal lumen 1·5 cm distal to the vocal cords (Fig. 2). Similar oedematous lumpy red mucosa lined the entire trachea, widened the carina and, by narrowing the major bronchi, prevented examination of the lower bronchial tree even with the adolescent bronchoscope. The macroscopic diagnosis was acute tracheobronchitis, possibly tuberculous, but the biopsy showed mucosal amyloidosis.

During the next six years she was readmitted nine times for increasingly severe airway obstruction due to reaccumulation of amyloid and infection. During

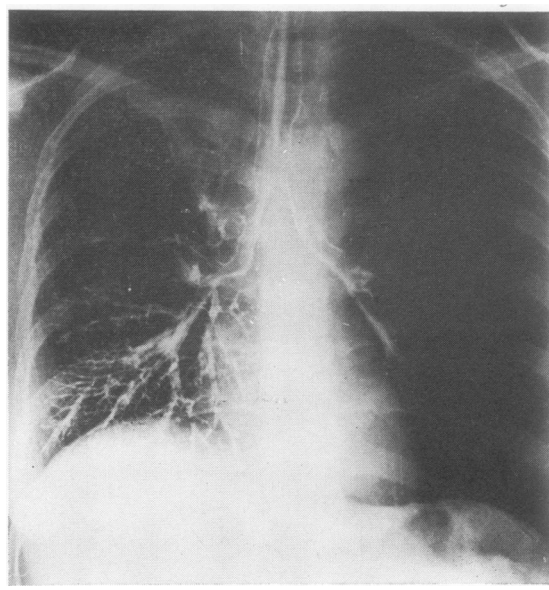

FIG. 1. *Bronchogram* (1964) *to show distortion of tracheobronchial tree originally interpreted as a malformation.*

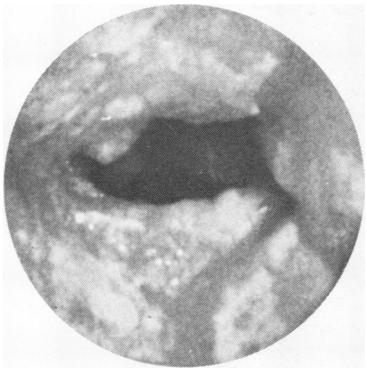

FIG. 2. *Bronchoscopic picture* (1965) *to show pale nodules of amyloid distorting mucosa.*

these years a further 13 bronchoscopies were done to ream out amyloid deposits and produce some relief of symptoms. In August 1965 and June 1967, the bronchoscopies were complicated by acute bleeding which necessitated repeat bronchoscopies to evacuate blood clot.

In December 1969 a bronchoscopy for increasing stridor yielded a large amount of amyloid tissue but was followed by bleeding and collapse of the right lower lobe due to retained clot. On 14 December 1969 increasing tracheal oedema made tracheostomy necessary. Some measure of relief was achieved with humidification of inspired air, antibiotics, and intravenous nutrition, but four weeks later increasing secondary infection of the trachea with coliform organisms and increasing carbon dioxide retention made intermittent positive pressure ventilation necessary. Infection, respiratory failure, and further bleeding caused her death on 13 January 1970.

INVESTIGATIONS During the six years of observation and treatment repeated laboratory examinations revealed no abnormalities in serum biochemistry or renal function. Serum antinuclear factor was negative on three occasions. A gum biopsy (2 October 1964) and a biopsy of rectal mucosa (22 October) were both negative for amyloid. Eleven of 17 bronchoscopic biopsies contained amyloid and one of these (18 February 1965) gave a positive fluorescence with anti-human gamma globulin. On first presentation sputum culture produced *Proteus vulgaris, Proteus mirabilis,* and *Klebsiella aerogenes.* Over the next six years these organisms were repeatedly cultured from sputum and caused major problems in the last six weeks of life.

Staphylococcus aureus was occasionally cultured from sputum during exacerbations of bronchitis which always responded to short courses of cloxacillin or chloramphenicol.

