Tracheobronchial calcification associated with Keutel syndrome

Nihal Özdemir[1], Refika Ersu[1], Figen Akalın[1], Bülent Karadağ[1], Arif Kut[2]
Fazilet Karakoç[1], Nursel Elçioğlu[1], Elif Dağlı[1]

Departments of Pediatrics, [1]Marmara University Faculty of Medicine, and [2]Social Security Göztepe Hospital, İstanbul, Turkey

SUMMARY: Özdemir N, Ersu R, Akalın F, Karadağ B, Kut A, Karakoç F, Elçioğlu N, Dağlı E. Tracheobronchial calcification associated with Keutel syndrome. Turk J Pediatr 2006; 48: 357-361.

Tracheobronchial cartilage calcification is an unusual radiologic finding in infants and children under 15 years old. Keutel syndrome is a rare, autosomal recessive disorder characterized by diffuse cartilage calcification, brachytelephalangia, pulmonary stenosis and midfacial hypoplasia. We report two children in whom abnormal tracheobronchial calcification was associated with Keutel syndrome. Keutel syndrome should be considered in the differential diagnosis of children with tracheobronchial calcification.

Key words: tracheobronchial calcification, Keutel syndrome, brachytelephalangia.

Calcification of the cartilaginous rings of the tracheobronchial tree is often seen on routine chest radiographs in healthy elderly subjects and is usually of no clinical significance[1]. Tracheobronchial calcification (TBC) is a distinctly unusual radiologic finding in infants and children under 15 years old[2]. Keutel syndrome (MIM 245150) is a rare, autosomal recessive disorder characterized by diffuse and abnormal cartilage calcification, brachytelephalangia (short, broad distal phalanges), peripheral pulmonary stenosis, midfacial hypoplasia and hearing loss[3]. We report two isolated children in which abnormal TBC was associated with Keutel syndrome. To our knowledge, there are fewer than 100 reported cases of Keutel syndrome in the literature thus far[4].

Case Reports

Case 1

TI is a four-year-old girl who was referred to our hospital because of recurrent cough and wheezing episodes. She had a history of frequent upper respiratory tract infections and was hospitalized with a diagnosis of bronchitis and pneumonia when she was two years old. Her parents were first-degree cousins, but the family history was otherwise unremarkable. The mother had no history of miscarriages and did not receive any medication during the pregnancy, which was uneventful. The proband was born at term, her birth weight was 2700 g and no problems were noted in the postnatal period. Her developmental stages were age-appropriate and she was of normal intelligence. Her weight was 14 kg (25th centile) and her height was 105 cm (75-90th centile). On physical examination she had a hypoplastic, short nose with a depressed nasal bridge and a high arched palate (Fig. 1a). Her fingers had a drumstick appearance with short terminal phalanges, short nails and hypoplastic fingertip pads. There was no stridor or wheezing on auscultation. Her chest radiograph showed a normal-sized heart and extensive tracheal and bronchial cartilage calcification (Fig. 1b). Computerized tomography also demonstrated the distinct calcification of the tracheobronchial tree (Fig. 1c). Blood chemistry tests including calcium, phosphorous and alkaline phosphatase serum levels were all normal. Bronchoscopy revealed purulent secretions and functional narrowing of left and right main bronchi which was related to the absence of elasticity of tracheobronchial tree because of abnormal calcification. Lung

Fig. 1a. Frontal view of the face showing hypoplastic short nose with a depressed nasal bridge (Case 1).

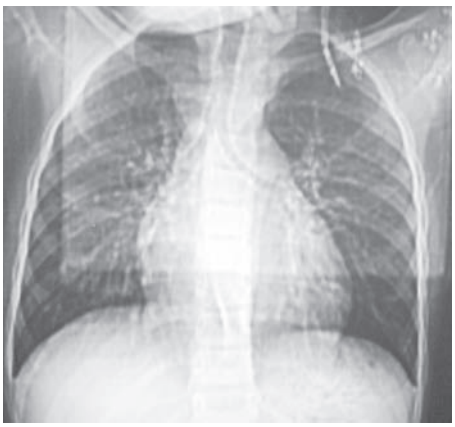

Fig. 1b. Anteroposterior X-ray of the chest showing calcification of the tracheobronchial tree (Case 1).

