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CASE REPORT

Tracheal Cartilaginous Sleeve in Antley-Bixler Syndrome With W290C Mutation in *FGFR2*

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A case is presented to show tracheal cartilaginous sleeve in Antley-Bixler syndrome, which is the second case to be reported so far. In this patient, W290C mutation in *FGFR2*, the mutation previously known to cause Pfeiffer syndrome, was newly identified. After receiving tracheostomy, the patient recovered from repetitive respiratory distress, and retrieved normal respiratory function. Thorough airway examination and active surgical management such as tracheostomy is necessary in children with syndromic craniosynostosis, including Antley-Bixler syndrome.

Keywords Antley-Bixler syndrome; Tracheal cartilaginous sleeve; *FGFR2*; Tracheostomy.

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INTRODUCTION

Tracheal cartilaginous sleeve (TCS) is an airway malformation where trachea consists of long, solid cartilaginous tube without individual C-shaped tracheal arches [1]. Most of the TCS cases are associated with craniosynostosis syndromes such as Apert syndrome, Crouzon disease, Pfeiffer syndrome, and Goldenhar syndrome. However, there has been only one case reported so far on TCS in Antley-Bixler syndrome (ABS). ABS is very rare craniosynostosis syndrome, associated with radiohumeral synostosis. Mutations in fibroblast growth factor receptor 2 gene (*FGFR2*) are known to cause many craniosynostosis syndromes [2]. Herein, we present a case of TCS in ABS caused by W290C mutation in *FGFR2*, the mutation previously reported in Pfeiffer syndrome.

CASE REPORT

An early-term (38 weeks, 1 day) female child was born with 3.48 kg by caesarean section due to breech presentation. The child presented with craniosynostosis (premature closure of bilateral coronal & both lambdoid sutures) with clover leaf skull deformity (Fig. 1A). Facial bone and brain CT scan demonstrated ventriculomegaly, exophthalmos, hypertelorism, low lying ear and bilateral external auditory canal atresia. The child was also having both elbow contractures due to radiohumeral synostosis (Fig. 1B), and bilateral wind-blown hand deformity, both 2nd finger contractures with proximal interphalangeal joint symphalangism (Fig. 1C). Foot x-ray showed delta phalanx of both big toes, and incomplete syndactyly of both 2nd and 3rd toes without bony reunion (Fig. 1D).

