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CASE STUDY

Tracheobronchial stenosis in Keutel syndrome

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Tracheobronchial stenosis in Keutel syndrome. M. Meier, L.P. Weng, E. Alexandrakis, J.Rüschoff, G. Goeckenjan. ©ERS Journals Ltd 2001.

ABSTRACT: In 1971 KEUTEL *et al.* described a new syndrome in two siblings presenting with peripheral pulmonary stenoses, brachytelephalangism, neural hearing loss and abnormal cartilage calcification. Recent investigations provided evidence that mutations in the gene encoding the human matrix GLA protein cause Keutel syndrome. With these new insights in the disease the symptomatology of Keutel syndrome was reassessed. The follow-up of the two siblings was studied by clinical and *post mortem* examination.

As a new feature of Keutel syndrome tracheobronchial stenosis and concentric calcification of pulmonary, coronary, hepatic, renal, meningeal and cerebral arteries were described.

Complementary to the results in molecular genetics the symptomatology of Keutel syndrome could be revised by clinical and *post mortem* examination.

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KEUTEL *et al.* [1] described a syndrome with brachytelephalangism, abnormal cartilage calcification, neural hearing loss and peripheral pulmonary stenoses in a brother and sister born to consanguineous parents. Meanwhile Keutel syndrome was detected in 17 patients in several countries. After a follow-up study tracheobronchial stenosis and abnormal calcification in this disease is described as an important feature.

Case reports

In 1971 KEUTEL *et al.* [1] observed multiple peripheral pulmonary stenoses, skeletal anomalies of the extremities, deafness and heterotopic calcifications of the bronchi, trachea and cartilage of the ribs in a male born in 1961 (case 1) and his sister born in 1958 (case 2). Both had been suffering from an exertional dyspnoea since childhood. The mother of the sibs was the daughter of her husband's cousin. Two other males and another female of the family were free of pulmonary complaints. Both children attended school and the male became a joiner and the girl a merchant. The young male never smoked and the female smoked 1–2 cigarettes·d^{-1} from 1976–1979.

Case 1

In 1991 the 30-yr-old male (height 1.70 m, body weight 68 kg) complained of increasing dyspnoea and cough. His craniofacial appearance was characterized by midfacial hypoplasia with a broad depressed nasal bridge. The auricles were stiff and the end phalanges of his fingers were thickened. At his thighs livid maculae were found.

He presented an inspiratory and expiratory stridor and wheezing on lung auscultation. A grade 3/6 systolic murmur was heard over the heart and an additional systolic murmur over both lungs.

Lung function test revealed severe obstructive airway disease without bronchodilator response, the signs of intra- and extrathoracic airway obstruction and increased thoracic gas volume (vital capacity (VC) 2.99 L, 61% pred; total lung capacity (TLC) 7.70 L, 128% pred; forced expiratory volume in one second (FEV_1) 1.36 L, 34% pred; FEV_1/VC 45.4%; airway resistance (R_{aw}) 1.09 kPa × s·L^{-1}; forced inspiratory volume in one second (FIV_1) 0.95 L).

Chest radiograph and computed tomography showed a decreased coronary diameter of the full length of trachea of 10 mm (13–25 mm pred, BREATNACH *et al.* [2]) and a sagittal diameter of 9 mm (13–27 mm pred, BREATNACH *et al.* [2]). In computed tomography the coronary diameter of the main bronchi was 7 mm (9–22 mm pred, KATZ *et al.* [3]). Fibrebronchoscopy confirmed the radiographical findings since a 6-mm fibrebronchoscope could not be advanced into the left main stem bronchus.

Right ventricular catheterization demonstrated an elevated right ventricular pressure of 13.33/0 kPa and a systolic gradient between the main pulmonary artery and the right pulmonary artery (2.53/1.47 kPa) of 10.8 kPa and the left pulmonary artery (3.47/1.47 kPa) of 9.86 kPa.

With an antiobstructive therapy clinical symptoms improved but lung function did not change significantly.

In 1993 seizures occured and several ischemic cerebral lesions were shown by magnetic resonance imaging.

In 1994 tracheostomy became necessary because of intubation difficulties on the occasion of nucleus pulposus surgery of lumbar spinal column.

