Case Report

Kartagener's syndrome: A multisystem disease in need of a "multidisciplinary approach" concept

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disorder, with considerable heterogenicity, characterized by a spectrum of corresponding defects in ciliary ultrastructure and/or ciliary function related to genetic mutations effecting motile cilia. The impaired ciliary function impedes mucociliary clearance, which predisposes the patient to upper and lower respiratory tract infections, chronic sinopulmonary infection, development of bronchiectasis and loss of lung function. Recurrent ear infections might lead to hearing loss. Many males with primary ciliary dyskinesia have immobile spermatozoa or dysfunction of cilia in the epididymal duct, leading to infertility. During embryogenesis, nodal cilia, which are motile cilia, determine the correct lateralization of the organs. Dysfunction of these cilia leads to random lateralization and thus situs inversus in patients with primary ciliary dyskinesia. Kartagener's syndrome describes the classic triad of situs inversus, bronchiectasis and chronic sinusitis due to a congenital reduction or absence of ciliary function. The severity of the disease in adults is highly variable. Herein we present 3 members of a family with PCD developing almost the entire spectrum of manifestations and requiring not only extensive pediatric and adult respiratory medicine management but also a specialized multidisciplinary approach.
Pneumon 2020, 33(4):1-6.

CASE REPORT

We present two young male brothers, 23- and 19-years-old, non-smokers who were referred to our department for recurrent upper and lower re-

Key words: Bronchiectasis, Dexocardia, Kartagener's syndrome, Primary ciliary dyskinesia

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spiratory tract infections. They were both born after an uncomplicated pregnancy and delivery but they both presented with chronic cough with purulent sputum and dyspnea since early childhood. Their 9-year-old sister presented the same signs and symptoms and she was the first one from the family to be referred for examination to a pediatrician. Another 3 brothers and 1 sister as well as the parents who had a positive history for consanguinity were completely asymptomatic (Figure 1).

Lung auscultation revealed wheezing and rales without signs of respiratory failure for all. Radiographs of the chest demonstrated dextrocardia (Figure 2) whereas high resolution computerized tomography of the chest scans revealed the presence of bilateral bronchiectasis (Figure 3). Situs inversus was also documented (Figure 4). Extensive work-up including sweat chloride determination, a1 antitrypsin measurement, serum immunoglobulin quantification, serology for autoimmune rheumatic disease, serum angiotensin converting enzyme and serology for viruses was normal. Sputum cultures were sterile for *Mycobacterium Tuberculosis* and non-tuberculous mycobacteria and revealed *Haemophilus Influenzae* and *Klebsiella Pneumoniae* respectively for each one of the adult patients.

Based on the clinical features, the above-described radiographic findings and the family history, the working diagnosis of primary ciliary dyskinesia syndrome with situs inversus (Kartagener's syndrome) was made. Patients underwent further diagnostic workup with assessment of ciliary beat frequency (CBF) and ciliary beat pattern (CBP) by the digital high-speed video microscopy technique.

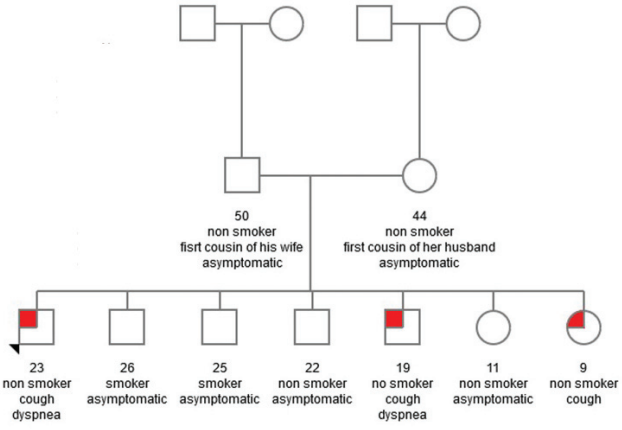

FIGURE 1. Family tree template presenting three members of the family, two brothers and one sister, with primary ciliary dyskinesia while the rest of the family remains asymptomatic.