Whole genome sequencing was implemented, and *FGFR2* [NM 022970.3] c.870G>T

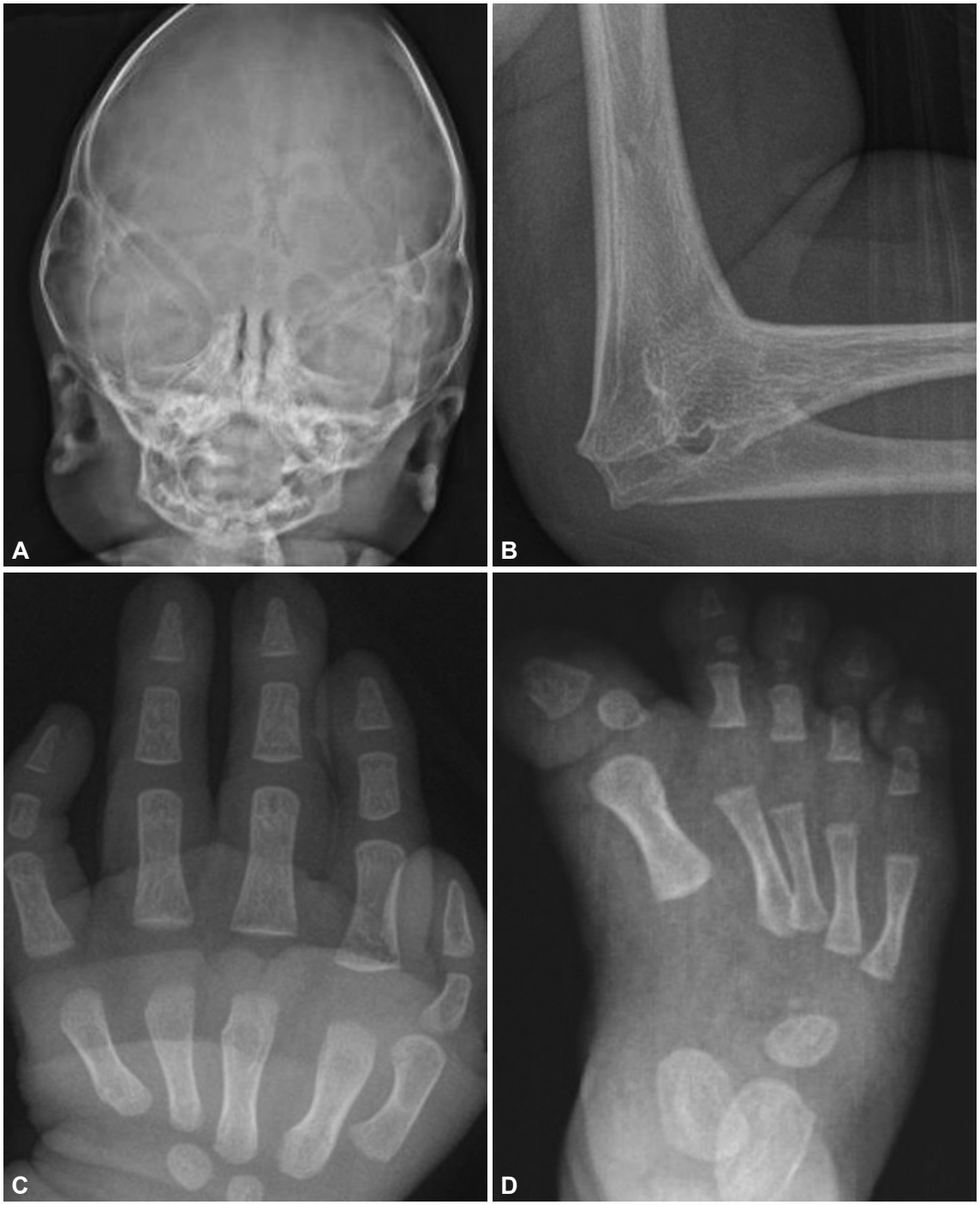

Fig. 1. Radiographic imaging. A: Anteroposterior skull radiograph. Clover leaf deformity is present. B: Anteroposterior right elbow radiograph. Radiohumeral synostosis is present. C: Anteroposterior right hand radiograph. Bilateral wind-blown hand deformity and both 2nd finger contractures with proximal interphalangeal joint symphalangism are seen in the image. D: Anteroposterior left foot radiograph. Delta phalanx of both big toes and incomplete syndactyly of both 2nd and 3rd toes without bony reunion are present.

(p.Trp290Cys) heterozygous mutation was identified. Sanger confirmation in her parents finally defined the mutation as de novo.

As the child showed recurrent cyanosis during feeding and poor oral intake, she was observed under admission, and soon moved to intensive care unit under intubation because of repetitive apnea and desaturation events. Thereafter, CPR events happened four times due to accidental extubation, so under the suspicion of upper respiratory obstruction, respiratory examination was performed under general anesthesia.