Fibrebronchoscopy revealed diffuse stenosis of trachea and central bronchi, tracheobronchial dyskinesia and chronic bonchitis by histological examination.

During tracheostomy a mediastinal lymph node was exstirpated and mediastinal seminoma was diagnosed. At that time no further treatment of mediastinal lymphoma was performed. A mediastinal recurrence of seminoma in January 1999 was treated by four cycles of carboplatin chemotherapy and partial remission was achieved.

In May 1999 he was admitted to the hospital with increasing dyspnoea. An exacerbation of chronic obstructive pulmonary disease was treated with corticosteroids, inhalative bronchodilators, theophylline, antibiotics and physical therapy but 2 days later he died of right heart failure.

Post mortem examination revealed abnormal calcification of the tracheobronchial tree (fig. 1 and 2) up to the lobular bronchi with a diameter of the trachea 10–15 mm. The cartilaginous rings with enchondral calcifications were smaller than normal but showed no posterior fusion. Purulent chronic bronchitis with bullous emphysema of the lungs and supravalvular pulmonary stenoses with concentric calcification of the arteries were responsible for acute failure of chronic cor pulmonale.

Concentric calcification of coronary, hepatic, renal, meningeal and cerebral arteries (fig. 3) with multiple brain infarctions could be demonstrated. Metaplastic bone tissue was found in the corium of the right thigh and calcifications of the cerebrum (fig. 2). Dermatosclerosis could not be diagnosed. A recurrence of a seminoma was not found.

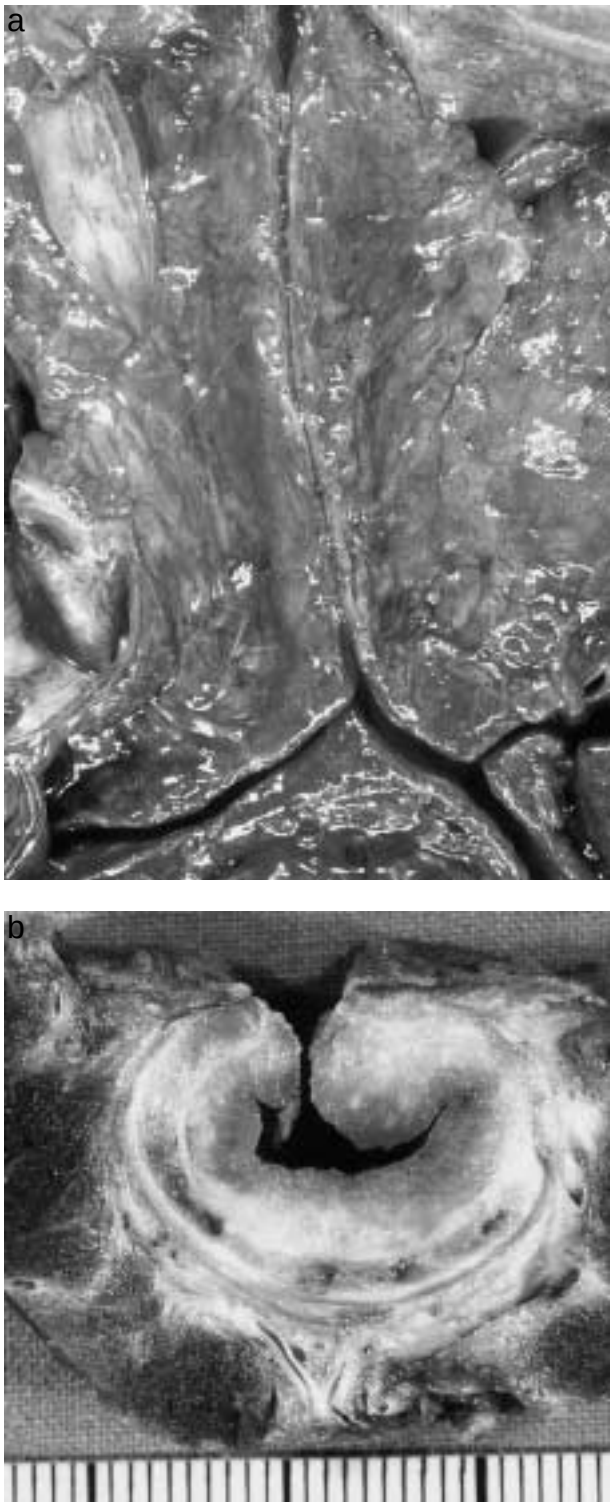

Fig. 1. – Reduced tracheobronchial lumen (a) and fibrous thickening of tracheal wall (b) in the male (case 1).