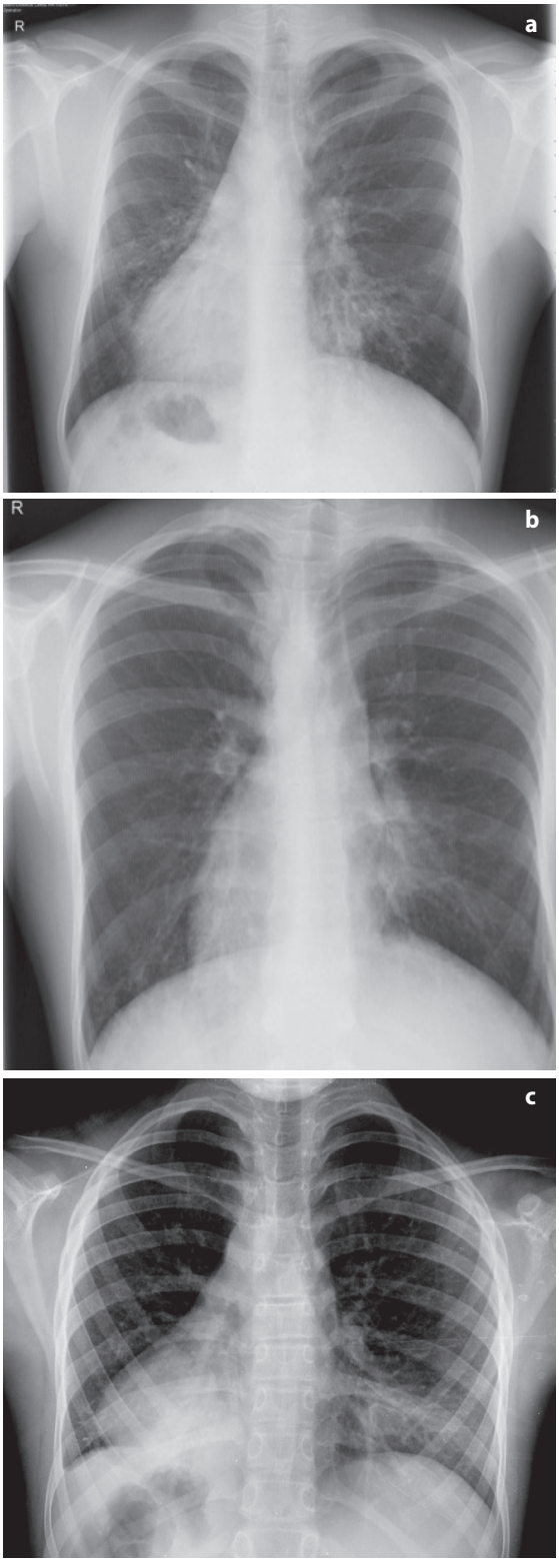

FIGURE 2. Posteroanterior chest radiographs demonstrating dextrocardia, bilateral lower zone opacities, and bronchiectasis.