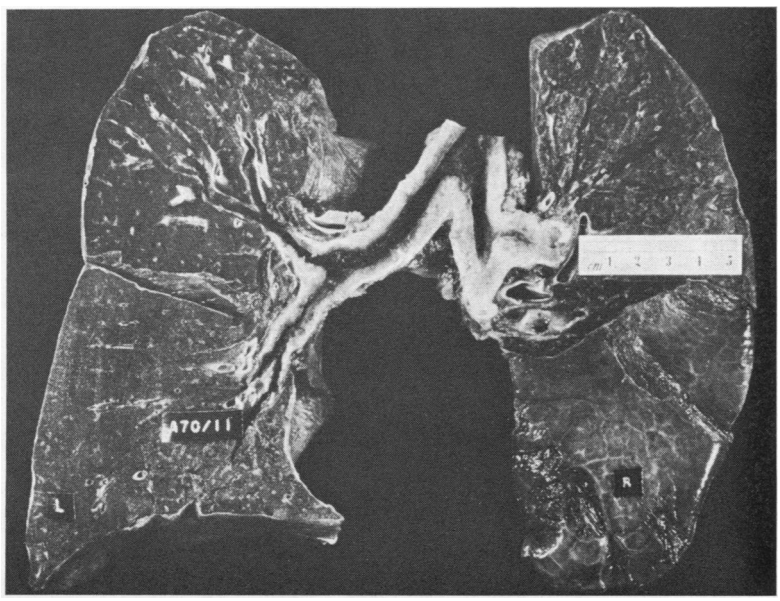

FIG. 3. *Anterior portion of trachea and bronchi is shown demonstrating severe narrowing and increased rigidity of tracheobronchial tree due to diffuse tracheobronchial amyloidosis. The subsegmental bronchi are spared.*

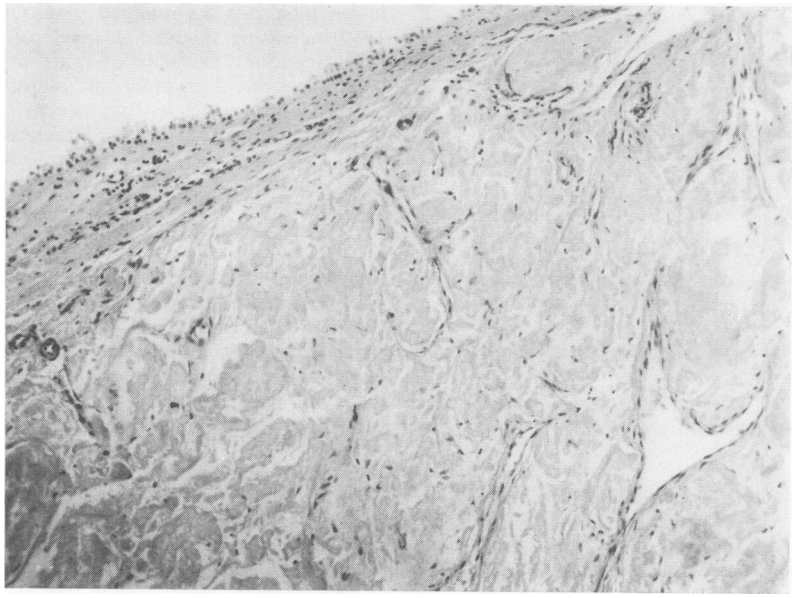

FIG. 4. *Large deposits of amyloid beneath partly autolytic epithelia with only sparse cellular infiltrate. (Necropsy specimen). (H. & E. ×80).*