Case 2

In 1992 the 34-yr-old female (height 1.63 m, body weight 65 kg) reported an exertional dyspnoea without deterioration since childhood. Her skin was thickened with livid maculae at the abdomen, both forearms and the lower extremities. The auricles were stiff and the phalanges of the thumb, the third finger and the first toe were shortened and thickened. There was no stridor or wheezing but her voice was sonorous. Auscultation revealed a 2/6 systolic murmur over the heart pronounced in the third intercostal space and an additional systolic murmur over both lungs increasing at inspiration.

Chest radiography showed a reduced coronary diameter of the trachea of 8 mm (10–21 mm pred, BREATNACH *et al.* [2]) and a diameter of the main bronchi of 8 mm and 6 mm (9–22 mm pred, KATZ *et al.* [3]).

Lung function test revealed obstructive airway disease without bronchodilator response (VC 2.16 L, 62% pred; TLC 4.26 L, 86% pred; FEV_1 1.28 L, 43% pred; FEV_1/VC 59.2%, R_{aw} 0.83 kPa × s·L^{-1}, FIV_1 1.80 L).

Blood tests in both persons were unremarkable, especially calcium and phosphorus in serum were normal. Further genetic examinations and tracheography were refused.

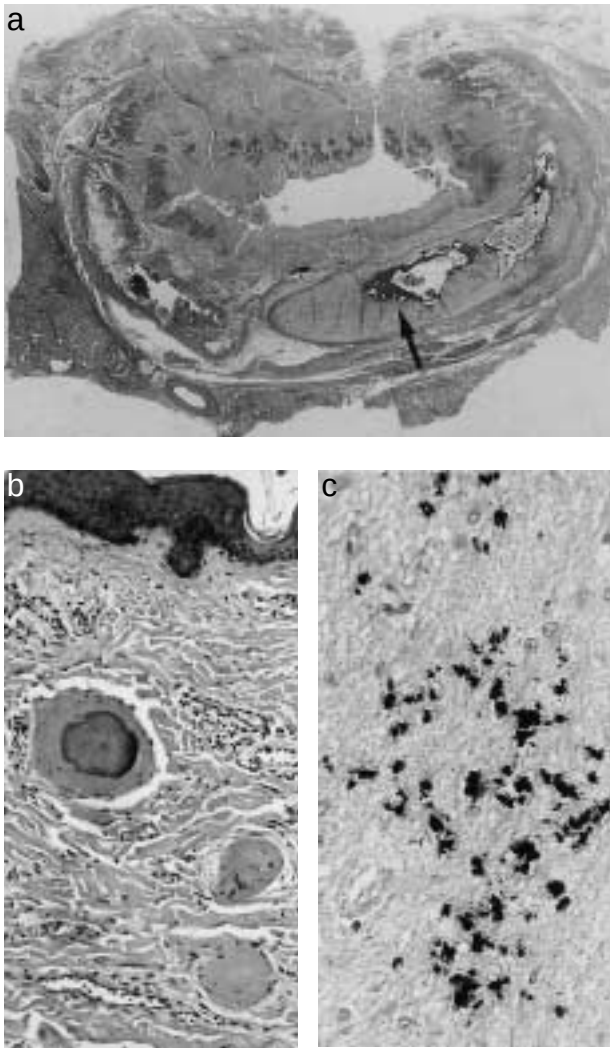

Fig. 2. – Reduced tracheobronchial lumen with calcification (arrow) of tracheal cartilage (a) (case 1). Ossifications in the dermis (b) and calcifications of the cerebrum (c). b: Hematoxylin-Eosin original magnification ×150. c: stained using Kossa and viewed at original magnification ×380.