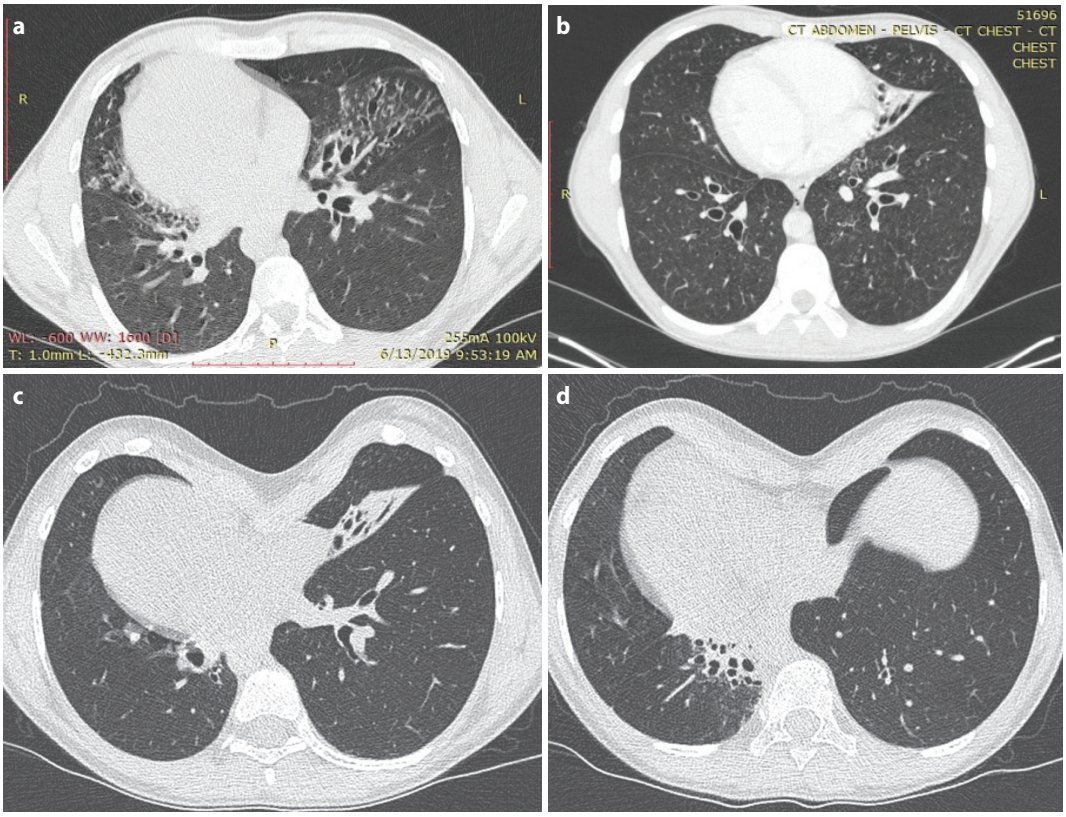

FIGURE 3. Axial plane chest computed tomography scans revealing bilateral bronchiectasis, with chronic atelectasis in the left "middle lobe" containing bronchiectasis (figure b and c) and an extended tree-in-bud pattern bilaterally (figure a). Pectus excavatum (figure c, d).

The young sister's cilia showed asynchronous beating compatible with PCD syndrome. The samples of the two older brothers showed vastly reduced numbers of motile cilia due to heavy secondary epithelial damage from the chronic nasal inflammation and a definite conclusion on their movement pattern could not be drawn. Also, nasal nitric oxide was measured (normal levels ≥77.0 nl/min) which was low in all three patients (1.88nl/ml, 9.44nl/ml,