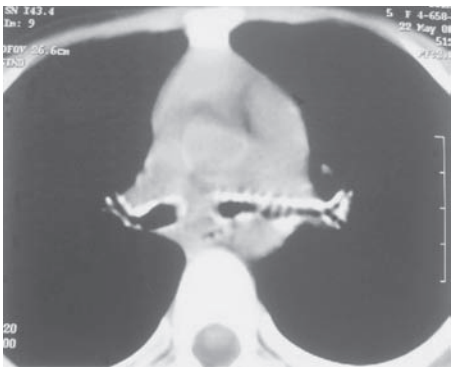

Fig. 1c. Computerized tomography of the chest demonstrating tracheobronchial calcification (Case 1).

function test demonstrated obstructive airway disease without bronchodilator response. Hand radiograph showed shortening and broadening of the first distal phalanx of the right hand (Fig. 1d). Epiphyseal stippling was not noted on radiographic survey of shoulders, hands, tarsal bones, hips and spinal column. Echocardiographic examination and audiogram were normal. Chest radiographs of the other family members did not demonstrate abnormal calcification. She is now eight years old. Her weight at last examination was 21 kg (25-50th centile) and her height was 126 cm (50-75th centile). She is using bronchodilating agents and physiotherapy. Wheezing and cough episodes decreased remarkably. Repeated chest radiograph showed no change.

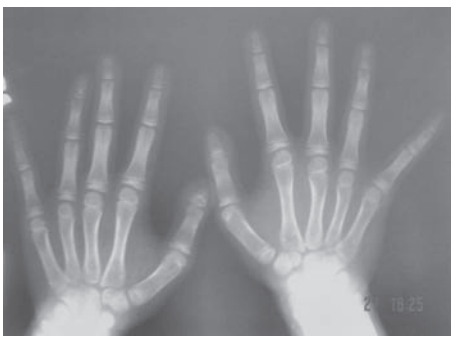

Fig. 1d. Radiograph of the hand showing brachytelephalangia of the first finger of the right hand (Case 1).

Case 2

ME is a seven-year-old girl who was referred to our hospital because of tracheal calcification discovered incidentally on her chest radiograph, taken before her tonsillectomy operation. She described persistent cough and wheezing episodes when questioned. Pregnancy and delivery were uneventful and she was born at term with a birth weight of 3100 g. Her parents were first-degree cousins and the family history revealed a four-year-old brother with diagnosis of cardiomyopathy of unknown origin. The mother had no history of miscarriages. The patient was of normal intelligence and her height and weight were at the 10th centile for age. Physical examination revealed midface hypoplasia with a broad, depressed nasal bridge and a small nose, short philtrum, prominent eyes, a high-arched palate, dental malocclusion and drumstick, clubbed fingers (Fig. 2a).

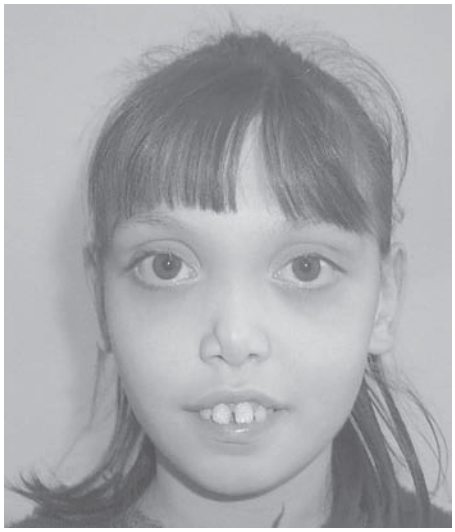

Fig. 2a. Full face graphy showing maxillary hypoplasia, hypoplastic small nose and hypoplastic nostrils (Case 2).

