Kartagener Syndrome: An atypical presentation

Kelly-Anne Lee & Lydia Penny

Background

Primary ciliary dyskinesia (PCD) is a rare genetic ciliary motility disorder categorised by reduced ciliary motility (Albino et al., 2024 & Hassan et al. 2009). Despite an incidence of 1 in 30,000 live births there is significant heterogeneity within the PCD population (Lucas et al., 2020). This has led to the classification of subset populations based on clinical manifestation (Huff et al., 2024). Approximately 50% of PCD patients have Kartagener syndrome (KS), which is characterised by the triad of situs inversus, chronic sinusitis and bronchiectasis (Huff et al., 2024). Bronchiectasis associated with PCD is often referred to as non-CF bronchiectasis, due to the significant symptomatic overlap between PCD and Cystic Fibrosis (CF). Both are rare, inherited, chronic diseases and are associated with multiple organ complications, with respiratory complications being the main cause of morbidity (Pereira, 2023). CF is caused by mutations in a single gene that encodes for the cystic fibrosis transmembrane conductance regulator (CTFR) protein (Pereira, 2023). In contrast to CF, approximately 45 pathogenic gene variants have been identified as causing 70% of diagnosed PCD and KS cases (Lucas et al., 2020). PCD is primarily inherited in an autosomal recessive manner, with genetic mutations leading to functional impairment of cilia motility (Lucas et al., 2020).

The primary role of cilia is to promote mucociliary clearance within the respiratory tract, thus PCD reduces lung clearance, ultimately resulting in recurrent respiratory tract infections (Schafer et al., 2018). Disease progression and pathology is driven by underlying inflammatory and cellular mechanisms which cause permanent bronchial and parenchymal damage, manifested as a progressive decline in lung function (Pifferi et al., 2021). In the absence of disease-specific evidence, current respiratory management of PCD is largely extrapolated from evidence based on CF patients given the substantial overlap in symptoms. (Pereira, 2023).

Case Report

We present an atypical presentation of KS in ‘Patient J’ who is a 35-year-old Caucasian male (Height 168 cm, Weight 73.9 kg, BMI 26.18 kg/ m2). Patient J presented to the Respiratory Investigation Unit at The Prince Charles Hospital during a 12-day admission. The patient was referred with a longstanding diagnosis of KS, established during paediatric investigations, which confirmed the presence of dextrocardia situs inversus totalis, right-sided aortic arch, impaired sperm motility, overlapping asthmatic phenotype and obstructive ventilatory defect quantified by spirometry.

Clinical Background

- Genetic profiling studies (paediatric investigation).
- Exclusion of cystic fibrosis via normal sweat test (paediatric investigation).
- Successful patent foramen ovale (PFO) closure in 2017.
- Normal flora on sputum microbiology; history of chronic *Pseudomonas aeruginosa* colonisation.
- Unresolved fatigue in reference to two documented infections of COVID-19 (Ciprofloxacin administered due to mild exacerbation of respiratory symptoms).
- Non-compliant with respiratory management regime (Azithromycin, Tobramycin, Symbicort, Salbutamol and Hypertonic Saline).
- Barriers to compliance and accessing services due to living regionally and burden of role as a carer to an immediate family member.
- Lack of formal chest physiotherapy regime (patient finds exercise sufficient for airway clearance).

Clinical Examination

Patient J was found to have bilateral harsh breath sounds, a loose cough and scattered bibasal crackles, particularly at the base of the right lung.

Respiratory Function Testing (RFTs)

All spirometry parameters demonstrate a reduction below the lower limit of normal (LLN) indicative of a possible mixed disorder with an FEV_1 z-score of –5.51 categorising the ventilatory defect as severe (Stanojevic et al., 2022). Subsequently lung volumes were performed to determine whether an element of restriction was present.

Elevation of TLC above the upper limit of normal (ULN) excludes restriction, and is indicative of hyperinflation. This is confirmed by the elevation of the RV/TLC above the ULN (Stanojevic et al., 2022). As per current department interpretation practices elevation in RV above the ULN is indicative of gas trapping.

Gas transfer results showed normal diffusion capacity with a single-breath carbon monoxide uptake in the lung corrected for haemoglobin (DLCOc) >LLN and < ULN (Stanojevic et al., 2022).

