A 28-year-old woman with chronic respiratory symptoms: navigating a diagnostic puzzle

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An intriguing case of a 28-year-old woman with chronic respiratory symptoms and situs inversus. Ultrastructural analysis by electron microscopy is a highlight in the discovery of a rare syndrome. A lesson in complex diagnostics! @cime_conicet, @virkinal https://bit.ly/4jHzdW5

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A 28-year-old woman from Argentina presented to Ángel C. Padilla Hospital with complaints of abdominal pain, a minimally productive cough and fever. Her medical history includes respiratory symptoms that began at 2 years of age, notably with an episode of whooping cough. Over the years, she has undergone recurrent nasal lavage and physiotherapy, but her respiratory symptoms, primarily acute obstructive bronchitis, were persistent. The patient's parents are first degree cousins and have three children: the index patient, a second child with congenital heart disease, and a third child without congenital pathology.

Task 1

What should be the first step in evaluating a patient with chronic respiratory symptoms, recurrent infections and a family history of congenital defects?

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Initial investigations

Initial imaging included a chest radiograph, which revealed dextrocardia and situs inversus totalis (figure 1a). A CT scan of the abdomen and chest was performed to rule out acute abdominal conditions, confirming pneumonia in the left lung base (figure 1b). Further investigation with high-resolution chest CT demonstrated situs inversus totalis, with thickened bronchial walls, saccular bronchiectasis, and mucus accumulation in the left middle lobe, suggestive of superinfection (figure 1c). Paranasal sinus radiography showed acute sinusitis in the maxillary sinuses (figure 1d).

Task 2

Given the findings of situs inversus on imaging, what differential diagnoses should be considered?

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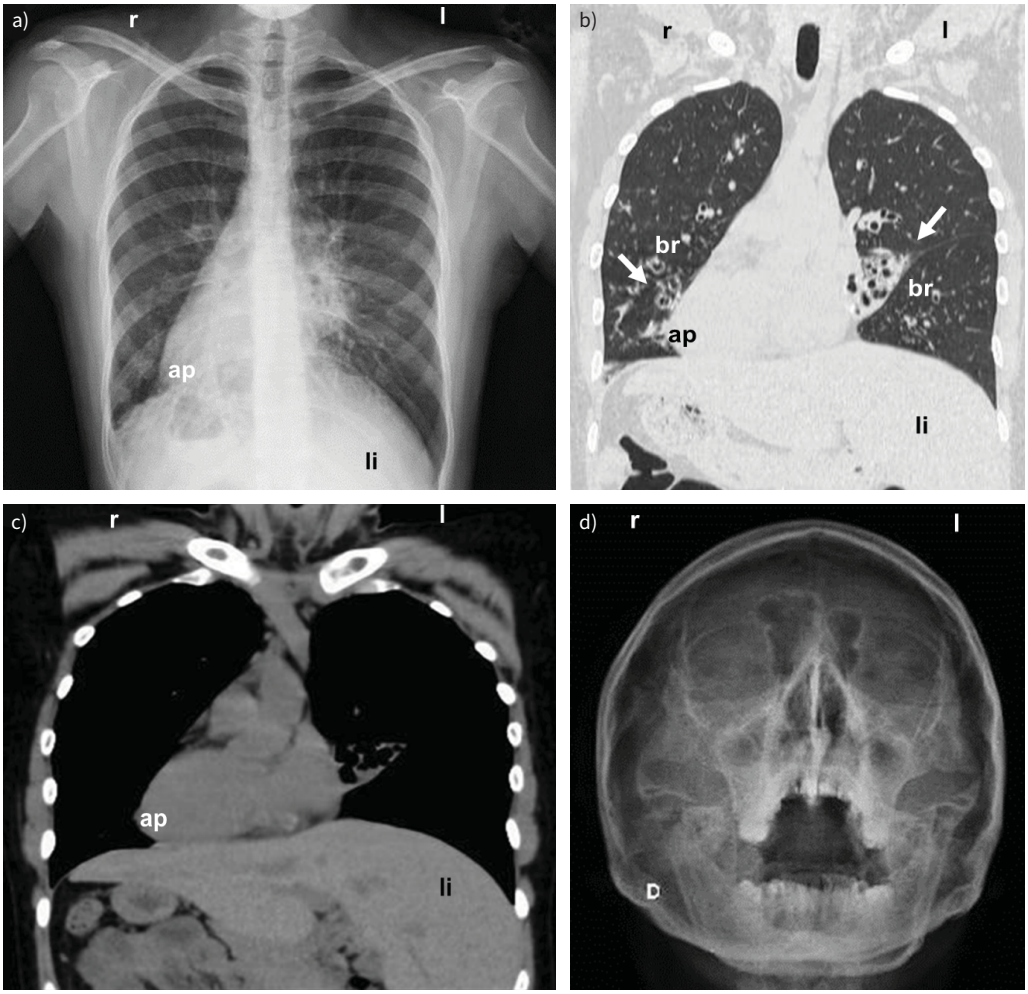