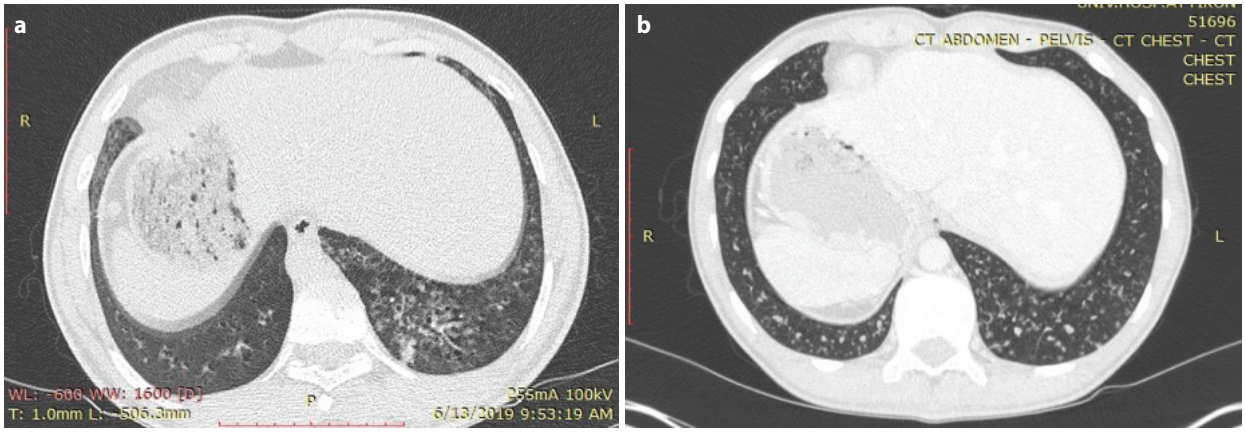

FIGURE 4. Axial plane chest computed tomography scans revealing centrilobular nodules, tree-in-bud formation and situs inversus.

and 9.07nl/ml, for the young sister and the two brothers, respectively).

Further multidisciplinary evaluation was performed with otorhinolaryngology examination confirming chronic sinusitis and hearing impairment (Figure 5) and urology and assisted reproduction unit consultation for subfertility based on spermodiagram analysis. Our patients received etiologic antimicrobial treatment and respiratory physiotherapy and were released from the hospital significantly ameliorated. Systematic multidisciplinary follow-up, preventive vaccination for influenza virus and *Streptococcus Pneumoniae*, as well as specialized genetic counselling was advised.

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disorder, with considerable heterogenicity, characterized by a spectrum of corresponding defects in ciliary ultrastructure and/or ciliary function.[1] The impaired ciliary function impedes mucociliary clearance, which predisposes the patient to recurrent sinopulmonary infection. It is caused by genetic mutations effecting motile cilia.[2] Mutations in over 40 genes have been reported to cause this syndrome, and genes continue to be discovered.[2] Abnormal ciliary motion in nasal epithelial samples may be visualized by high- speed video microscopy and is useful in the documentation of primary ciliary dyskinesia syndrome. Both ciliary beat frequency (CBF) and cilia beat pattern (CBP) are evaluated.[3] Unfortunately, there is no gold standard for the diagnosis and a combination of tests is necessary.[4] That being the case, clinical manifestations continue to play an important role in the diagnosis of primary ciliary dyskinesia.[5] It is characterized by upper and lower respiratory tract infections, chronic sinopulmonary infection, development of bronchiectasis and loss of lung function.[2] Recurrent ear infections might lead to transient or permanent hearing loss. Many males with primary ciliary dyskinesia have immobile spermatozoa or dysfunction of cilia in the epididymal duct, leading to infertility.[6] During embryogenesis, nodal cilia, which are motile cilia, determine the correct lateralization of the organs. Dysfunction of these cilia leads to random lateralization and thus situs inversus in patients with primary ciliary dyskinesia.[6] Situs inversus occurs in 50% of patients with primary ciliary dyskinesia.[2] Kartagener's syndrome describes the classic triad of situs inversus, bronchiectasis and chronic sinusitis due to a congenital reduction or absence of ciliary function. [7] The severity of the disease in adults is highly variable.[8] The general prognosis of bronchiectasis due to PCD is good, as the rate of decline of lung function is much slower than that in cystic fibrosis.[9] There is no doubt that primary ciliary dyskinesia presents with a variety of symptoms affecting different organs. Herein we present 3 members of a family with PCD developing almost the entire spectrum of manifestations and requiring not only extensive pediatric and adult respiratory medicine management but also a specialized multidisciplinary approach.