There was no cyanosis. An ejection systolic murmur grade 2/6 was heard equally well over the entire thorax. Chest radiograph (Fig. 2b) and computerized tomography (Fig. 2c) demonstrated striking tracheal calcification.

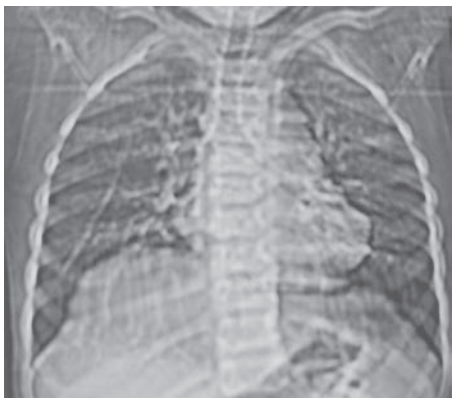

Fig. 2b. X-ray of the chest demonstrating tracheal calcification (Case 2).

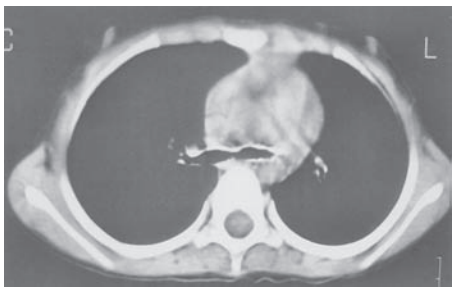

Fig. 2c. Computerized tomography of the chest demonstrating tracheal calcification (Case 2).

Her full blood count and blood chemistry tests including calcium, phosphorous and alkaline phosphatase serum levels were normal. Bronchoscopy revealed narrowing of the trachea with purulent secretions. Lung function test showed obstructive airway disease without bronchodilator response. Hand radiographs at 10 years old demonstrated noticeably short distal phalanges of all fingers with fused epiphyses (Fig. 2d). Echocardiography demonstrated peripheral pulmonary artery stenosis. Audiogram was normal. Chest radiographs of the other family members were taken and no abnormality was found. She is now 10 years old and her symptoms improved noticeably after she started using bronchodilator treatment despite the absent bronchodilator response on pulmonary function tests. She weighs 24 kg (5-10th centile) and her height is 130 cm (10th centile). There is still tracheal calcification on the repeated chest radiograph.

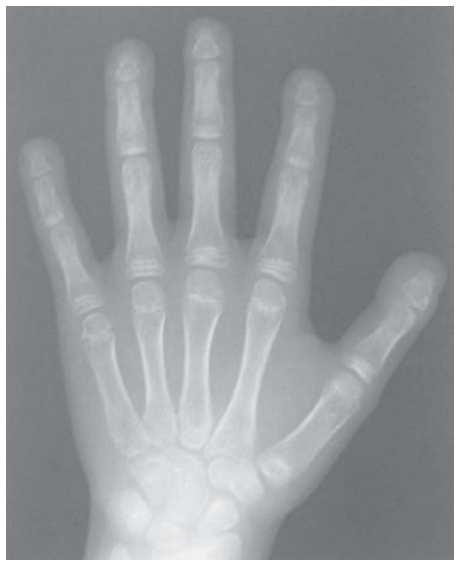

Fig. 2d. Radiograph of the hand showing brachytelephalangia (Case 2).

Discussion

Calcification of the tracheobronchial cartilage rings is frequently noted on routine radiographs of healthy elderly people and is usually of no clinical significance[1]. It is a degenerative process and tends to be more frequent with increasing age. TBC, on the other hand, is distinctly unusual in infants and children under 15 years old[2], with approximately 34 cases reported in the literature as of 1993[5].

