Front. Med. 2021, 15(6): 933–937
https://doi.org/10.1007/s11684-021-0860-7

CASE REPORT

Case report of neurofibromatosis type 1 combined with primary ciliary dyskinesia

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Abstract **Neurofibromatosis (NF) is a genetic disease in which the lungs are rarely involved. However, in NF cases with lung involvement, chest computed tomography may show bilateral basal reticulations, apical bullae, and cysts without bronchiectasis. Herein, we report a patient diagnosed with NF on the basis of the results of genetic testing who presented with early-onset wet cough and bronchiectasis. Considering the differential diagnosis of bronchiectasis combined with his early-onset wet cough, sinusitis, and sperm quality decline, we considered the possibility of primary ciliary dyskinesia (PCD). Further electron microscopy analysis of cilia and identification of homozygous mutations in the *RSPH4A* gene confirmed the diagnosis of PCD. Therefore, for patients with NF, when an image change exists in the lungs that does not correspond to NF, the possibility of other diagnoses, including PCD, must be considered.**

Keywords primary ciliary dyskinesia; neurofibromatosis; bronchiectasis; transmission electron microscopy; genetic sequencing

Introduction

Neurofibromatosis (NF) is an autosomal dominant genetic disease [1]. NF type 1 (NF1), which is caused by mutations in the *NF1* gene, can be characterized by café-au-lait macules, freckles, Lisch nodules, peripheral neurofibromas, optic gliomas, and other neurological abnormalities, such as cognitive defects [1–3]. Cases of NF1 with pulmonary involvement are rare [2], and chest computed tomography (CT) performed on NF1 patients most frequently detects bilateral basal reticulations, apical bullae, and cysts [2,4].

Most primary ciliary dyskinesias (PCDs) are considered as autosomal recessive diseases whose estimated prevalences among live-born children are approximately 1:10 000 to 1:20 000 [5]. Over 40 genes have been determined to be related to PCD [6,7]. Related gene mutations cause structural or functional abnormalities in cilia, leading to bronchitis, bronchiectasis, sinusitis, otitis media, infertility, and hydrocephalus [5,7,8]. Over 75% of full-term neonates with PCD have "neonatal respiratory distress" (few are diagnosed with PCD at this age), and most children have chronic year-round wet cough, sputum production, and chronic wheezing [9], as well as chronic airway infection resulting in bronchiectasis in most cases [9]. Thus far, no single gold-standard diagnostic test for PCD has been developed [5,8].

Cases with PCD combined with NF are extremely rare, and to the best of our knowledge, only one similar case had been previously reported [10]. We hope that our case can be helpful in the differential diagnosis of rare diseases with pulmonary involvement.

Case presentation

A 21-year-old man who had been diagnosed with NF presented to our hospital complaining of productive cough

Received December 25, 2020; accepted April 8, 2021
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since he was 2 years old and shortness of breath for approximately one year and a half. In his past medical history, he had a fever with maximum body temperature of 38 °C after birth, accompanied by wheezing in the throat while drinking milk. Thus, his ailment was diagnosed as "aspiration pneumonia," and his condition improved after receiving antibiotics. He had no history of tuberculosis or measles infection. His parents were not in a consanguineous marriage. Both his parents and his younger brother are in good health, without respiratory symptoms and infertility. Rhonchi could be heard in his lungs. He did not show cyanosis or digital clubbing. *Pseudomonas aeruginosa* was detected from his bronchial aspiration. Chest high-resolution computed tomography showed bronchiectasis in the right middle lobe and multiple centrilobular micronodules in both lungs; the micronodules were predominantly distributed on the right side, forming the tree-in-bud structure (Fig. 1).

Aside from respiratory symptoms, the patient also suffered from mental retardation, memory loss, walking instability, and café-au-lait macules in the skin (Fig. 2). Head magnetic resonance imaging revealed expansion of the supratentorial ventricular system (Fig. 3), and the proximal midbrain aqueduct may have adhered, causing obstructive hydrocephalus.

Several tests were performed upon admission to obtain an exact diagnosis. His bronchial mucosa was examined via transmission electron microscopy, which clearly showed that the ciliated microtubule ultrastructure was abnormal. Deficiency of central microtubules, radial spoke, and peripheral microtubule deletion were detected,

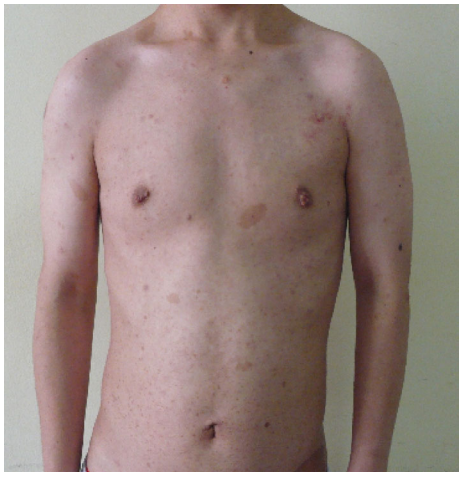

Fig. 2 Café-au-lait macules could be seen on the patient's skin.