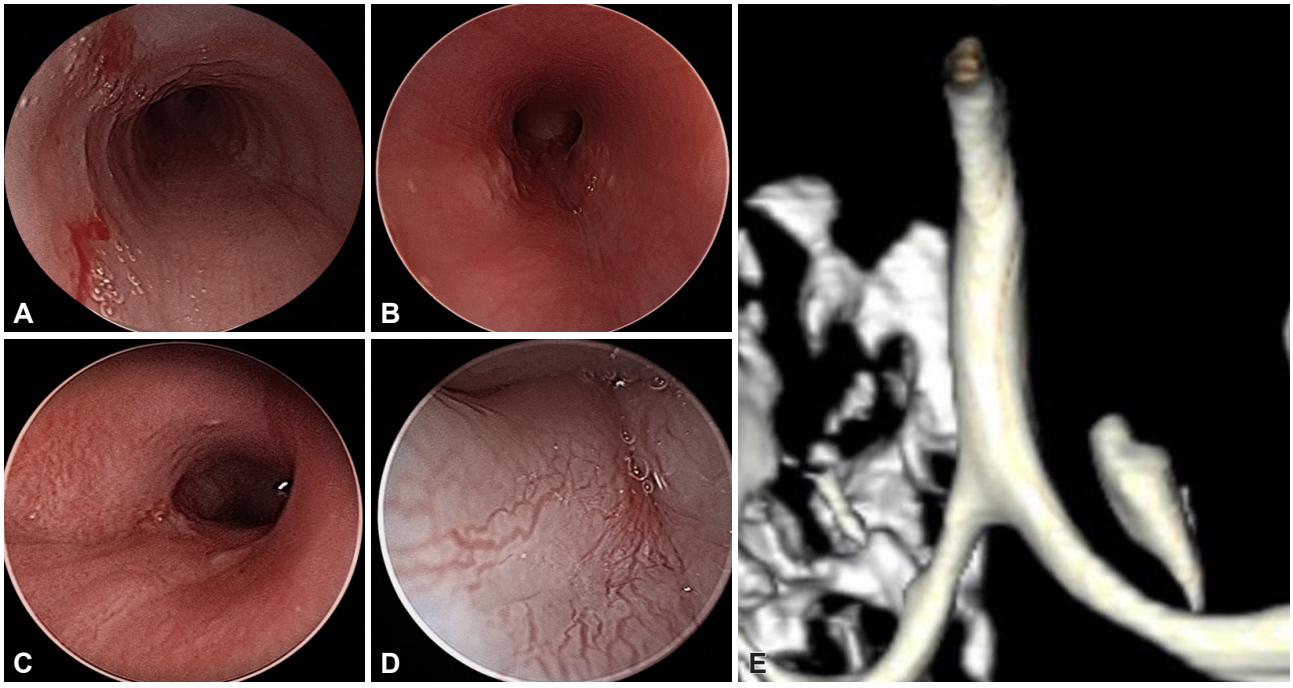

Fig. 2. Direct laryngoscopic view and three-dimensional CT reconstructions. A: Normal trachea with separated tracheal rings. B: TCS showing smooth wall without notifiable tracheal rings. C: TCS extending to right sided segmental bronchus. D: Endoscopic view showing choanal narrowing. E: Three-dimensional CT reconstructed image showing absence of C-shaped tracheal rings. TCS, tracheal cartilaginous sleeve.

The examination demonstrated TCS, showing no inter-cartilage fibrous annulus (Fig. 2B and E). Such finding was extending to right sided segmental bronchus (Fig. 2C). Left sided bronchomalacia and bilateral choanal narrowing were also identified (Fig. 2D). Tracheostomy was done by making an incision right below the cricoid cartilage due to short neck. She was discharged two weeks later with normalized respiratory function, and routinely followed up for 14 months with laryngoscopic examination twice a year. Her airway was well patent except for mild granulation tissue. Ethical approval to report this case was obtained from the Institutional Review Board of Seoul National University Hospital (IRB No. 2110-024-1260).

DISCUSSION

To our knowledge, we are first to report the case of TCS in ABS carrying W290C mutation in *FGFR2*, the mutation previously known to cause Pfeiffer syndrome. Although previous studies identified that identical mutations in *FGFR2* can cause either Crouzon or Pfeiffer syndrome (i.e W290G) [3], W290C mutation in *FGFR2* has never been reported in patients with ABS. Since there is extensive overlap of phenotypic manifestations among craniosynostosis syndromes [4,5], we experienced hard time determining clinical diagnosis between Pfeiffer syndrome type 2 and ABS. However, findings of radiohumeral synostosis without broad thumbs or toes were reasonable clinical evidences to diagnose her with ABS.

Our case is the second ABS case accompanying TCS to be reported so far. The estimated prevalence of TCS in syndromic craniosynostosis, mostly reported among Apert, Pfeiffer, and Crouzon syndromes, is reportedly 22% [3]. FGFR mutations especially affect airways by boosting proliferations of tracheal cartilage progenitor cells, resulting in rigid airway with limited distention [3]. One report has revealed that all five patients with W290C mutation in the study manifested TCS [3], but more future studies are needed to demonstrate mutation-specific risk of TCS.

The repetitive respiratory distress events such as cyanosis episodes observed in our case may have been due to limited distensibility of the trachea and deceased natural ability of airway to clear secretions following tracheal rigidity, as well as choanal stenosis. The fusion of the cartilage rings or lack of their formation anteriorly makes the trachea rigid, and the lack of complete fibrous pars membranacea prevents the necessary elasticity needed to provide distension. The dynamic airflow of the stiffened trachea disrupts effective cough mechanics resulting in an increased risk for infection, mucus plugging, and bronchospasm. TCSs that extend beyond the carina compound this risk.

The mortality rate of patients with TCS and craniosynostosis has been reportedly 90% at 2 years of age [4], possibly due to dual airway pathology including upper airway obstruction related with craniofacial anomalies and tracheal occlusion as a re-

sult of failure of airway growth. Tracheostomy is the safest and the most efficient way to manage TCS patients, and close monitoring is necessary due to high risk of forming granulation tissue and obstruction due to low flexibility.

In conclusion, children with syndromic craniosynostosis, including ABS, are at high risk of having TCS. Thorough airway examination including direct laryngoscopic examination is important in identifying airway problems. Once diagnosed, active surgical management such as tracheostomy should be considered to reduce the mortality due to airway compromise.

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None

Conflicts of Interest
The authors have no financial conflicts of interest.

Authors' Contribution
Conceptualization: Seong Keun Kwon, Jayoung Oh. Data curation: Jayoung Oh. Formal analysis: Seong Keun Kwon, Jayoung Oh. Supervision: Seong Keun Kwon. Writing—original draft: Jayoung Oh. Writing—review & editing: Seong Keun Kwon, Jayoung Oh. Approval of final manuscript: Jayoung Oh, Seong Keun Kwon.

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