Acquired TBC is observed in tracheobronchopathia osteochondroplastica[6], relapsing polychondritis and tracheal amyloidosis in adults. TBC is seen by the teratogenic effect of warfarin[7]. Nasal hypoplasia, punctate epiphyses, brachytelephalangia, rhizomelia and microcephaly are other hallmarks of warfarin embryopathy. Premature cartilage calcification and nasal hypoplasia are also reported following maternal exposure to phenytoin and alcohol as well as rubella embryopathy and deficiency of vitamin K caused by embryonic enzyme deficiency[8]. Recently, association of pathological calcification with maternal systemic lupus erythematosus (SLE) has been reported in two sibs[8].

Differential diagnoses of congenital TBC include Williams syndrome, chondrodysplasia punctata (CDP) and Keutel syndrome. Children with Williams syndrome have typical facial dysmorphism (elfin face), mental retardation, supravalvular aortic stenosis and hypercalcemia. Calcium deposits are present in heart, thyroid gland and bronchial cartilages. CDP is a term given to a heterogeneous group of skeletal dysplasias characterized by punctate calcification of epiphyses and other cartilaginous structures such as larynx. Skeletal abnormalities include stippled epiphyses, limb shortness, short stature and craniofacial defects. Abnormal cartilage calcification including the respiratory tract, mental retardation, ichthyosis, alopecia and cataract are seen in different forms of CDP[9].

Keutel syndrome was first described in a brother and sister born to consanguineous parents in 1972 by Keutel et al.[10]. It is a rare autosomal recessive syndrome characterized by diffuse calcification of the cartilage, brachytelephalangia, pulmonary stenosis, midfacial hypoplasia, stippled epiphyses and hearing loss. Since then, fewer than 100 cases have been reported in several countries and Turkey[11-14]. The most consistent finding in this disorder is abnormal cartilage calcification, which was detected in all cases. The calcification is diffuse and may involve larynx, trachea, bronchi, nose and ears[3]. Stippled epiphyses may be noted in long bones and vertebrae. Brachytelephalangia was described in 12 of 17 patients reported so far but hand radiographs were not mentioned in the other cases[4]. Clinically, the patients have drumstick appearance fingers with short nails. Radiologically short and broad terminal phalanges of all or some of the fingers and early fusion of epiphyses of the fingers may be noted. Other manifestations of Keutel syndrome are seen with variable occurrence. The midface is often hypoplastic with a depressed nasal bridge, and a high-arched palate may be noted. Cardiac abnormalities, particularly pulmonary stenosis and/or ventriculoseptal defect, were reported in most of the patients[3]. Hearing loss is common and is usually a mixed conductive and sensorineural type[15]. Respiratory problems involving recurrent upper respiratory tract infections, pneumonia, wheezing or asthma were observed in the reported cases[3]. Mild to moderate mental retardation and developmental delay may be present in patients[15]. Familial consanguinity is prevalent and most of the cases are offspring of cousins[3]. Gilbert et al.[16] reported a mother of a Keutel syndrome case with repeated miscarriages in 1999 but this was not reported in other patients. Patients with Keutel syndrome do not appear to have problems with fractures or premature osteoporosis, and no increased incidence of coronary arterial disease or rupture of abdominal aortic aneurysm was reported.

Recent investigations in consanguineous Turkish and Belgian families showed evidence that mutations in the gene encoding the human matrix G1a protein (MGP) are responsible for Keutel syndrome[17]. Human MGP, mapped to locus 12p13.1-p12.3, is a skeletal extracellular matrix (ECM) protein and a member of the G1a protein family, which includes osteocalcin and a number of coagulation and anticoagulation factors (factors II, VII, IX, X and proteins S and C)[17]. All members use vitamin K as a cofactor.