FIGURE 1 a) Chest radiograph, showing the heart on the right and the liver on the left, demonstrating the presence of situs inversus totalis. b) computed tomography (CT) scan of the abdomen and chest. The diagnosis of acute pneumonia was confirmed by the observation of a pneumonic block at the left lung base, and situs inversus totalis was also evident. c) High-resolution chest CT scan confirmed situs inversus totalis, with thickening of the bronchial wall of the lower and middle lobes, mucus-filled saccular bronchiectasis in the left middle lobe, "tree-in-bud pattern" opacities in the same lobes, predominantly the lower ones, suggesting added superinfection. d) Radiograph of the paranasal sinuses showing acute sinusitis in the maxillary sinuses. r: right; l: left; ap: apex of the heart; li: liver; br: bronchiectasis.

Further investigations

Spirometry results indicated non-reversible bronchial obstruction (table 1). The patient was then referred for a nasal biopsy to investigate potential ciliary abnormalities, which were fixed for TEM analysis. Figure 2 shows a schematic of a normal cilium in cross-section at the axoneme level. The biopsy sample was processed and high-resolution electron microscopy revealed significant ultrastructural defects, including the absence of dynein arms (class 1 defect) (figure 3a) and microtubule disorganisation (class 2 defect), consistent with PCD (figure 3b–d).

Task 3

After observing situs inversus and bronchiectasis, what other diagnostic test would be crucial in confirming the diagnosis of PCD?

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TABLE 1 Spirometry before and after β_2 salbutamol

	FVC	FEV_1	FEV_1/FVC	$FEF_{25–75\%}$
Before	2.14 L	1.84 L	86.0%	2.27 L
% predicted	65%	66%	105%	57%
After	1.77 L	1.56 L	88.1%	3.19 L
Change	−17%	−15%	2%	40%

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC.

Final diagnosis

After analysing the clinical history, imaging findings and TEM results, the patient was diagnosed with Kartagener syndrome, a subtype of PCD, which is characterised by situs inversus, bronchiectasis and chronic sinusitis.

Task 4

What are the key diagnostic challenges in diagnosing PCD?

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Task 5

Why is TEM still considered extremely important in the diagnosis of PCD, despite the availability of genetic testing?

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Discussion

PCD is a rare, genetically inherited condition that disrupts the structure and function of motile cilia [1, 2]. Diagnosing PCD remains challenging due to overlapping symptoms with other respiratory diseases. Key features of PCD include neonatal respiratory distress, chronic rhinitis and recurrent infections of the upper and lower respiratory tracts. The patient experienced multiple respiratory infections during childhood and, by early adulthood, presented with abdominal pain, a barely productive cough and fever.

