Bronchoalveolar disease in dyskeratosis congenita

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ABSTRACT: Dyskeratosis congenita (DC) is an unusual familial disorder primarily affecting the skin and its appendages. We report the case of a DC patient with chronic respiratory tract involvement, confirming the features previously reported by a small number of authors: 1) chronic bronchoalveolar involvement is not unusual in this disorder; 2) the main features are early sputum production with subsequent bronchial and alveolar destruction; 3) after onset of dyspnoea the course is rapidly fatal, with progressive respiratory failure. Immune deficiency and repeated bronchoalveolar infections may be involved in the pathogenesis of these manifestations.
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Dyskeratosis congenita (DC) is an infrequent familial disorder, hindering the development of the epidermis and its appendages [1–4]. Progressive bone marrow aplasia and malignancies are the most serious complications [1]. Although respiratory disease has been mentioned in the literature, no detailed reports have been made. We report the case of a patient with DC associated with fatal bronchoalveolar modifications.

Case report

A 39 yr old Caucasian man presented with cough and progressive dyspnoea in September 1987. He described himself as a life-long nonsmoker.

DC had been diagnosed at the age of 24 yrs on the basis of characteristic features. Hyperpigmentation, forming a network pattern, was mainly present on the side of the neck, the chest and around the armpits. The fingernails and toenails were strongly dystrophic, and were either destroyed or fused with keratotic skin. Leucoplasia was present on the tongue. Blood tests revealed mild anaemia (haemoglobin, 11.6 g·dl⁻¹), a platelet count of $45 \times 10^9 \cdot l^{-1}$ and a normal white cell count. Bone marrow biopsy revealed slight hypoplasia, whilst isotopic assessment of haematopoiesis (^{59}Fe metabolism and ^{51}Cr-labelled erythrocyte survival) revealed slight medullary involvement with mild intravascular lysis.

There was also a 10 yr history of annual bouts of yellow sputum production requiring antibiotic treatment. The lungs were clear and an X-ray film of the chest was normal. Pulmonary function tests disclosed only slight airflow limitation (table 1).

Over the following 15 yrs, haematological test results remained unchanged but sputum production occurred daily. Bronchiectasis was suspected at the age of 30 yrs, on the basis of subtle tubular shadows on the basal segment of the lower left lobe; the chest X-ray film was otherwise normal. Slight exertional dyspnoea developed when the patient was 38 yrs old, but he was able to live normally over the following 12 months.

In September 1987, the exertional dyspnoea worsened and the patient was referred to the chest unit. Physical examination disclosed unchanged cutaneous and nail abnormalities. No clubbing or cyanosis was present. Large wet rales were audible in both lung fields. Pulmonary function tests (PFT) disclosed mild restrictive impairment (table 1). The chest X-ray film revealed considerable loss of left lung volume, with a coarse reticulonodular pattern. High-resolution computed tomography (HRCT), with 1.5 mm thick sections, disclosed clusters of ring lucencies on several adjacent slices, with segmental distribution in the left lower lobe and in the lingula. A linear network was observed in the right lung but no bronchiectasies were identified (fig. 1). Fibreoptic bronchoscopy disclosed no abnormalities in the right bronchial tree but showed copious pus exuding from left basal and lingular bronchi.

Blood tests revealed mild anaemia (haemoglobin: 10.9 g·dl⁻¹); there were $7 \times 10^9 \cdot l^{-1}$ platelets and $5.7 \times 10^9 \cdot l^{-1}$ white blood cells with normal differentiation. The lymphocyte count was $1.7 \times 10^9 \cdot l^{-1}$ (CD4+: 21%, CD8+: 45%, CD4/CD8 ratio: 0.47). The immunoglobulin (IgG) was 31.56 g·l⁻¹, the IgA 5.49 g·l⁻¹¹ and the IgM 0.94 g·l⁻¹¹. Cutaneous responses to seven

recall antigens were negative (Multitest IMC®, Merieux). No anti-human immunodeficiency virus (HIV) antibodies were detected in enzyme-linked immunosorbent assay (ELISA) tests. The peripheral lymphocyte chromosomes were 46 XY, with no qualitative changes.