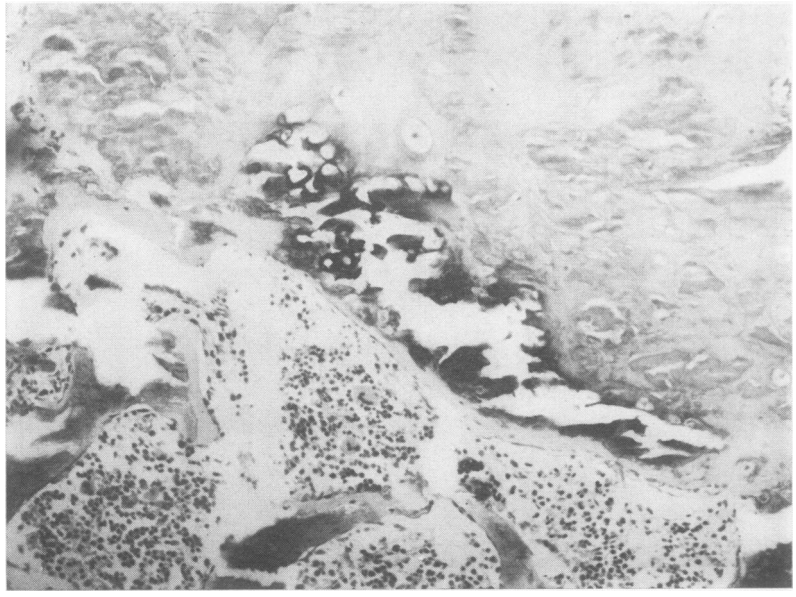

FIG. 5. *Amyloid deposit undergoing cartilaginous metaplasia, calcification, and ossification. (Necropsy specimen). (H. & E. ×240).*

NECROPSY The heart (380 g) was heavy with slight hypertrophy of the right ventricular myocardium (0·3 cm). The vocal cords were thickened and congested. The mucosa of the trachea, main stem bronchi, and major segmental bronchi was replaced by a hard light orange tissue which had a red, granular, quite irregular surface. Deposits varied greatly in thickness (0·3 to 1 cm) (Fig. 3), greatly reduced the lumen of the trachea and major segmental bronchi, and made rigid the conducting airways. The subsegmental bronchi were generally dilated and contained either plugs of mucus or pus but were free from amyloid deposits. Widespread focal pneumonic changes were present throughout both lungs with early breakdown in the apical segment of the right lower lobe. The apical segment of the right upper lobe was collapsed and fibrotic.

The pulmonary arteries contained no recent thrombi and no bands could be seen on dissection of the major vessels.

The kidneys (right 250 g, left 245 g) were slightly enlarged (right 14 cm, left 13·5 cm), severely congested, and showed slight fetal lobulation. The spleen (260 g) was enlarged and congested. The thymus (12 g) was easily identified. The paratracheal and hilar nodes were enlarged and congested but no other lymph nodes were enlarged.

HISTOLOGICAL EXAMINATION Many sections were examined from the trachea and bronchi. All sections showed similar appearances. Thick, nodular deposits of amyloid lay beneath an irregularly ulcerated mucosa (Fig. 4) which on occasions showed squamous metaplasia. The amyloid was metachromatic with methyl violet, became strongly stained with Congo red, following which there was a typical apple-green birefringence in polarized light. The amyloid often extended between the bars of cartilage where it appeared to undergo cartilaginous metaplasia, calcification, and, on occasions, ossification (Fig. 5).

Many sections from each lung were examined. These showed a fibrinopurulent bronchiolitis and bronchopneumonia with areas of organization, epithelial necrosis, epithelial regeneration, and proliferation of alveolar cells. These changes were regarded as non-specific. Occasional deposits of amyloid were present within the walls of small venous channels and a portion of a main pulmonary vein close to a main stem bronchus. No amyloid deposits were seen in the pulmonary parenchyma, and the smaller bronchi and bronchioles were entirely free from deposits.

Sections from small gut, large gut, appendix, stomach, adrenal, tongue, urinary bladder, gall bladder, skeletal muscle, thymus, pancreas, cervix, uterus, ovary, thyroid, parathyroid, pituitary, heart, kidney, spleen, liver, brain, pineal, and bone marrow were all stained with Congo red and viewed under polarized light. Only the material in the tracheobronchial mucosa gave a positive staining reaction and an apple-green birefringence. Sections of the bone marrow showed no plasmacytosis.