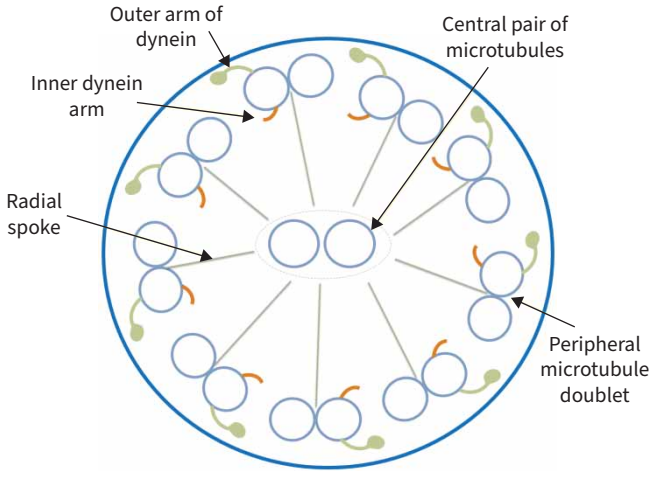

FIGURE 2 Diagram of a cross-section of a cilium at the level of the axoneme. The normal ultrastructural organisation can be seen. It consists of a central pair of core microtubules surrounded by nine peripheral microtubule doublets attached to the central pair by radial spokes. Each doublet has outer and inner dynein arms.

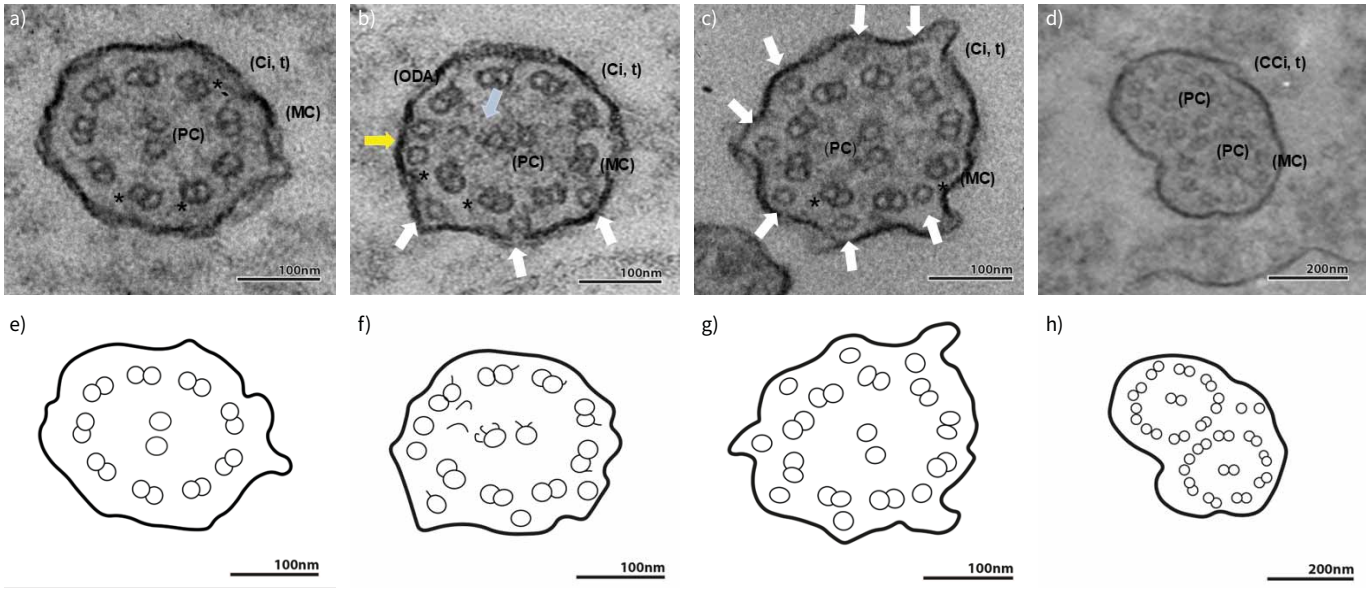

FIGURE 3 Micrographs obtained by transmission electron microscopy. The upper panels (a–d) show cross-sections of cilia, while the lower panels (e–h) provide a schematic of the axoneme ultrastructure shown in the panel above. a) The absence of external dynein arms in some of the lateral microtubule pairs can be observed (class 1 alterations). The asterisks indicate the sites with the absence of an outer dynein arm (ODA). b) Alterations can be observed at the level of the axoneme. The yellow arrow indicates dissociation of one of the lateral pairs and the white arrows show extra single microtubules surrounding the lateral pairs. The light blue arrow indicates possible disorganisation of the radial structure. c) Alterations in the ultrastructure of the axoneme corresponding to multiple extra single microtubules surrounding the lateral pairs (white arrows). A disorganisation of the membrane surrounding the cilium is also observed, especially at the level of the single microtubules. d) The fusion of two cilia is observed, and two axonemal structures can be seen within the same membrane. Ci, t: cilia, cross-section; Cci, t: compound cilia, cross-section; PC: central pair; MC: ciliary membrane. Scale bars: a–c) 100 nm; d) 200 nm.