which led to the formation of central microtubule displacement, "9 + 0" arrangement, and "8 + 2" arrangement (Fig. 4), which are typical of mutations in radial spoke proteins and consistent with PCD. In addition, his sinus CT indicated sinusitis. Semen analysis revealed that the total sperm number and semen density were 39.03×10^6 and 12.59×10^6/mL, respectively. Among them, grade A, grade A + B, grade A + B + C, and grade D sperm accounted for 2.82%, 5.16%, 8.92%, and 91.08%, respectively, revealing that most of the sperm was immobile. He was diagnosed via whole-exome sequencing performed on the Illumina HiSeq XTen platform. The

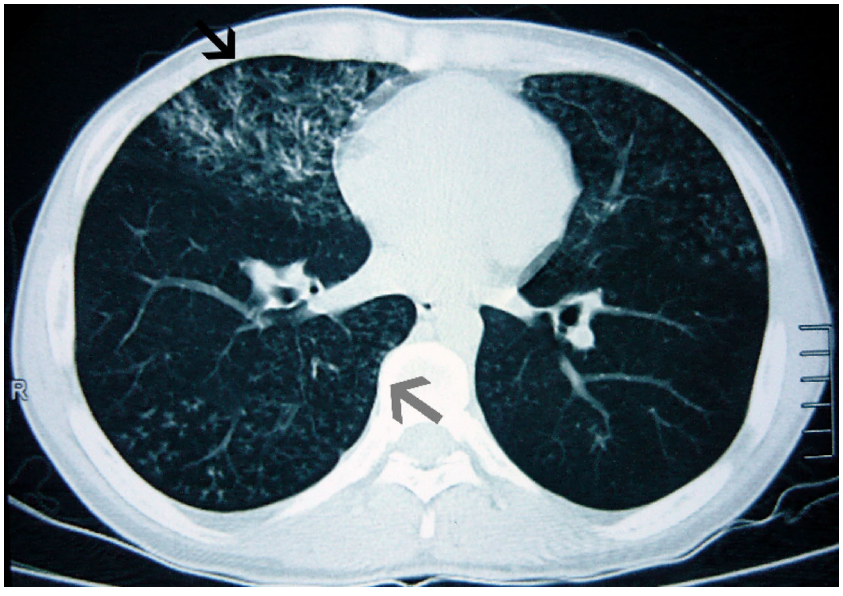

Fig. 1 Chest high-resolution computed tomography showed bronchiectasis in the right middle lobe (black arrow) and multiple centrilobular micronodules in both lungs; the micronodules were predominantly distributed on the right side, forming the tree-in-bud structure (gray arrow).

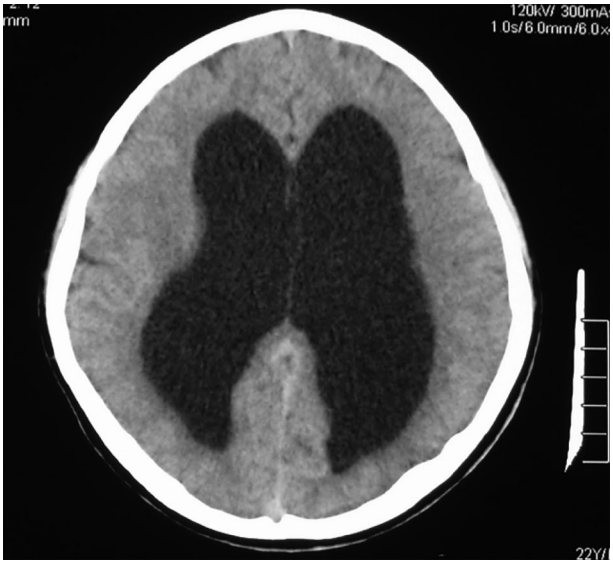

Fig. 3 Head magnetic resonance imaging showed the expansion of the supratentorial ventricular system, suggesting that the proximal midbrain aqueduct may have adhered.