DISCUSSION

Amyloidosis of the respiratory tract can be divided into three categories:

1. a solitary nodule affecting the larynx, trachea, bronchial tree or pulmonary parenchyma;
2. multiple amyloid deposits confined to the pulmonary parenchyma;
3. diffuse tracheobronchial amyloidosis (Prowse, 1958).

Of these various forms a solitary nodule in the larynx, trachea or bronchial tree is the most common and, depending on its site, it can present as hoarseness,, wheezing, dyspnoea or haemoptysis. A solitary nodule in the pulmonary parenchyma, on the other hand, is much less common, usually symptomless, and may present as a 'coin lesion' on a routine chest radiograph (Chaudhuri and Parker, 1970). Such nodules frequently contain cartilage and both calcify and ossify. It is possible that some of these are hamartomata in which amyloid has been deposited. The solitary nodule is easily treated surgically and neither solitary nor multiple parenchymatous nodules (Prowse, 1958) have ever been associated with amyloidosis in other sites.

Diffuse pulmonary parenchymatous amyloidosis (alveoloseptal) is rare, produces impairment of gas transfer, and has generally been associated with a widespread primary amyloidosis or the amyloidosis associated with myelomatosis (Beck, 1970; González-Cueto *et al.*, 1970). However, Zundel and Prior (1971) reported a case in which deposits other than those in the lung were not found at necropsy.

Some 20 cases of diffuse tracheobronchial amyloidosis have now been reported (Antunes and Vieira da Luz, 1969; Noring and Paaby, 1952). Necropsy findings have been reported in only five. There is a slight male preponderance (14:6, 7:3) and the age of onset is later in men (mean 58 years in males compared to 46 years in females). The clinical history may extend back for as long as 30 years (Dood and Mann, 1959) and the common symptoms are cough, wheezing, dyspnoea, and haemoptysis. The condition may be relatively benign, and reaming out deposits can give pro-

longed relief although bleeding may produce complications or death. Although the deposits may often appear red on bronchoscopy, histologically they are relatively avascular. Serious bleeding may result because the amyloid deposits in vessels prevent their adequate contraction.

In none of the cases of diffuse tracheobronchial amyloidosis has there been any evidence of amyloid deposits elsewhere. Admittedly, few necropsies have been done, but in that reported by Prowse and Elliott (1963) and in the one now reported, very extensive histological surveys were carried out and deposits elsewhere were not found.

The unusual features in this patient were the widespread deposition of amyloid on first presentation at the early age of 31 years after a short clinical history of respiratory obstruction. Bronchographic appearances were originally interpreted as due to tracheobronchial malformation, and the diagnosis could have been delayed except for bronchoscopy which permitted biopsy. Bronchoscopic biopsy is necessary for an accurate diagnosis. Similar radiological features could be produced by tumours or tracheopathia oesteoplastica. On bronchoscopy the macroscopic features were first interpreted as a tracheobronchitis, possibly tuberculosis.

Localized deposits of amyloid are easily treated surgically. In this patient the extent of the amyloid deposits on first presentation precluded any surgical excision and reconstruction. Reaming out the deposits was occasionally complicated by severe bleeding and gave only temporary relief of increasingly severe respiratory obstruction.

The aetiology and pathogenesis are unknown. However, Cathcart, Mullarkey, and Cohen (1970) have suggested that amyloid may be an expression of immunological tolerance and that a clone of inactivated cells may be confined to one organ. This hypothesis is certainly in keeping with the restriction of the amyloid deposits to the tracheobronchial tree. The absence of deposits in segmental bronchi is otherwise quite unexplained.

Cartilaginous transformation, calcification, and ossification of the amyloid deposits appears to be peculiar to the tracheobronchial and pulmonary sites (Symmers, 1956) and may reflect the metaplastic potentiality of the site rather than a particular form of amyloid. Staining reactions and ultrastructural characteristics of the respiratory amyloid are similar to those elsewhere (Mainwaring, Williams, Knight, and Bassett, 1969).

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