Kartagener syndrome, a hallmark subset of PCD, features the classic triad of sinusitis, bronchiectasis and situs inversus totalis [3]. In ∼50% cases of PCD situs inversus is present [4]. During gastrulation the normal left–right asymmetric axis is established. Nodal motile cilia move clockwise, circularly, creating a leftward fluid flow through the ventral node. This flow generates a signalling gradient that guides normal visceral organogenesis, and the typical anatomical arrangement known as situs solitus [5, 6]. This was not the case for our patient who exhibits complete mirror-image organisation of the thoracic and abdominal organs. This finding was crucial for the diagnosis. However, it is important to highlight that the diagnosis was delayed due to the initial chest radiograph taken at age 24 years being incorrectly adjusted by the technician, who mistakenly assumed an error upon observing the abnormal organ positioning. As a result, situs inversus totalis went undetected until further imaging was performed years later.

The PCD diagnosis can be complicated by the lack of a single definitive test. A multifaceted approach is preferred using clinical evaluation, imaging, functional and structural analyses, and genetic testing [7].

Techniques such as nNO measurement, high-speed video microscopy and immunofluorescence microscopy support the diagnostic process, but TEM and genetic testing provide definitive confirmation [8–11]. The diagnostic criteria recommended for this syndrome include the history of chronic bronchial infection and rhinitis from early childhood, combined with one or more of the following features: situs inversus or dextrocardia in a patient or a sibling, alive but immotile spermatozoa, absent or impaired tracheobronchial clearance, and cilia showing a characteristic ultrastructural defect [12].

Historically, TEM has been instrumental in the diagnosis of PCD, allowing detailed analysis of axonemal ultrastructure to identify characteristic defects [1]. It provides high-resolution images of ciliary cross-sections, allowing the detection of several PCD-associated abnormalities, such as dynein arm defects and disorganisation of lateral and central pair microtubules. These observations are critical to confirm a diagnosis of PCD in suspected cases [13].

In the case presented here, the patient's nasal biopsy revealed significant ciliary ultrastructural abnormalities, including a lack of outer dynein arms, and the presence of single microtubules outside of

the nine doublet axonemal pairs. These findings align with class 1 and 2 ultrastructural defects according to Shoemark *et al.* [8]. In a similar study conducted in Iran, anomalies such as the appearance of extra microtubules, compound cilia and defects in the outer and inner dynein arms were detected [13].

Nowadays, it is possible to establish a genotype–phenotype correlation of characteristic clinical symptoms and ultrastructural defects on TEM [14–16]. For example, a study in Portugal highlighted the importance of TEM in identifying ciliary alterations that confirm PCD diagnoses, further suggesting that this condition is underdiagnosed in clinical practice [17]. In another study, software-based analysis of TEM images confirmed dynein arm defects by averaging ciliary cross-sections [16].

Currently, 54 genes have been associated with PCD, and these genes play roles in cilia assembly, structure and function [18]. Mutations in ∼50 genes account for ∼70% of PCD cases [19]. Whole-exome sequencing has facilitated the discovery of new genes linked to PCD and is now an extremely useful technique to complement the diagnosis of PCD. It is also particularly valuable for the diagnosis of those cases where normal ciliary ultrastructure is observed by TEM, improving the understanding of genotype–phenotype correlations [1]. However, in the case presented, next-generation sequencing (NGS) was not performed as the patient refused it.

Understanding the clinical characteristics of PCD is critical for timely diagnosis and multidisciplinary treatment. While no therapies currently restore ciliary function, airway clearance and infection management are essential to preserve lung health and minimise complications [20].

