

CASE REPORT

Open Access



# A novel entity of HIPK2::YAP1 pulmonary fibromatosis

Yuqiang Liu<sup>1</sup>, Meng Liang<sup>2</sup>, Kai Chen<sup>3</sup>, Lucas Wang<sup>4</sup>, Yaxian Yang<sup>4</sup>, Qi Li<sup>4</sup>, Bin Lian<sup>4</sup>, Tongxu Zhuo<sup>4</sup> and Jian Huang<sup>4,5\*</sup>

## Abstract

**Background** Pulmonary fibromatosis (PF) is a specific variant of fibromatosis, which is rarely reported occurring in the lung. PF with *HIPK2-YAP1* fusion was a novel entity.

**Case presentation** In this report, a 66-year-old male with PF had been smoking over 40 years. Multiple cords and small nodules in both lungs had been detected in a health examination two years earlier at our hospital. But approximately twofold enlarged in the lingual segment of the upper lobe in the left lung were disclosed in this year. Immunohistochemical analysis demonstrated that the vimentin and  $\beta$ -Catenin were positive in the largest nodule. After underwent a DNA/RNA panel next-generation sequencing (NGS), missense mutations and *HIPK2-YAP1* fusion were found in this sample. Ultimately, the case diagnosis as PF with *HIPK2-YAP1* fusion after multidisciplinary treatment. Currently, the patient is doing well and recurrence-free at 14 months post-surgery.

**Conclusions** It's difficult for patients with complex morphology to make accurate diagnosis solely based on morphology and immunohistochemistry. But molecular detection is an effective method for further determining pathological subtypes.

**Keywords** Pulmonary fibromatosis, Heterogeneity, HIPK2-YAP1

## Background

Fibromatosis, first described by Stout et al. [1], is classified as benign in histological, but with the character of local invasiveness and local recurrence. Fibromatosis

usually originating in intermuscular location, and identified at a median age in the 30 s.

Fibromatosis, also known as desmoids tumor, is classified into superficial and deep [2, 3]. Fibromatosis may involve essentially any location such as head and neck region, breast, colon, pelvic cavity, etc. [4]. Pulmonary fibromatosis (PF) is a specific variant of fibromatosis, which is rarely reported in the literature as occurring in the lung. Like other classifications of fibromatosis, PF is a widespread, locally aggressive fibroblastic tumor that occasionally recurs but never metastasizes [5]. Here we report a case of PF with *HIPK2-YAP1* fusion, the patient underwent thoracoscopic surgery and the resected specimen identified by histopathological, clinicopathological, immunohistochemical (IHC) and the genetics feature analysis.

\*Correspondence:

Jian Huang  
18665763598@163.com

<sup>1</sup> Department of Proctology, Honliv Hospital, Xinxiang 453400, Henan Province, China

<sup>2</sup> Department of Academic Affairs, Xinxiang Medical University, Xinxiang 453003, Henan Province, China

<sup>3</sup> Department of Respiratory Medicine, Yongcheng People Hospital, Yongcheng 476600, Henan Province, China

<sup>4</sup> Precision Medicine Center, Guangzhou Huayin Health Medical Group Co., Ltd, No.33 Binhe Road, Huangpu District, Guangzhou 510700, Guangdong Province, China

<sup>5</sup> Department of Pathological Diagnosis and Research Center, the Affiliated Hospital of Guangdong Medical University, No.57 South Renmin Avenue, Xiashan District, Zhanjiang 524001, Guangdong Province, China



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

### Case presentation

A 66-year-old man with asymptomatic 40 years-smoking history was admitted to hospital due to multiple lung nodules detected in routine health checkup had roundly doubled in size in two years. Followed computed tomography (CT) imaging showed multiple small cystic translucent shadows with clear borders in both lungs. Besides, multiple small solid nodular shadows with clear borders were found in the upper lobe of both lungs and the lower lobe of the left lung. The largest nodules were found in the apical posterior segment of the upper lobe of the left lung with the size of about 5 mm × 4 mm × 1 mm (Fig. 1). Lymph node enlargement in the mediastinum was not detected. Scattered striated foci with clear borders were also seen in both lungs.

