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Case Report

Tracheobronchial Tree Ossification in a 5-Year-Old Boy with Keutel Syndrome: A Case Report

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Abstract

Keutel syndrome (KS) as a scarce autosomal recessive disorder is characterized by hearing loss, multiple peripheral pulmonary stenoses, abnormal cartilage calcification, and morphological defects including midface hypoplasia and brachytelephalangism. We herein describe a 5-year-old boy who was referred for the evaluation of incidentally auscultated heart murmurs. He had no obvious abnormalities at birth but suffered from recurrent episodes of infectious otitis media during infancy.

Physical examination revealed facial abnormalities, such as a broad nasal bridge, a sloping forehead, maxillary hypoplasia, and brachytelephalangism. Chest radiography showed tracheobronchial tree calcification. Transthoracic echocardiography illustrated peripheral pulmonary artery stenosis, moderate tricuspid regurgitation, and pulmonary hypertension.

Computed tomography angiography confirmed calcification and segmental stenosis in the peripheral pulmonary arteries.

The patient was diagnosed with KS. Most of these patients have a good prognosis. During the follow-up of these patients and examinations, we should pay attention to their symptoms related to upper respiratory tract infections, the extent of hearing, and the possibility of tracheal and pulmonary artery stenosis development.

KS is a disease with a good prognosis, and a careful initial examination of babies, including facial appearance and heart auscultation, may lead to the early diagnosis of this disease.

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Keywords: *Keutel syndrome; Calcification of cartilages; Pulmonic stenosis, brachytelephalangism*

Introduction

Keutel syndrome (KS) was first defined in 1971 based on the observation of brachytelephalangism, neural hearing loss, peripheral pulmonary stenosis, and abnormal calcification of multiple cartilages in 2 siblings.[1] KS is clinically suspected and diagnosed by genetic testing as being due to a homozygous mutation in the matrix Gla protein (MGP) gene (OMIM 154870), thought to be a vitamin K-dependent extracellular protein with inhibitory effects on calcification

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inherited in an autosomal recessive manner.[2,3]

KS is characterized by cardiac disorders accompanied by various skeletal deformities due to the pathologic calcification of cartilages. Biopsies of ear cartilages have shown direct ossification without any tissue reaction or calcification, resulting in neurosensory and conductive hearing loss.[4,5]

Peripheral pulmonary stenosis is a cardiac manifestation of KS, which may subsequently lead to right ventricular pressure overload, hypertrophy, and dysfunction. It causes systemic venous congestion by increasing right atrial pressure. The resulting drop in cardiac output leads to exercise intolerance and even cyanosis in cases with associated intracardiac defects or in severe cases with very restricted pulmonary blood flow.[6]

Case Report

A 5-year-old boy was referred to our congenital heart disease clinic for the evaluation of a heart murmur. He was born in Iran as the third child of an Afghan family with low socioeconomic status. His parents were relatives (cousins). According to their statement, his older brother was mentally retarded and was born with craniosynostosis.

The patient was born via normal vaginal delivery with a birth weight of 2800 g at 38 weeks of gestational age without significant complications during delivery. Regular vaccinations were given according to the national protocol. In the following months, his weight, head circumference, and height development were within an acceptable range (in the 50th percentile of the growth chart) for his age. Furthermore, he presented no neurodevelopmental delays warranting the attention of the parents or physicians. As an infant, he suffered from recurrent episodes of infectious otitis media with no hospitalization. He was limited in his normal activities, and his functional class was classified as Class II of the modified Ross classification for heart failure in children. Finally, at the age of 5 years, after an accidental auscultation of a systolic murmur, he was referred to our center for further investigation.

At first glance, the baby's face looked normal, and his epicanthal folds were attributed to his race. However, closer inspection revealed facial abnormalities, including a broad nasal bridge, a sloping forehead, and maxillary hypoplasia (Figure 1).

The boy's systemic blood pressure was 103/72 mmHg, and his peripheral oxygen saturation was estimated to be approximately 93.0% by pulse oximetry. Physical examination revealed hypoplasia and shortening of the distal phalanges (brachytelephalangism) (Figure 2).

On chest examination, bilateral wheezing was auscultated without significant rales or rhonchi, and a systolic ejection murmur was heard at the right upper sternal border, distributed to the periphery of the chest.

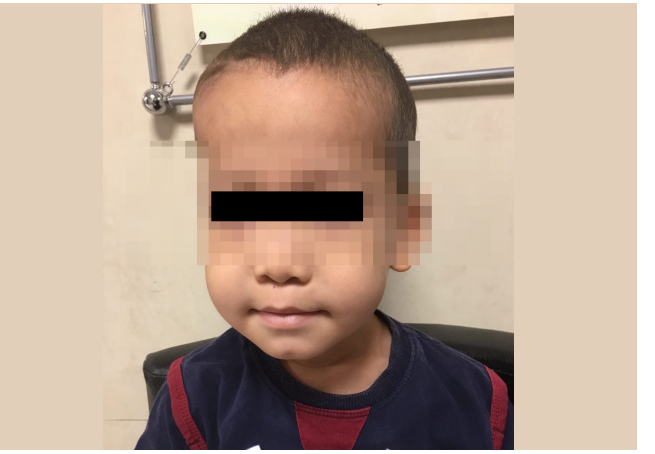

Figure 1. The image shows the patient's abnormal facial appearance.