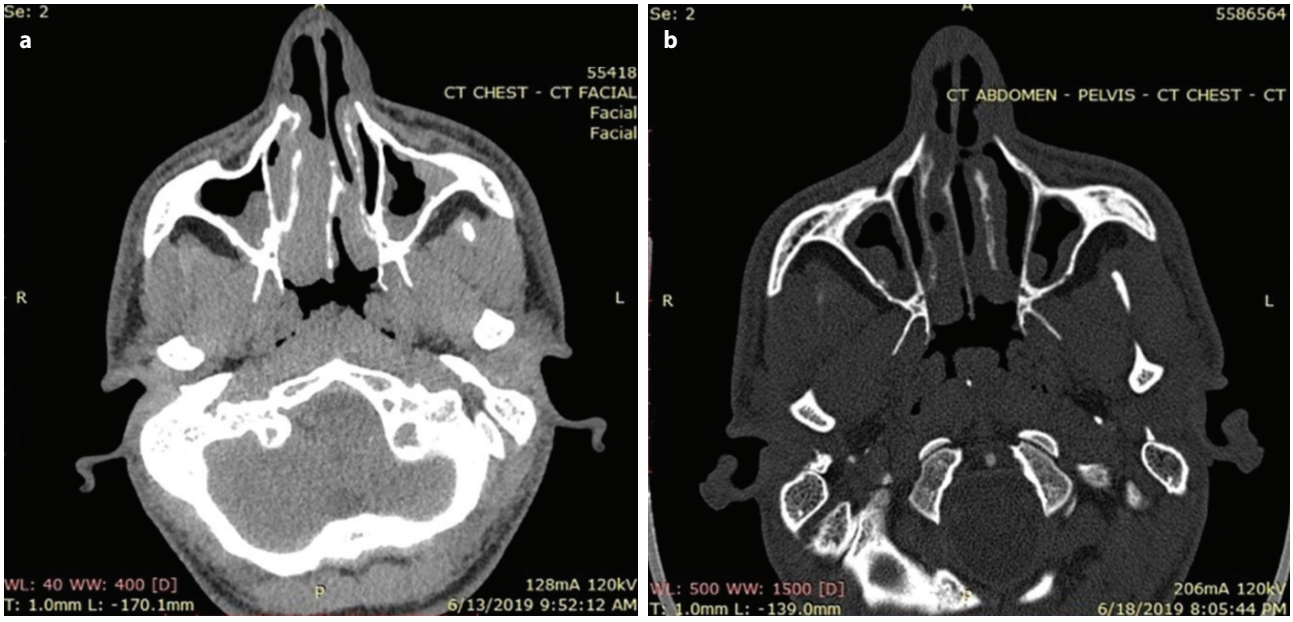

FIGURE 5. Axial plane chest computed tomography scans revealing mucosal thickening of the sinuses.

ΠΕΡΙΛΗΨΗ

Σύνδρομο Kartagener's: Μια πολυσυστηματική νόσος που χρήζει διεπιστημονικής προσέγγισης