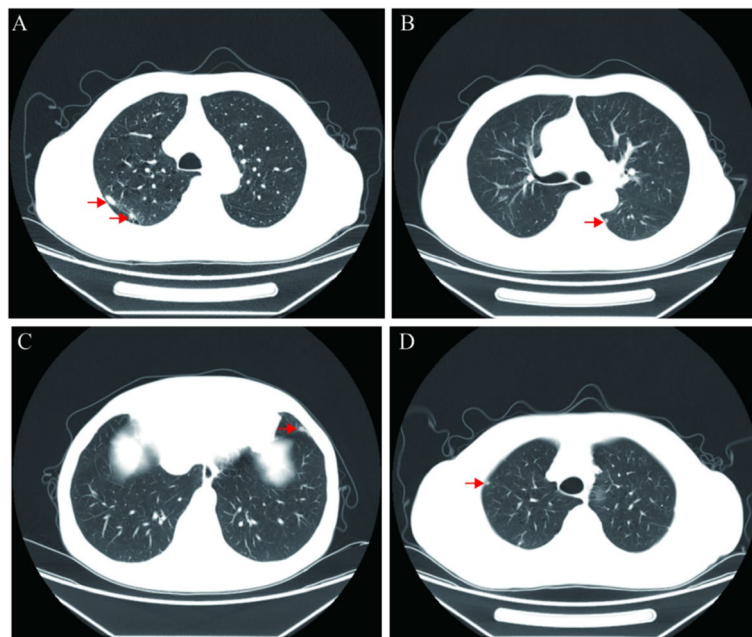
The patient underwent lung nodule removal surgery. Postoperative pathological examination suggested the lingual segment of the upper lobe left lung were nodal spindle cell tumor, consistent with low-grade malignancy of mesenchymal origin. The tumor cells exhibited bundled or woven pattern, with clear demarcation between the tumor and the surrounding lung tissue. The tumor cells were uniformly shuttle-shaped and of consistent size. While most areas showed no significant heterogeneity in the morphology of the tumor cells, some areas exhibited active growth with occasional nuclear fission images, indicating certain heterogeneity in the nuclei (Fig. 2A-B).

Other nodules shown proliferating spindle cells and collagen fibers, which were consistent with benign lesions. All nodules were close to the pleura but did not break through the pleura, and morphology was mainly characterized by proliferating spindle cells, collagen fibers and carbon deposits (Fig. S1 A-D).

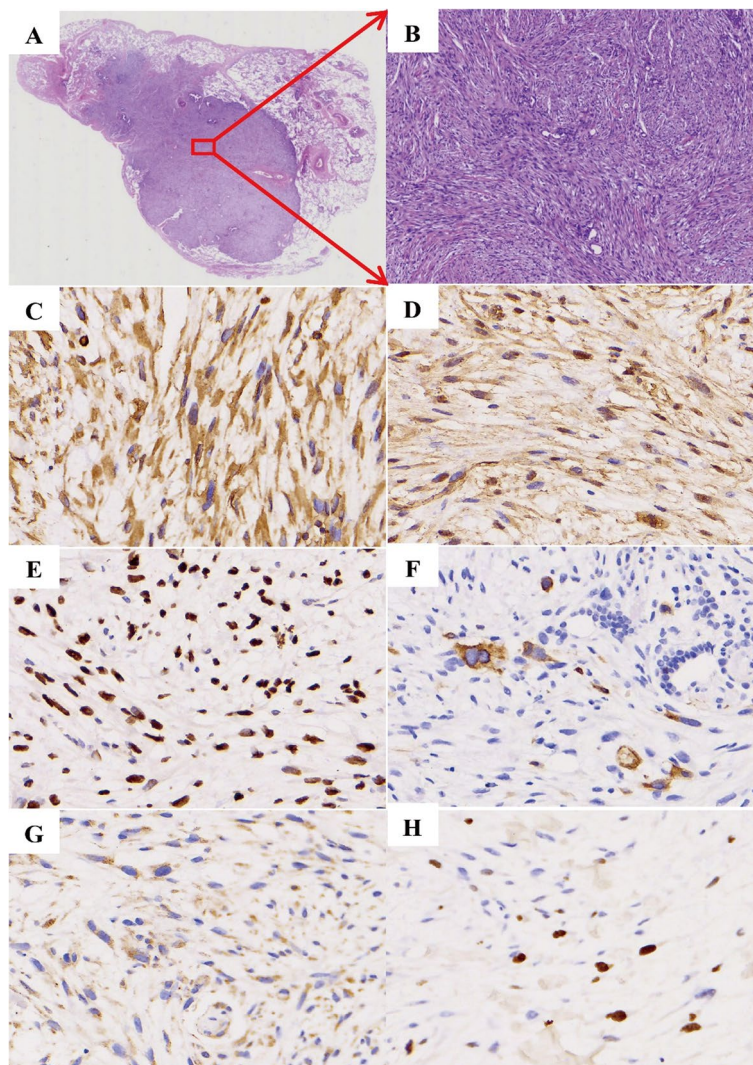
Immunohistochemical of the upper lobe of the left lung (the largest nodule) results shown that the spindle cells stained positively for vimentin,  $\beta$ -Catenin and P53, negatively for NF and STAT-6. The percentage of Ki-67 positive nuclei was around 10% (Fig. 2C-H).