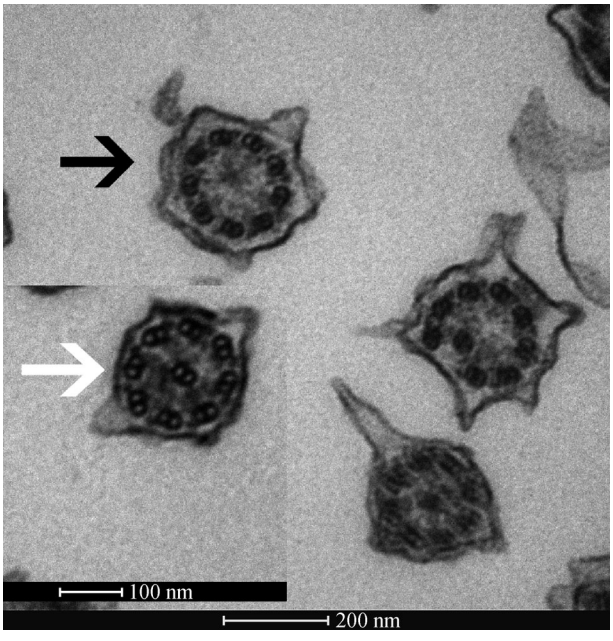

Fig. 4 Electron microscopy analysis of respiratory mucosa revealed deficiency consistent with primary ciliary dyskinesia. The black arrow shows the deficiency of central microtubules, forming a "9 + 0" arrangement. The white arrow shows the peripheral microtubules deletion, forming an "8 + 2" arrangement.

reads were aligned to the Genome Reference Consortium Human Build 37 (GRCh37/hg19) human assembly by using the Burrows–Wheeler Aligner. Results showed a homozygous mutation, c.667delA, p.S223Afs*15, in the *RSPH4A* gene, which is associated with PCD [6,7,11,12]; and a heterozygous mutation, c.730 + 1G > A, in the *NF1* gene, supporting the diagnosis of NF1 [2] (Fig. 5). All mutations were confirmed by Sanger sequencing. *RSPH4A*, whose mutation can be found in patients with PCD, is a gene-encoded radial spoke head protein associated with cilia–axoneme defects, causing clinical features of respiratory disease similar to those seen in patients with PCD with "classic" dynein arm defects [11,12].

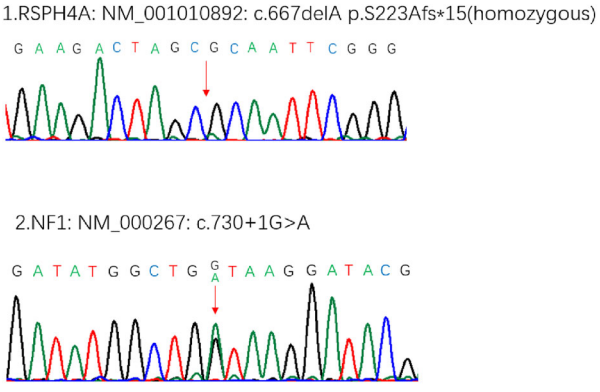

Fig. 5 Sanger sequencing results and mutations identified in the patient.

Unfortunately, the patient and his family refused to continue treatment because they lacked financial resources. Eventually, he died at the age of 27 years due to respiratory failure caused by pulmonary infection. The patient's medical timeline is shown in Fig. 6.

Discussion

At the time of admission, the patient was diagnosed with NF, which led us to think that the first consideration of the causes of his lung disease was NF. However, according to the literature, the chest CT of patients with NF with lung involvement presents as bilateral basal reticulations, apical bullae, and cysts [2,4]. The predominant bronchiectasis manifestation cannot be explained by his NF diagnosis on the chest image. Therefore, we attempted to make a differential diagnosis of his bronchiectasis.

Combined with the early-onset year-round wet cough, sinusitis, and sperm quality decline, we considered the possibility of diagnosing the patient with PCD. Further electron microscopy analysis and identification of homozygous mutations in the *RSPH4A* gene confirmed the diagnosis of PCD. Given that these two gene loci are not