Conclusion

This report presents the first documented case of Kartagener syndrome in Tucumán, Argentina. The diagnosis was made through a comprehensive clinical evaluation, imaging studies and detailed analysis of ciliary ultrastructure using TEM. Based on the patient's clinical findings (bronchiectasis and situs inversus totalis) and TEM-detected ciliary ultrastructural abnormalities, a diagnosis of Kartagener syndrome was suggested with high certainty. Although NGS was not performed due to the patient's refusal, this case represents the first report in our province and establishes a foundation for future diagnostic approaches to PCD.

This case highlights the importance of an interdisciplinary approach in diagnosing rare conditions like Kartagener syndrome and stresses the need for greater awareness and diagnostic capacity for PCD in Argentina.

The patient's clinical progression emphasises the need for early diagnosis to prevent further complications, such as chronic lung damage, hearing loss from recurrent otitis media and fertility issues. Timely diagnosis and appropriate management, including airway clearance therapies and infection control, are essential for improving patient outcomes.

Answer 1

A detailed clinical history should be obtained, with a focus on symptoms like chronic rhinitis, cough, recurrent sinusitis and neonatal respiratory distress. Imaging studies, including chest radiography and computed tomography (CT) scans, and nasal nitric oxide (nNO) levels, should be considered to evaluate structural and functional aspects of the respiratory system.

<< Go to Task 1

Answer 2

Differential diagnoses include primary ciliary dyskinesia (PCD), which often presents with situs inversus (Kartagener syndrome). Other potential conditions include congenital heart defects or laterality defects without situs inversus. Additional diagnostic testing, including high-speed video microscopy or transmission electron microscopy (TEM), is needed to narrow the differential diagnosis.

<< Go to Task 2

Answer 3

TEM is critical for evaluating the ultrastructure of cilia. TEM can detect defects in the dynein arms and microtubule disorganisation, which are characteristic of PCD. Other complementary tests like nNO levels and genetic testing may be used to confirm the diagnosis.

<< Go to Task 3

Answer 4

The primary diagnostic challenge lies in the overlap of symptoms with other chronic respiratory diseases. In addition, the absence of a single diagnostic test for PCD complicates the diagnosis. A combination of clinical evaluation, high-resolution imaging, spirometry and ultrastructural analysis (*via* TEM) is essential for a definitive diagnosis.

TEM plays a pivotal role in diagnosing PCD by revealing structural defects in ciliary axonemes. TEM allows for high-resolution imaging of the ciliary ultrastructure, identifying abnormalities such as defects in the outer and inner dynein arms, microtubule disorganisation, and the absence of the central pair of microtubules. This approach remains critical for diagnosing patients with normal or inconclusive results from genetic testing or other diagnostic methods.

Genetic testing is increasingly used in the diagnosis of PCD, identifying mutations in over 50 genes responsible for ciliary structure and function. However, 30% of PCD patients show normal axonemal ultrastructure, emphasising the need for a multifaceted diagnostic approach.

<< Go to Task 4

Answer 5

TEM provides direct visualisation of ciliary ultrastructure and is able to detect specific defects, such as the absence of dynein arms or disorganisation of the microtubules, which are hallmark signs of PCD. While genetic testing can identify mutations, TEM remains indispensable in cases where genetic results are inconclusive or where ultrastructural defects play a crucial diagnostic role.

<< Go to Task 5

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Author contributions: D. Abdala conceptualised the case and coordinated the clinical management. D. Abdala, F. Gonzalez and M.A. Vaca Segovia supervised the case stages. M.C. D'Arpino and V.H. Albarracín designed and wrote the original draft, while M.C. D'Arpino, V.H. Albarracín, M.A. Vaca Segovia, M. Carrizo and C. Moreno revised the manuscript. A. Torres and L.J. Martínez processed the biopsy and analysed TEM images. A. Torres and M.C. D'Arpino produced the figures. D. Abdala, F. Gonzalez, V. Fernández Gómez, M.A. Vaca Segovia and R. Del Rio provided patient care and clinical consultation. V.H. Albarracín provided resources and equipment for electron microscopy. V. Salas participated in respiratory rehabilitation.

Conflicts of interest: The authors have nothing to disclose.

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