Table 1. – Pulmonary function tests

	April 1973	September 1987	February 1988	July 1988
TLC*	5.99 (94)	4.79 (76)	3.20 (51)	2.97 (47)
VC*	4.46 (94)	2.53 (57)	1.81 (40)	1.35 (30)
FEV$_1$*	3.19 (78)	2.31 (65)	1.54 (42)	1.19 (33)
FEV$_1$/VC*	0.72 (82)	0.91(114)	0.84 (104)	0.88 (110)
Pao$_2$†	12.40 (93)	10.40 (78)	8.67 (65)	6.40 (48)
Paco$_2$†	56.6 (43)	55.3 (42)	51.3 (39)	44.7 (34)
Tco**	-	-	30	13

*: result expressed as absolute values (in litres) and percentage of predicted value in parenthesis; †: kPa and mmHg in parenthesis; **: percentage of predicted values; TLC: total lung capacity; VC: vital capacity; FEV$_1$: forced expiratory volume in one second; Pao$_2$ and Paco$_2$: arterial oxygen and carbon dioxide tension, respectively; Tco: carbon monoxide transfer coeffficient.
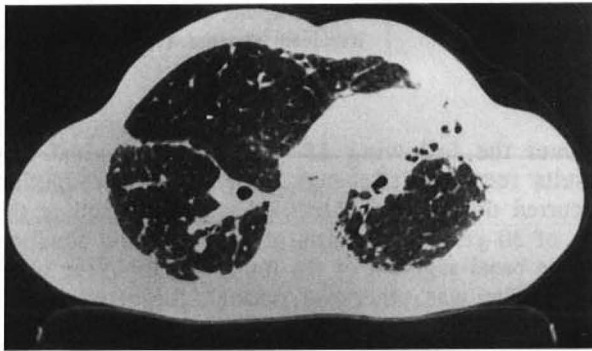

Fig. 1. – Transverse high-resolution computed tomographic (CT) scan, 4 cm below the carina (September, 1987). Clusters of ring lucencies are seen in the left lower lobe and the lingula. A linear network, consisting of short thickened lines perpendicular to the pleural surface, the fissure and the vessels, can be seen in both lungs.

Clinical examination of the patient's two children showed the 12 yr old daughter to be unaffected but the 16 yr old son had some evidence of DC, with fingernail dystrophy, fingerprint loss and a slight hyperpigmented network on the lateral neck. Unfortunately, no further tests could be carried out to confirm DC in the son.

Despite physiotherapy, the disease had an unrelenting downhill course, leading to respiratory disability. PFT deteriorated (table 1) over a few months and in August 1988 the patient was admitted for acute respiratory failure precipitated by left pneumothorax. Despite chest tube insertion and oxygen therapy, the patient died 10 days later of intractable respiratory failure. Autopsy was limited to a right lung necropsy which disclosed a nonspecific collagenous interstitial fibrosis with cuboidal metaplasia of alveolar epithelial cells in an area devoid of bronchectasis. No evidence of opportunistic infections was found on the necropsy specimen.

Comments

The patient whom we describe had the characteristic ectodermal and haematological defects of DC [2–4]. Bronchiectasis was suspected in view of heavy sputum production and was confirmed by HRCT [5, 6]. However, this respiratory disease was unusual in several respects: 1) bronchiectasis was associated with fibrotic alveolar changes (suggested by HRCT and confirmed histologically) in an area devoid of bronchiectasis; 2) after the onset of exertional dyspnoea, the course was rapidly fatal with purely restrictive impairment.

Poorly documented chronic disabling respiratory disorders have also been reported in association with DC and include asthma [7], bronchiectasis [8. 9], fibrocystic dysplasia [10], lung fibrosis [11] and chronic pneumonitis [12]. In all of these cases, sputum production occurred early in life. Diffuse radiological chest abnormalities were usual [10, 11, 13]. There was scarce pathological evidence of alveolar involvement with descriptions such as fibrocystic dysplasia [10], segmental fibrosis with leucocyte infiltration [11] and chronic pneumonitis [12]. Survival was poor, ranging between 12–40 months after the onset of dyspnoea [7, 10, 11, 13, 14]. Taken together with the present observations, these findings suggest that peculiar respiratory manifestations occur within the setting of DC, and consist of early sputum production, with subsequent bronchial and alveolar changes leading to rapidly progressive respiratory failure.

The pathogenesis of this respiratory involvement is unclear. T-cell deficiencies are common in DC [1, 14], including the present case. This immunodeficiency could partly explain the reported cases of fatal acute lung infections [1, 13, 15, 16]. *Pneumocystis carinii* pneumonia and disseminated cytomegalovirus infection have occasionally been documented [1], while in other cases recurrent bacterial lung infections have been reported [11, 13, 14]. Repeated bouts of bronchoalveolar infections, leading to respiratory tract injury, with subsequent fibrotic repair, may therefore be involved in the pathogenesis of the bronchial and alveolar changes.

The case we report was also unusual since one of the patient's sons was affected. Indeed, DC is

considered by most authors to be an X-linked recessive trait and father-to-son transmission should not, therefore, be possible [1, 12, 17–19]. Nevertheless, a number of documented cases of parent-to-child transmission have been reported, raising the possibility of a dominant mode of transmission [20–22]. SCOGGINS et al. [23] reported two males and four females in three generations with evidence of DC, inherited in an autosomal dominant pattern. Unfortunately, it was impossible to confirm DC in the son of our patient.

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