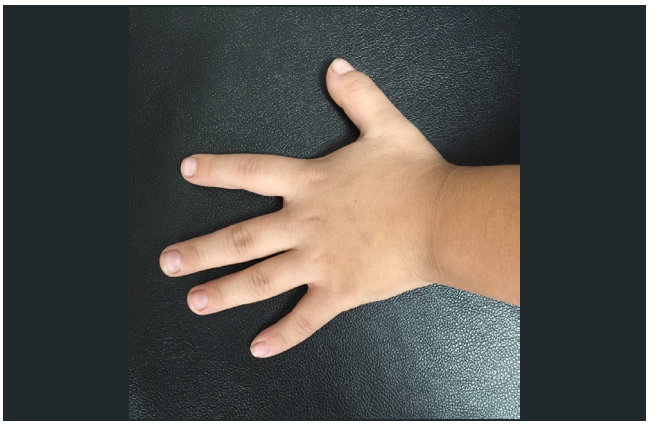

Figure 2. The image shows the boy's brachytelephalangism.

His thyroid, liver, and kidney function tests and complete cell count revealed no significant impairment. Serum levels of calcium, phosphorus, vitamin-D, alkaline phosphatase, and parathyroid hormone were also normal.

The boy's audiometry reported a lower limit of normal function, consistent with his history of recurrent otitis media.

Given the patient's recurrent upper respiratory tract infections, an upright posterior-anterior chest radiograph was obtained. Surprisingly, it revealed prominent tree-shaped tracheobronchial calcification that followed the course of the airway (Figure 3). Moreover, a radiograph of the patient's fingers indicated hypoplasia in the distal phalanges (Figure 4).

Twelve-lead electrocardiography showed right ventricular hypertrophy (RVH), which was subsequently confirmed by transthoracic echocardiography. A gradient of 62 mmHg above the level of the pulmonary valve represented peripheral pulmonary stenosis, and a moderate tricuspid regurgitation (TR) (gradient =130 mmHg) indicated pulmonary hypertension (gradient >68 mmHg) and concomitant segmental peripheral pulmonary stenosis. The inferior vena cava diameter was normal in echocardiography.

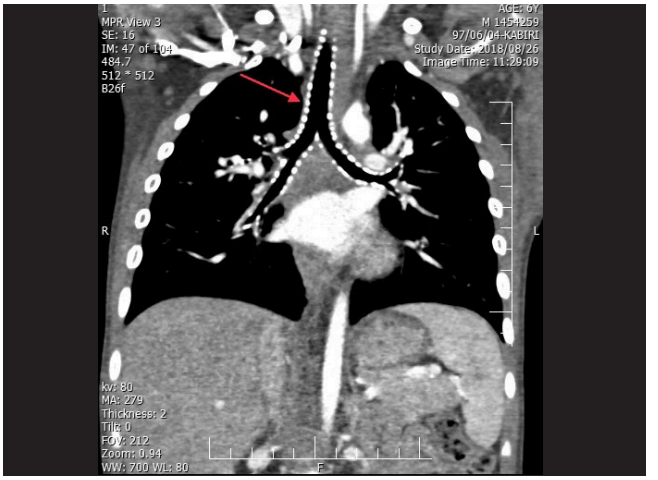

Figure 3. The image shows calcification in the patient's tracheobronchial tree.

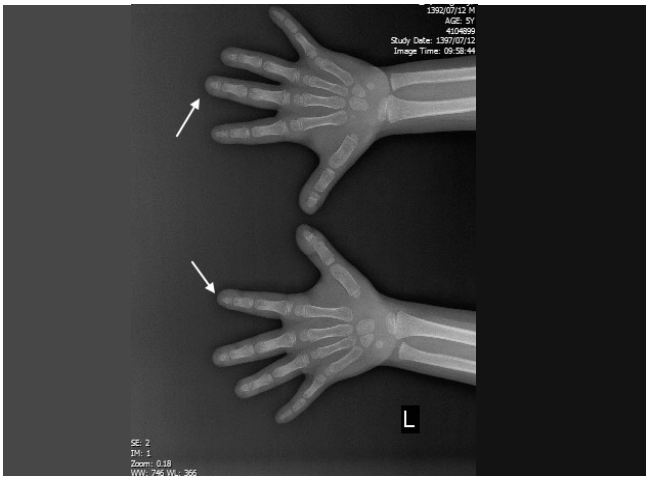

Figure 4. The X-ray of the boy's hands shows shortened first through fourth distal phalanges.