Genome sequencing was conducted using NGS (DNA-based 600 genes panel and RNA-based 86 fusion genes panel, panel lists were shown in Supplementary Tables 1 and 2) to make a precise diagnosis of the largest nodule. RNA-based NGS results showed a *HIPK2-YAPI* fusion (see detail fusion model in Supplementary Fig. 2). DNA-based NGS results shown 33.51% mutation abundance of *TP53* and 19.33% mutation abundance of *ARID1B*, which are considered as tumorigenic alterations.

The patient was finally diagnosed as PF with *HIPK2-YAPI* fusion mutations based on a multidisciplinary team discussion, which involved comprehensive consideration of past history, clinical manifestations, radiographic, histopathological, IHC and molecular pathology results. The patient is doing well without any signs of recurrence 14 months after surgery.



**Fig. 1** Enhanced computed tomography (CT) results of lung lobe: **A** 5.0 × 4.0 × 1.0 cm nodule was detected in the post-apical segment of the left upper lobe, 1.5 × 1.0 × 1.0 cm nodule was detected in the apical segment of the left upper lobe; **B-D** Three tiny lung nodules (benign nodule with a measured diameter of 0.2–0.9 cm) detected in the lung and other parts of the right lung



**Fig. 2** Histopathological features: **A** Overall the histopathology. **B** (HE-40x) Lung nodule biopsy revealing spindle-shaped cells within low malignant tendency. (C-H). IHC markers staining showed vimentin(+),  $\beta$ -Catenin(+), P53(+), NF(-), STAT-6 (-) and Ki-67 proliferation index in most of the tumor areas was around 10%

## Discussion and conclusions

As a rare benign pulmonary lesion, PF with *HIPK2-YAP1* fusion has not been reported previously. Histopathological and molecular features supply evidence for the final diagnosis. The tumor cells of fibromatosis have been reported to be positive for SMA, desmin, calponin, and estrogen receptor  $\beta$ , but negative for CD34. At molecular levels, fibromatosis sporadically harbors *CTNNB1* mutation, which encodes  $\beta$ -catenin protein [6]. In this case, *CTNNB1* mutation was not detected. It is possible that PF involve the *CTNNB1* independent signaling pathway, but further confirmation is needed.

Although the function of the fusion variant between *HIPK2* and *YAP1* in the organism is not known, previous

studies have shown that *HIPK2* expression was decreased in mouse model of pulmonary fibrosis, accompanied by the massive proliferation of alveolar collagen fibers with altered alveolar structure [7, 8]. This study [8] also suggested that low expression of *HIPK2* facilitated the proliferation and migration of mouse lung fibroblasts, inhibited apoptosis, and advanced the expression of mesenchymal markers and  $\beta$ -catenin. Similar view of was identified in human fibroblasts cell model [9] and anti-fibrotic therapy by targeting *HIPK2* may be a potentially effective therapeutic option. *HIPK2* is also reported as a tumor suppressor, because it's involved in DNA damage repairment and apoptosis induction [10, 11]. In additionally, *HIPK2* is considered as a caretaker tumor-suppressor, its

inactivation increases tumorigenicity [12]. Even down-regulation and mutations of HIPK2 are associated with poor prognosis in many types of human tumors [13].