Our two cases presented with repeated respiratory symptoms requiring treatment with bronchodilating agents. Respiratory problems in the form of recurrent upper respiratory infections, pneumonia, wheezing and asthma are frequently observed in Keutel syndrome. The two cases had diffuse calcification of the tracheal and/or bronchial tree. The facial phenotypes were remarkably similar with midfacial hypoplasia, small nose and depressed nasal bridge. Also in common was the familial consanguinity. Both patients had brachytelephalangia - one patient showed involvement of all distal phalanges while in the other only the first distal phalanx of one

hand was involved. Our second case also had peripheral pulmonary stenosis. Both patients were diagnosed as Keutel syndrome.

Keutel syndrome, although rare, should be considered in the differential diagnosis of children with tracheobronchial calcification, especially in the presence of brachytelephalangia, midfacial hypoplasia, stippled epiphyses and cardiac defects. More studies are needed to understand the pathophysiology of this disease and its possible relation to CDP.

REFERENCES

1. Rifkin MD, Pritzker HA. Tracheobronchial cartilage calcification in children. Case reports and review of the literature. Br J Radiol 1984; 57: 293-296.
2. Santos JM. Laryngotracheobronchial cartilage calcification in children. A case report and review of the literature. Pediatr Radiol 1991; 21: 377-378.
3. 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.
4. Miller SF. Brachytelephalangy with sparing of the fifth distal phalanx: a feature highly suggestive of Keutel syndrome. Pediatr Radiol 2003; 33: 186-189.
5. 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.
6. Nienhuis DM, Prakash UB, Edell ES. Tracheobronchopathia osteochondroplastica. Ann Otol Rhinol Laryngol 1990; 99: 689-694.
7. Van Driel D, Wesseling J, Sauer PJ, Touwen BJ, Van Der Veer E, Heymans HA. Teratogen update: fetal effects after in utero exposure to coumarins: overview of cases, follow-up findings, and pathogenesis. Teratology 2002; 66: 127-140.
8. Elçioğlu N, Hall CM. Maternal systemic lupus erythematosus and chondrodysplasia punctata in two sibs: phenocopy or coincidence. Am J Med Genet 1998; 35: 690-694.
9. International working group on constitutional diseases of bone. 1998. International nomenclature and classification of the osteochondrodysplasias. Am J Med Genet 1997; 79: 376-382.
10. Keutel J, Jorgensen G, Gabriel P. Ein neues autosomal-rezessiv vererbbares syndrom. Dtsch Med Wochenschr 1972; 149: 188-191.
11. Meier M, Weng LP, Alexandrakis E, Rüschoff J, Goeckenjan G. Tracheobronchial stenosis in Keutel syndrome. Eur Respir J 2001; 17: 566-569.
12. Say B, Balcı S, Pınar T, et al. Unusual calcium deposition in cartilage associated with short stature and peculiar facial features: a case report. Pediatr Radiol 1973; 1: 127-129.
13. Kınık E, Balcı S, Bilgiç A. Multipl periferal stenoz, kartilajlarda noktavi kalsifikasyon, işitme kaybı, yünümsü saç (woolyhair) ile birlikte ailevi akdeniz ateşi (FMF): muhtemelen yeni bir antite. Çocuk Sağlığı ve Hastalıkları Dergisi 1977; 20: 74-82.
14. Khosrashahi HE, Uluoğlu Ö, Olguntürk R, et al. Keutel syndrome: a report of four cases. Eur J Pediatr 1989; 149: 188-191.
15. Tüysüz B, Üngür S, Akalın F, Cenani A, Tunnessen WW. Picture of the month. Keutel syndrome. Arch Pediatr Adolesc Med 1999; 153: 765-766.
16. Gilbert B, Lacombe D. Keutel syndrome and miscarriages. Am J Med Genet 1999; 83: 209-211.
17. Munroe PB, Olgunturk RO, Fryns JP, et al. Mutations in the gene encoding the human matrix G1a protein cause Keutel syndrome. Nat Genet 1999; 21: 142-144.