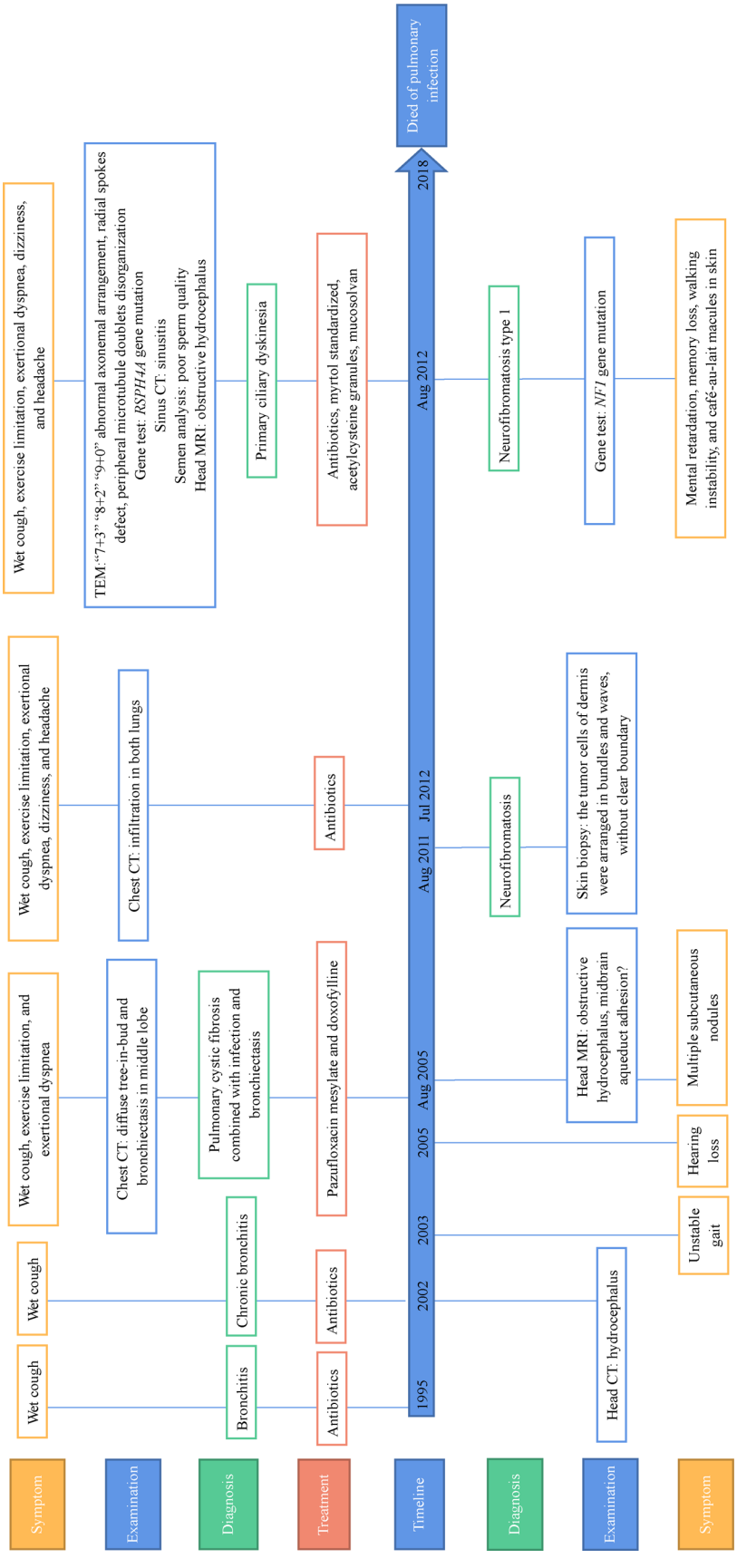

Fig. 6 Timeline of the patient's medical history.

adjacent and are unlikely to mutate at the same time, this phenomenon may be an episodic one.

Furthermore, patients with NF1 may have optic pathway gliomas or other central nervous system tumors that may cause obstructive hydrocephalus [13]. However, no tumor was found in his head magnetic resonance imaging as the cause of the hydrocephalus observed in this patient. Therefore, we considered that the ependymal cilia dysfunction caused by PCD may be the reason for the hydrocephalus.

Regrettably, his family was unable to support his continued treatment because of the lack of financial resources. Unfortunately, he died of lung infection 6 years later. This outcome warns us that patients with PCD must be carefully investigated and properly treated; otherwise, it may lead to serious health consequences or even death of the patient.

This case report emphasized that when an image change exists in the lungs (or other symptoms) that does not correspond to the primary disorder (in this case, NF), the possibility of other diagnoses must be considered, and PCD is one of the respiratory disorders that should be prioritized in such cases.

Conclusions

In this case, an extremely rare case of combined PCD and NF1 was described. Although the diagnosis of NF was clear, lung changes inconsistent with NF led us to consider the differential diagnosis of bronchiectasis. Finally, the diagnosis of PCD combined with NF was made by observing relevant clinical manifestations, transmission electron microscopy changes, and related gene (i.e., *RSPH4A*) mutations.

Acknowledgements

This research was supported by the National Key Research and Development Program of China (No. 2016YFC0901502) and CAMS Innovation Fund for Medical Sciences (Nos. CIFMS-2018-I2M-1-003, CIFMS-2017-12M-2-001, CIFMS-2020-I2M-C&T-B-002, and CIFMS-2016-I2M-1-002).

Compliance with ethics guidelines

Chun Bian, Xinyue Zhao, Yaping Liu, Minjiang Chen, Shuying Zheng, Xinlun Tian, and Kai-Feng Xu declare that they have no conflict of interest. Informed consent was obtained from the patient for publication of all related materials.

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