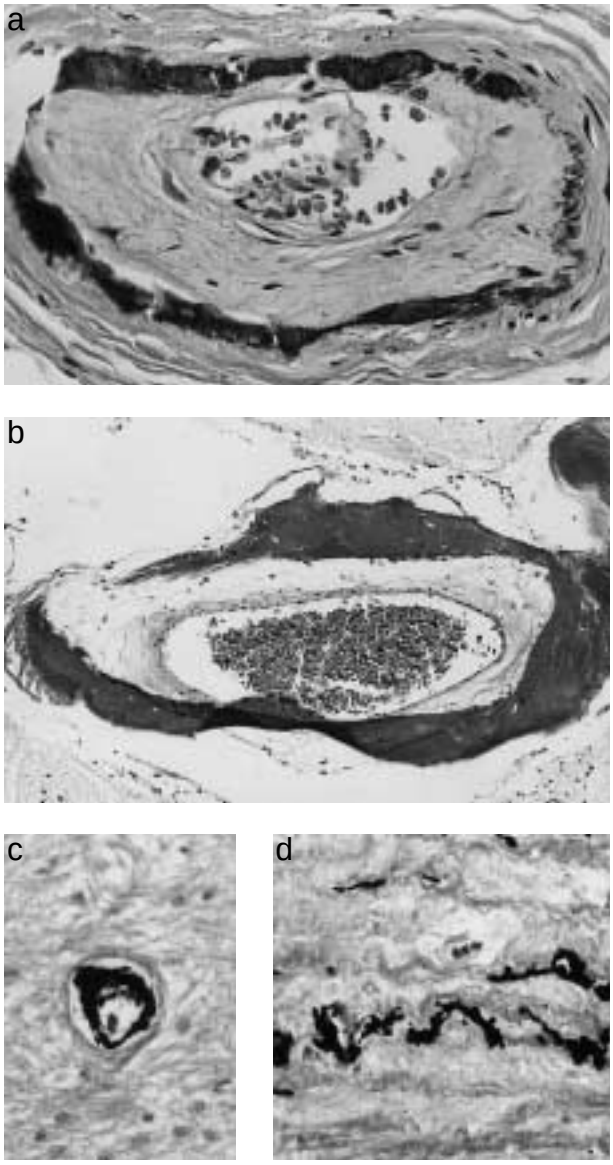

Fig. 3. – Vascular lesions in Keutel Syndrome. Calcification of elastica interna of an artery of soft tissue (a), of a meningeal artery (b) and an intracerebral artery (c) (case 1). a: stained using Hematoxylin-Eosin, original magnification ×380. b: stained using Elastica-van Gieson, original magnification ×150. c and d: stained using Kossa, original magnification ×380.

Discussion

Keutel syndrome is a rare disorder and meanwhile 17 patients aged between 2 months and 21 yrs were reported (1,4–14). All of them showed premature tracheobronchial calcification, but stenosis of the tracheobronchial tree and the resulting functional limitations have not been appreciated until now.

Only Buchsteiner *et al.* [11] reported subglottic laryngeal stenosis in two brothers at the age of 14 and 21 yrs leading to emergent tracheostomy on occasion of elective adenotonsillectomy in the 14 yr-old-male.

To avoid complications in anesthaesia tracheobronchial stenosis and impairment of lung function should carefully be verified in patients with midfacial hypoplasia, brachytelephalangism, hearing loss, pulmonary stenosis with a systolic murmur and abnormal calcifications.

Early in 1922 Sankott [15] described stenosis of trachea and the main bronchi caused by cartilage rings lacking pars membranacea. Congenital stenosis of the trachea is not common and is classified as generalized hypoplasia, funnel-like stenosis and segmental stenosis [16]. Generalized stenosis of the trachea and the bronchi in the siblings was found. In the young male *post mortem* examination revealed small cartilaginous rings with abnormal enchondral calcification causing stenosis of the trachea and the bronchi. Early in 1971 Keutel *et al.* [1] described abnormal calcification of the male's trachea. The status in early childhood to determine a congenital generalized hypoplasia of the trachea according to the classification of Cantrell [16] is unknown, but the morphology of the trachea is similar to it.

Acquired tracheal stenosis is observed in polychondritis, mediastinal fibrosis, sarcoidosis, syphilis,

tuberculosis, rhinosclerma, sabre sheath trachea and tumourous and vascular compression.