As illustrated by Figure 1, Patient J was investigated for bronchodilator responsiveness (dose = 400 mcg Salbutamol). On this occasion Patient J did not meet ERS/ATS criteria for determining a significant bronchodilator response (>10% of FEV_1 and/or FVC relative to the predicted value), with a maximal percentage change of 5% in FVC (Stanojevic et al., 2021). A significant bronchodilator response has been exhibited by Patient J on three previous occasions.

Predicted Equations: Global Lung Initiative (Spirometry, Quanjer 2012; Gas Transfer, Stanojevic 2020; Lung Volumes, Hall 2021).
Patients with an age above the UL of these equations will have predicted values calculated at the UL: 80 years for Lung Volumes; 85 years for Gas Transfer; 95 years for Spirometry.
Severity grading (reduction): Mild ≥-2.5 to <-1.65, Moderate ≥-4 to <-2.5, Severe <-4 || Severity grading (elevation): Mild >1.65 to ≤2.5, Moderate >2.5 to ≤4, Severe >4

Test Date: 10.01.24

Note: Predicted equations for Gas Transfer and Lung Volumes have changed.
Please only use raw data when comparing these results to those completed before October 26, 2023.

Spirometry

		Pre	LLN	Pred	Z-Score	%Pred	Post	Z-Score	%Chg
Level time		01:28PM					02:09PM		
FEV 1	[L]	0.97	3.04	3.83	-5.51	25 %	1.06	-5.36	2 %
FVC	[L]	3.33	3.73	4.66	-2.36	71 %	3.57	-1.92	5 %
FEV 1 % FVC	[%]	29	72	82	-5.22	35 %	30	-5.20	1 %
PEF	[L/s]	3.47	6.97	8.96	-4.54	39 %	3.45	-4.56	-0 %

Vital Capacity

		Pre	LLN	Pred	Z-Score	%Pred
VC MAX	[L]	3.73	3.95	4.92	-2.02	76 %

Lung Volumes (Body Plethysmography)

		Pre	LLN	Pred	ULN	Z-Score	%Pred
TLC	L	9.19	5.06	6.27	7.50	3.87	146 %
FRCpleth	L	6.40	1.92	2.82	3.97	4.31	227 %
RV	L	5.46	0.71	1.37	2.21	6.40	398 %
RV % TLC	%	59.40	12.32	21.67	31.62	5.92	274 %

Gas Transfer

		Pre	LLN	Pred	ULN	Z-Score	%Pred
DLCO	ml/(min*mmHg)	31.73	22.35	28.51	35.59	0.78	111 %
KCO	ml/(min*mmHg*L)	6.14	3.92	4.94	6.03	1.80	124 %
VA	L	5.17	4.76	5.81	6.94	-0.99	89 %
VIN	L	3.73	3.95	4.92	5.92	-2.02	76 %
Hb	g(Hb)/dL	14.90					
DLCOc	ml/(min*mmHg)	31.47	22.35	28.51	35.59	0.71	110 %
KCOc	ml/(min*mmHg*L)	6.09	3.92	4.94	6.03	1.73	123 %

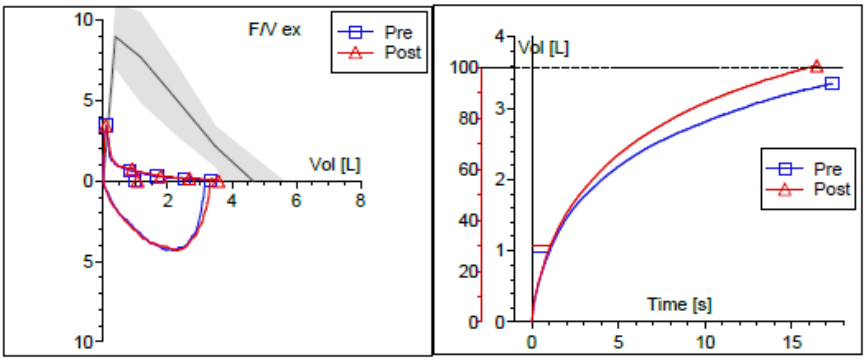

Figure 1: RFT report following full lung function performed during January 2024 admission.

Medical Imaging

HRCT findings included:

- Situs inversus with dextrocardia and right-sided aortic arch.
- Left and right bronchial morphology reversed.
- Minor nodular atelectasis.
- Ground-glass abnormality within the apex of the left lung (morphological right apical segment).
- Marked bilateral airways gas trapping.
- Marked bronchiolitis obliterans supported by presence of:
  - Mosaic perfusion pattern (Fig. 2B).
  - Generalised bronchial attenuation.