In this case, *HIPK2-YAP1* fusion involving exon 1 of *HIPK2* and exons 3–9 of *YAP1*. This fusion disrupts the structure of HIPK2, which may lead to a partial or complete loss of function of the HIPK2 protein, allowing for an over proliferation of collagen fibers in epithelial cells such as lung fibroblasts, resulting in massive fibrosis of the patient's lung tissue, which in turn leads to fibromatosis. Consequently, further research is needed to illustrate its clinicopathological characteristics.

The diagnosis based on pathological morphology is the foundation of disease diagnosis, and molecular diagnosis is an important tool for accurate classification of diseases, which may bring more treatment opportunities for patients.

#### Abbreviations

PF	Pulmonary fibromatosis
NGS	Next-generation sequencing
IHC	Immunohistochemical
CT	Computed tomography

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12890-024-03026-5>.

**Supplementary Material 1.**

**Supplementary Material 2.**

#### Authors' contributions

Y.L. collected and analysed data, and wrote the main manuscript text; M.L., K.C. and T.Z. collected and analysed data; L.W., Y.Y., Q.L. and B.L. wrote and revised and edited the manuscript; J.H. had the conception and design of the study, and revised and edited the manuscript. All authors read and approved the final manuscript.

#### Funding

This work was supported by a grant from the National Natural Science Foundation of China (#81572610 to Jian Huang).

#### Availability of data and materials

The data that support this case report are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

##### Competing interests

The authors declare no competing interests.

#### References

1. Stout AP. Juvenile fibromatoses. *Cancer*. 1954;7(5):953–78.
2. Akhavan A, Binesh F, Kargar K, Navabii H. Juvenile female with chest wall fibromatosis located posteriorly to the right breast: radiation therapy or wait and watch? *BMJ Case Rep*. 2013;2013.
3. Allen PW. The fibromatoses: a clinicopathologic classification based on 140 cases. *Am J Surg Pathol*. 1977;1(3):255–70.
4. Valentino K, Tothy AS. Fibromatosis Colli. A Case Report. *Adv Emerg Nurs J*. 2020;42(1):13–16.
5. Qian X. Chapter 16 - Soft Tissue. In: Cibas ES, Ducatman BS, editors. *Cytology*. 3rd ed. Philadelphia: W.B. Saunders; 2009. p. 451–94.
6. Chi Z, Mangus RS, Kubal CA, Chen S, Lin J. Multivisceral transplant is a viable treatment option for patients with non-resectable intra-abdominal fibromatosis. *Clin Transplant*. 2018;32(3):e13186.
7. Garufi A, Pistrutto G, D'Orazi G. HIPK2 as a Novel Regulator of Fibrosis. *Cancers (Basel)*. 2023;15(4):1059.
8. Wang F, Zhang Y, Ren J, Yu W. HIPK2 attenuates bleomycin-induced pulmonary fibrosis by suppressing the Wnt/beta-catenin signaling pathway. *Folia Histochem Cytobiol*. 2022;60(3):247–59.
9. Ricci A, Cherubini E, Olivieri A, Lavra L, Sciacchitano S, Scozzi D, Mancini R, Ciliberto G, Bartolazzi A, Bruno P, et al. Homeodomain-interacting protein kinase2 in human idiopathic pulmonary fibrosis. *J Cell Physiol*. 2013;228(1):235–41.
10. Ke CY, Mei HH, Wong FH, Lo LJ. IRF6 and TAK1 coordinately promote the activation of HIPK2 to stimulate apoptosis during palate fusion. *Sci Signal*. 2019;12(593):eaav7666.
11. Conrad E, Polonio-Vallon T, Meister M, Matt S, Bitomsky N, Herbel C, Liebl M, Greiner V, Kriznik B, Schumacher S, et al. HIPK2 restricts SIRT1 activity upon severe DNA damage by a phosphorylation-controlled mechanism. *Cell Death Differ*. 2016;23(1):110–22.
12. Valente D, Bossi G, Moncada A, Tornincasa M, Indelicato S, Piscuoglio S, Karamitopoulou ED, Bartolazzi A, Pierantoni GM, Fusco A, et al. HIPK2 deficiency causes chromosomal instability by cytokinesis failure and increases tumorigenicity. *Oncotarget*. 2015;6(12):10320–34.
13. Conte A, Valente V, Paladino S, Pierantoni GM. HIPK2 in cancer biology and therapy: Recent findings and future perspectives. *Cell Signal*. 2023;101:110491.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 14 November 2023 Accepted: 19 April 2024

Published online: 07 May 2024