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Η Πρωτοπαθής δυσκινησία κροσσών (ΠΔΚ) είναι μια σπάνια αυτοσωμική υπολειπόμενη διαταραχή, με σημαντική ετερογένεια, που σχετίζεται με παθογόνες μεταλλάξεις που επηρεάζουν την δομή ή/και την λειτουργία των κροσσών. Η διαταραχή στην λειτουργία των κροσσών δυσχεραίνει την βλεννοκροσσωτή κάθαρση, η οποία προδιαθέτει σε λοιμώξεις ανώτερου και κατώτερου αναπνευστικού, χρόνια λοίμωξη παραρρινίων κόλπων, δημιουργία βρογχιεκτασιών και έκπτωση αναπνευστικής λειτουργίας. Επαναλαμβανόμενες ωτίτιδες μπορεί να οδηγήσουν σε έκπτωση ακοής. Πολλοί άρρενες ασθενείς με πρωτοπαθή δυσκινησία κροσσών παρουσιάζουν ακίνητα σπερματοζωάρια ή δυσλειτουργία των κροσσών στον επιδιδυμικό πόρο, με αποτέλεσμα στειρότητα. Κατά την εμβρυογένεση, οι κομβικοί κροσσοί, που είναι κινητοί κροσσοί, καθορίζουν την σωστή διάταξη των οργάνων. Δυσλειτουργία αυτών των κροσσών οδηγεί σε τυχαία διάταξη των οργάνων και έτσι σε πλήρη αναστροφή των σπλάγχνων (situs inversus) σε ασθενείς με πρωτοπαθή δυσκινησία κροσσών. Το σύνδρομο Kartagener's αντιστοιχεί στην κλασσική τριάδα: situs inversus, βρογχιεκτασίες και χρόνια ιγμορίτιδα ως αποτέλεσμα συγγενούς μείωσης ή απουσίας λειτουργίας των κροσσών. Η βαρύτητα της νόσου στους ενήλικες ποικίλλει. Παρουσιάζουμε 3 μέλη μιας οικογένειας με πρωτοπαθή δυσκινησία κροσσών, δύο άρρενες και ένα θήλυ, με συμπτωματολογία επαναλαμβανόμενων λοιμώξεων ανώτερου και κατώτερου αναπνευστικού. Από τον απεικονιστικό έλεγχο στις ακτινογραφίες θώρακος σημειώθηκε δεξιοκαρδία, ενώ από τις αξονικές τομογραφίες θώρακος αποκαλύφθηκαν βρογχιεκτασίες αμφοτερόπλευρα. Ο έλεγχος με υψηλής ταχύτητας βίντεο μικροσκόπιο ανέδειξε παθολογική κινητικότητα κροσσών. Καθώς οι ασθενείς που παρουσιάζουμε ανέπτυξαν σχεδόν όλο το φάσμα εκδηλώσεων της νόσου είναι σαφές ότι χρήζουν όχι μόνο ενδελεχούς παιδιατρικού και πνευμονολογικού ελέγχου αλλά και μιας εξειδικευμένης πολύπλευρης προσέγγισης που απαιτεί τη συνεργασία πολλαπλών ειδικοτήτων.

Πνεύμων 2020, 33(4):1-6.

Λέξεις - Κλειδιά: *Βρογχιεκτασίες, Δεξιοκαρδία, Σύνδρομο Kartagener, Πρωτοπαθής δυσκινησία κροσσών*

REFERENCES

1. Lucas JS, Walker WT. Nasal nitric oxide is an important test in the diagnostic pathway for primary ciliary dyskinesia. Ann Am Thorac Soc 2013; 10:645-7.
2. Lucas JS, Davis SD, Omran H, Shoemark A. Primary ciliary dyskinesia in the genomics age. Lancet Respir Med 2020; 8:202-16.
3. Peabody JE, Shei RJ, Bermingham BM, et al. Seeing cilia: imaging modalities for ciliary motion and clinical connections. Am

J Physiol Lung Cell Mol Physiol 2018; 314:L909-1.
4. Lucas JS, Barbato A, Collins SA, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J 2017; 49:1601090.
5. Goutaki M, Meier AB, Halbeisen FS, et al. Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. Eur Respir J 2016; 48:1081-109.
6. Boon M, Jorissen M, Proesmans M, et al. Primary ciliary dyskinesia, an orphan disease. Eur J Pediatr 2013; 172:151-62.
7. Adam T Hill, Anita L Sullivan, James D Chalmers et al., British Thoracic Society Guideline for bronchiectasis in adults. Thorax 2019; 74(Suppl 1):1-69.
8. Kuehni CE, Goutaki M, Carroll M, Lucas JS. Primary ciliary dyskinesia: the patients grow up. Eur Respir J 2016; 48:297-300.
9. Pappas K, Pentheroudaki A, Ferdoutsis E, et al. Bronchiectasis in congenital diseases: Pathogenesis, imaging, diagnostic approach. Pneumon 2011; 24:235-62.