Post mortem examination ruled out these disorders and revealed abnormal calcifications especially in the tracheobronchial tree and the arterial vessels. Luo *et al.* [17] demonstrated spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Matrix GLA protein belongs to the family of mineral-binding GLA proteins including osteocalcin and a number of coagulation and anticlotting factors. All members of the family have glutamic acid residues modified to gamma-carboxyglutamic acids (GLA). Keutel syndrome is an autosomal recessive disorder and Munroe *et al.* [18] performed a genome search using homozygosity mapping. Their data provided evidence of linkage to chromosome 12p12.3-13.1 and indicated that mutations in the gene encoding the human matrix GLA protein cause Keutel syndrome.

References

1. Keutel J, Jörgensen G, Gabriel P. Ein neues autosomal-rezessiv vererbbares Syndrom; multiple periphere Pulmonalstenosen, Brachytelephalangie, Innenohrs-chwerhörigkeit, Knorpelverknöcherungen bzw. -verkalkungen. *Dtsch med Wschr* 1971; 96: 1676 – 1681.
2. Breatnach E, Abbott GC, Fraser RG. Dimensions of the normal human trachea. *AJR Am J Roentgenol* 1984; 142: 903 – 906.
3. Katz I, LeVine M, Herman P. Tracheobron-chiomegaly: the Mounier-Kuhn syndrome. *AJR Am J Roentgenol* 1962; 88: 1084 – 1094.
4. Cormode E, Dawson JM, Lowry RB. Keutel syndrome: clinical report and literature review. *Am J Med Genet* 1986; 24: 289 – 294.
5. Fryns JP, van Fleteren A, Mattelaer P, van den Berghe H. Calcification of cartilages, brachytelephalangy and peripheral pulmonary stenosis: confirmation of the Keutel syndrome. *Eur J Pediatr* 1984; 142: 201 – 203.
6. Haddad MC, Sharif HS, Jared MS, Sammak BM, Al Shahed MS. Premature tracheobronchial, laryngeal and costochondral cartilage calcification in children. *Clin Radiol* 1993; 47: 52 – 55.
7. Say B, Balci S, Pirnar T, Israel R, Atasu M. Unusual calcium deposition in cartilage associated with short stature and peculiar facial features: a case report. *Pediatr Radiol* 1973; 1: 127 – 129.
8. Teebi AS, Lambert DM, Kaye GM, Al-Fifi S, Tewfik TL, Azouz EM. Keutel syndrome: further characterization and review. *Am J Med Genet* 1998; 78: 182 – 187.
9. Walbaum R, Boniface L, Tonnel A, Desaulty A, Decroix G. Le syndrome de Keutel. *Ann Pediatr* 1975; 51: 461.
10. Ziereisen F, De Munter C, Perlmutter N. The Keutel syndrome; report of a case and review of the literature. *Pediatr Radiol* 1993; 23: 314 – 315.
11. Buchsteiner I, Kempf H-G, Arslan-Kirchner M, Schulze-Florey T. Kongenitale subglottische Larynxstenose bei zwei Brüdern mit einem Chondro-dysplasiesyndrom (Keutel-Gabriel-Syndrom). *Laryngo-Rhino-Otol* 1998; 77: 363 – 366.
12. Khosroshahi HE, Uluoglu Ö, Olguntürk R, Basaklar C. Keutel syndrome: a report of four cases. *Eur J Pediatr* 1989; 149: 188 – 191.
13. Gilbert BD. Lacombe: Keutel syndrome and miscarriages. *Am J Med Genet* 1999; 83: 209 – 211.
14. Tüysüz B, Üngür S, Akalin F, Cenani A, Tunnessen WW. Picture of the month. *Arch Pediatr Adolesc Med* 1999; 153: 765 – 766.
15. Sankott AM. Über einen Fall mit angeborener Enge der Trachea und der Bronchien, Fehlen der Paries membranaceus tracheae, Divertikelbildung usw. *Wien klin Wschr* 1922; 35: 391 – 393.
16. Cantrell JR, Guild HG. Congenital stenosis of the trachea. *Am J Surg* 1964; 108: 297 – 305.
17. Luo G, Ducy P, McKee MD, *et al.* Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997; 386: 78 – 81.
18. Munroe PB, Olgenturk RO, Fryns J-P, *et al.* Mutations in the gene encoding the human matrix Gla protein cause Keutel Syndrome. *Nat Genet* 1999; 21: 142 – 144.