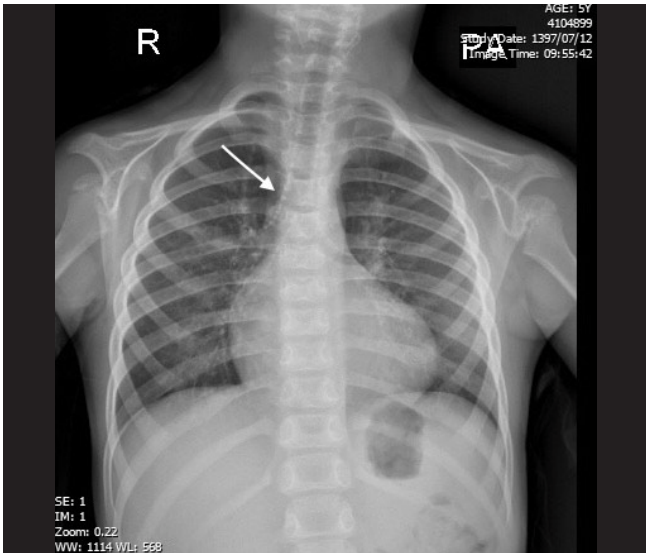

Figure 5. The patient's computed tomography is presented herein. The coronal slice demonstrates abnormal calcification in the tracheobronchial tree.

For further evaluation of the cardiopulmonary system, multislice spiral computed tomography (MSCT) of the ventricles and the great arteries was performed (Figure 5).

MSCT angiography illustrated mild narrowing in the lobar branches of the right pulmonary artery and significant stenosis in the lobar and segmental branches of the left pulmonary artery. The diameters of the main and proximal right and left pulmonary arteries were estimated to be 14 mm, 9.3 mm, and 10 mm, respectively. Moreover, the Z-score of all 3 was between 0 and 1. The CT scan revealed RVH and diffuse calcification in the tracheobronchial tree.

Discussion

Forty-two cases of KS have been reported so far, half of them in the Turkish population.[7] The distinctive features of KS, including abnormal cartilage calcification, facial features, and brachytelephalangism, can be readily identified by clinical observation, allowing a definitive diagnosis. Additionally, mutations in the MGP gene, identified by DNA sequencing, confirm the diagnosis.[7,8]

Findings in the present case report included facial features, recurrent otitis media, tracheobronchial calcification, peripheral pulmonary stenosis, and pulmonary hypertension.

Sun et al[9] suggested that 100.0% of their studied patients with KS had abnormal cartilage calcification and brachytelephalangism. They also reported that nasal bridge depression, midface hypoplasia, peripheral pulmonary stenosis, recurrent otitis media, and hearing loss were observed in 95%, 93%, 72%, 67%, and 91.0% of their cases, respectively, most of which were detectable in our patient.

Based on echocardiographic findings, our patient did not have a primary valvular disease, and it seemed that his TR was secondary to peripheral pulmonary stenosis and pulmonary hypertension. Although pulmonary pressure was normal in most reported cases, some cases, similar to our patient, presented with concomitant pulmonary hypertension and segmental peripheral pulmonary stenosis.

In a study by David et al,[10] 2 of 3 patients had pulmonary hypertension. Moreover, pulmonary hypertension was reported concomitantly with segmental peripheral pulmonary stenosis in adults and was classified as idiopathic pulmonary hypertension.[11] Finally, echocardiogram analysis has revealed RVH resulting in severe pulmonary artery hypertension in several cases.[10]

Tracheobronchial calcification is caused by Larsen syndrome, chondrodysplasia punctata, and tracheopathia osteoplastica, as well as acquired causes such as the long-term use of warfarin.[12,13] However, peripheral pulmonary stenosis has not been reported in any of the above diseases. Larsen syndrome is more likely to present with symptoms similar to Marfan syndrome, including aortic dissection,[14] and tracheopathia osteoplastica is rarely seen before

midlife.[12]

Regarding the presence of peripheral pulmonary stenosis, one of the most significant differential diagnoses of KS is Williams syndrome,[15] manifested in most children by the striking features of the elfin face, the presence of hypercalcemia and supravalvular aortic stenosis, and the absence of tracheobronchial calcification.

Although an accurate diagnosis of KS can be made by genetic testing, and one of the limitations of this study was the lack of a genetic diagnosis, given the obvious symptoms of the disease, it seemed that the first clinical diagnosis for this patient was KS.

There is no specific and definitive indication for interventional and surgical measures in KS. Depending on the severity of the disease, medical therapy, surgery, and intervention may be considered for these patients. Moreover, the treatment is symptomatic, often addressing indicators associated with peripheral pulmonary artery stenosis. Laryngotracheal calcification resulting in dyspnea can be treated with bronchodilators.

Most patients with KS have a good prognosis. During the follow-up of these patients and examinations, we should pay attention to their symptoms related to upper respiratory tract infections, the extent of hearing, and the possibility of tracheal and peripheral pulmonary stenosis development.

Conclusion

KS is a rare and little-known disease. Although the prognosis of most of these patients is good, their specialized treatment depends on the severity of the disease symptoms. Accordingly, early diagnosis and appropriate follow-up may prevent disease progression and the need for invasive procedures. It seems that accuracy in the initial examination of the newborn, including the detection of an abnormal face and abnormal heart murmurs, provides good diagnostic keys for initiation.

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