HRCT excluded the hallmark features of bronchiectasis to reveal an atypical presentation of KS (Fig. 2A), including the cardinal sign described as a lack of tapering of the bronchial lumina, the signet ring sign (dilation of the bronchial lumina internal diameter > diameter adjacent pulmonary artery), and the tree-in-bud sign exhibited by centrilobular nodular and linear branching opacities (Grenier et al., 2021).

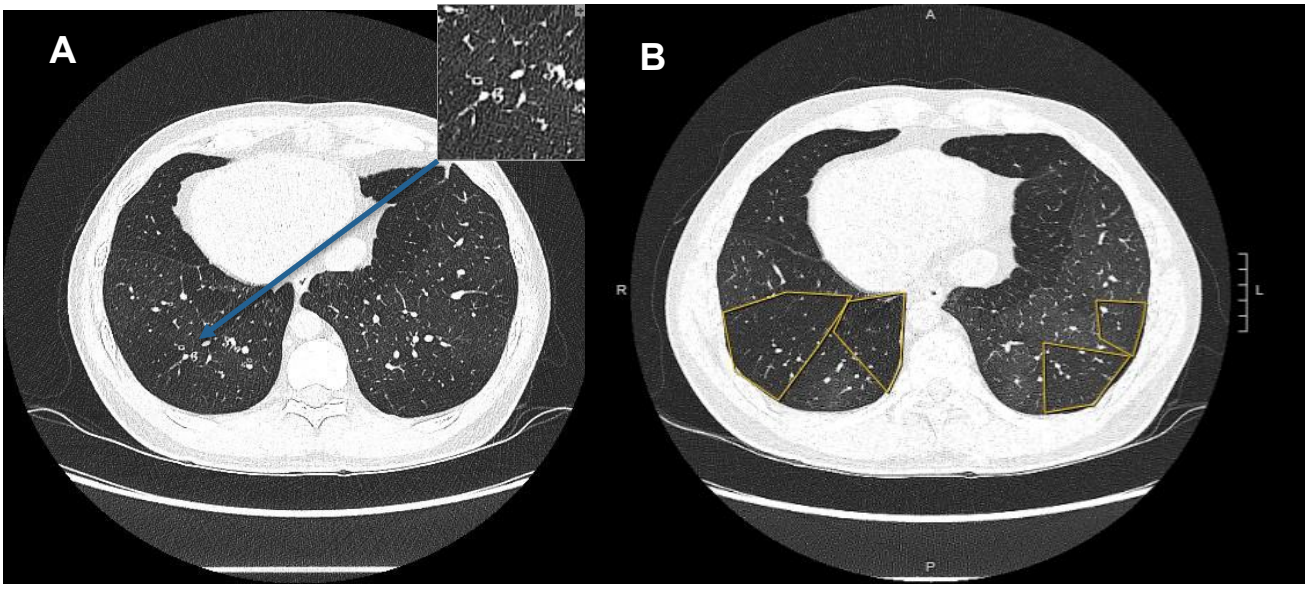

Figure 2: Patient J HRCT performed January 2024. A). Axial view lung section demonstrating a lack of dilation of the bronchi which can occur with or without bronchial wall thickening (Grenier et al., 2021). B). Supine, expiratory axial view of the lungs, demonstrating presence of mosaic attenuation; indicative of bronchiolitis obliterans and gas trapping.

Discussion

Patient J's RFTs illustrate preserved diffusion capacity, a severe obstructive airflow limitation, hyperinflation and gas trapping. As described by HRCT, Patient J's investigations excluded the presence of bronchiectasis to reveal an atypical presentation of KS but revealed marked bronchiolitis obliterans (BO). The aetiology of BO has not been distinguished in this case however, respiratory infection is a precipitating factor within the literature (Grenier et al., 2021). BO is characterised by submucosal fibrosis and inflammation, that leads to narrowing of the bronchiolar lumen (Grenier et al., 2021). BO is linked to airflow obstruction on RFTs, however, is not typically associated with severe DLCO impairment in keeping with Patient J's results (Grenier et al., 2021).

In obstructed patients, limitation to expiratory flow arises due to increased airway resistance and/ or the obstruction to the lumen (Papandrinopoulou et al., 2012). For example, the presence of increased secretion or increased bronchial smooth muscle tone (Papandrinopoulou et al., 2012). A hallmark of obstructive airways is slow lung emptying and an extended expiratory time leading to an increase end-expiratory volume due to the interruption of expiration by the next inspiratory effort before natural relaxation volume (VT) is reached (Papandrinopoulou et al., 2012). This results in gas trapping and dynamic hyperinflation (↑RV). Lung hyperinflation and increased lung compliance (↑TLC & RV/TLC) can also occur due to loss of elastic recoil, often due to pathophysiological mechanisms which reduce the elastic tissue in the pulmonary parenchyma (Papandrinopoulou et al., 2012).

Symptom burden in PCD patients affects quality of life. Symptoms are largely driven by mucus, frequent bacterial infections and inflammation, which in turn can lead to pulmonary exacerbations and bronchiectasis. Mucociliary clearance (MCC) is the primary defense mechanism of the lungs against pollutants, allergens and pathogens (Hassan

et al., 2009). In healthy lungs, mucus cleans and protects airways, trapping microbes and debris. Coordinated movements from ciliated cells lining the trachea clear mucus across the epithelial barrier and propel mucus upwards to the pharynx (Schafer et al., 2018). Poor MCC in the context of KS results in retention of mucus and bacteria in the respiratory tract which manifests as a chronic productive cough, chronic nasal congestion, wheezing, dyspnoea and chronic active inflammation (Dishop, 2018). There are concerns for PCD patients with chronic Pseudomonas aeruginosa colonisation, as there has been a demonstrated risk associated with increased lung function decline and deterioration in structural lung changes (Cohen-Cymberknoh et al., 2017). Mucus retention is generally patient specific, and airway clearance techniques are widely used to manage patient symptoms.

Prior to his admission Patient J had lapsed in most of his treatment regime. A primary component of which was the management of his asthma. International treatment guidelines do not recommend use of inhaled corticosteroids (ICS) unless PCD patients have co-existing asthma, airways reactivity or wheezing with reversible bronchial obstruction (Dehlink et al., 2018 & Shapiro et al., 2016). However, many PCD patients are being prescribed ICS purely for recurrent wheezing without evidence of type 2 airway inflammation; the efficacy of this practice is contentious (Dehlink et al., 2018). Patient J is the primary carer for an immediate family member, he is often unable to follow his therapeutical regime, access healthcare for himself or take extended periods of leave from full time employment. The real benefit of this most recent admission was the demonstrated merit of the prescribed therapies, which was perceived by the patient. During his admission Patient J, in addition to recommencement of an ICS, was advised on physiotherapy techniques to promote and support airway clearance coupled with the ongoing use of hypertonic saline. As a hyperosmolar agent, hypertonic saline hydrates viscous airway secretions and stimulates cough (Paff et al., 2021). In a further effort to reduce barriers of Patient J accessing care, on discharge he was supplied sufficient scripts with repeats, and encouragement to remain compliant with his physiotherapy regime and maintain adequate hydration and electrolyte levels.

The identification of specific genotypes in PCD and underlying disease mechanisms is the first step toward personalised medicine, with the ultimate goal being to restore ciliary function (Paff et al., 2021). Much of Patient J's symptom burden stems from the overlap of his asthma and bronchial hyperreactivity. Salbutamol is effective as a reliever, but biologic control in monoclonal antibody therapy for the asthmatic component of his current respiratory disease has been discussed. Blood tests screening for peripheral eosinophilia +/- elevated IgE count will determine Patient J's eligibility for this treatment avenue. Given the barriers to accessing care, the introduction of a biological agent, in addition to potentially reducing ICS dose and mitigating side effects, may also offer greater disease control and reduced morbidity (Menzies et al., 2021).

Summary

In summary, current PCD management is often based on anecdotal evidence from CF patients and is focused on symptomatic relief by reducing sputum viscosity and providing early treatment of infections. Patient J demonstrates very severe obstructive airways airflow limitation with bronchial hyperreactivity and significant bronchodilator response on repeated lung function testing. This case is atypical of KS, in that the patient does not have significant bronchiectasis but does have significant gas trapping, in keeping with bronchiolitis obliterans or possibly his asthma. Optimisation of his care must be delivered in a manner sensitive not just to the pathophysiology of his disease but also to the complexities of the individuals' circumstances.

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