

# Pulmonary Capillary Hemangiomatosis as a Rare Underlying Cause of Primary Pulmonary Hypertension: A Case Report in an Adolescent

Mohammad Mahdavi, MD;<sup>1</sup>  
Hossein Shahzadi, MD;  
Mohsen Ghasemnezhad, MD;  
Soheila Hoseinzadeh Moghadam, MD<sup>1</sup>

Shaheed Rajaie Cardiovascular Medical and Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

## Correspondence:

Soheila Hoseinzadeh Moghadam, MD;  
Department of Pediatric Cardiology, Rajaei Cardiovascular Research and Medical Center, School of Medicine, Iran University of Medical Sciences, Intersection of Niayesh Highway and Valiasr St., Postal code: 19956-14331, Tehran, Iran  
**Email:** soheila1moghadam@yahoo.com  
Received: 30 December 2023  
Revised: 30 January 2024  
Accepted: 14 February 2024

## What's Known

- Pulmonary capillary hemangiomatosis (PCH) manifests as pulmonary hypertension due to excessive proliferation of pulmonary capillaries. It is frequently difficult to differentiate from other disorders such as pulmonary veno-occlusive disease.
- Typical symptoms include dyspnea, chest pain, cough, as well as radiological signs such as centrilobular ground-glass opacities, which necessitate lung biopsy or post-mortem examination for a conclusive diagnosis.

## What's New

- This case marked the first documented instance of PCH in the adolescence period in Iran, which was confirmed through genetic testing and revealed EIF2AK4 mutations. It expanded geographical understanding while emphasizing the significance of genetic analysis for conclusive diagnosis.
- This report provided comprehensive clinical and radiological details of PCH, enhancing physicians' ability to diagnose this rare condition effectively.

## Abstract

Despite its rarity, pulmonary capillary hemangiomatosis (PCH) presents a significant diagnostic challenge. Due to its similarity to other pulmonary vascular diseases, such as pulmonary veno-occlusive disease, it is characterized by abnormal pulmonary capillary proliferation, which is a rare cause of primary pulmonary hypertension. This case was the first reported instance of PCH in Shahid Rajaee Heart Hospital in Tehran, Iran, in 2023, which was confirmed by genetic testing. It highlighted the importance of considering PCH among the differential diagnoses for pulmonary hypertension, even in adolescent patients. The 13-year-old patient's main complaints were progressive exertional dyspnea and chest pain. He had no previous medical history and had not taken any pharmaceutical or herbal medications. Critical clinical findings included a heart murmur, an electrocardiogram revealing right ventricular hypertrophy, and echocardiogram evidence of pulmonary hypertension. The main diagnosis was PCH, as shown by CT findings of pulmonary artery dilatation and diffuse nodular ground glass opacities. Genetic tests indicated pathogenic EIF2AK4 mutations and suspicion of PCH. Therapeutic intervention included vasodilator therapy, which exacerbated the patient's condition. This case emphasized the importance of maintaining a high index of suspicion for rare causes of pulmonary hypertension, such as PCH. The outcome was to prepare the patient for lung transplantation. To differentiate PCH from other pulmonary vascular diseases, a combination of clinical presentation, radiologic studies, genetic analysis, and response to treatment is required to determine appropriate management, particularly lung transplantation.

Please cite this article as: Mahdavi M, Shahzadi H, Ghasemnezhad M, Hoseinzadeh Moghadam S. Pulmonary Capillary Hemangiomatosis as a Rare Underlying Cause of Primary Pulmonary Hypertension: A Case Report in an Adolescent. Iran J Med Sci. doi: 10.30476/ijms.2024.101215.3385.

**Keywords** • Hypertension, Pulmonary • Familial primary pulmonary hypertension • Lung transplantation

## Introduction

Pulmonary hypertension is a condition in which the mean pulmonary arterial pressure exceeds 20 mmHg.<sup>1</sup> This phenomenon can be caused by a vast spectrum of disorders involving the lungs, heart, or pulmonary vascular system.<sup>2</sup> Pulmonary capillary hemangiomatosis (PCH) is an infrequent cause of primary pulmonary hypertension (PPH), with an

estimated incidence of less than one per million population.<sup>3</sup> PCH appears due to the proliferation of capillaries and invasion of the pulmonary interstitium, alveolar septae, and pulmonary vasculature. In some cases, a more extensive invasion involves lung parenchyma or pleura.<sup>4</sup>

There are two issues with PCH diagnosis. The first one is that it is associated with non-specific symptoms, such as cough or dyspnea, which leads to a diagnostic puzzle. The second issue is its resemblance with other clinical identities such as idiopathic pulmonary hypertension (IPAH) or pulmonary veno-occlusive disease (PVOD).<sup>5, 6</sup> Differentiating PCH, IPAH, and PVOD from one another is critical since they require different therapeutic approaches. Misdiagnosis of PCH and subsequent wrong treatment choice can cause exacerbation of the disease or even lead to lethal outcomes.<sup>7</sup> Thus, rigorous examinations and evaluations are required to ensure the exact diagnosis of patients who are clinically suspicious of having these disorders.

Overall, clinical symptoms, imaging, and genetic mutations in PVOD and PCH are similar, with pathological specimens being the only means to differentiate them.<sup>8</sup> Performing a biopsy in PCH patients carries the risk of bleeding, and most diagnoses are made post-mortem. Accordingly, this study focused on a potential case with concentrated PPH symptoms and diagnosed it as PCH.

### Case Presentation

A 13-year-old patient presented to Shahid Rajaei Heart Hospital (Tehran, Iran), with a history of exertional dyspnea and chest pain that began 5 months ago and worsened in the last 2 months. He was healthy 5 months ago, with no history of medical or surgical issues. He had no medical history and did not take any pharmaceutical or herbal medications. The patient's weight, height, and growth status were all within normal parameters. A physical examination revealed no significant findings other than a tachycardia of approximately 120 bpm. A systolic murmur in the tricuspid area with a loud P2 was also found. Moreover, no history or evidence of wheezing, fever, coughing, or hemoptysis was found.

Alterations in electrocardiography indicated right ventricular hypertrophy and right axis deviation. Echocardiography also revealed findings consistent with pulmonary hypertension. The systolic and diastolic pulmonary artery pressure (PAP) were 41 and 16.5 mmHg, respectively, with a mean PAP of 24.6 mmHg. The mild right atrium and right

ventricle enlargement were also observed. There was also moderate tricuspid regurgitation. However, no evidence of an atrial septal defect (ASD) or ventricular septal defect (VSD) was found. The chest X-ray revealed no pleural effusion or pulmonary edema. However, it demonstrated dilatation of the main pulmonary artery (figure 1). Moreover, the computed tomography (CT) scan of the thorax revealed dilatation of the main pulmonary artery and branches (figure 2).

Furthermore, a CT scan of the lungs revealed diffuse centriacinar ground-glass opacities in nodular patterns throughout both lungs (figure 3).

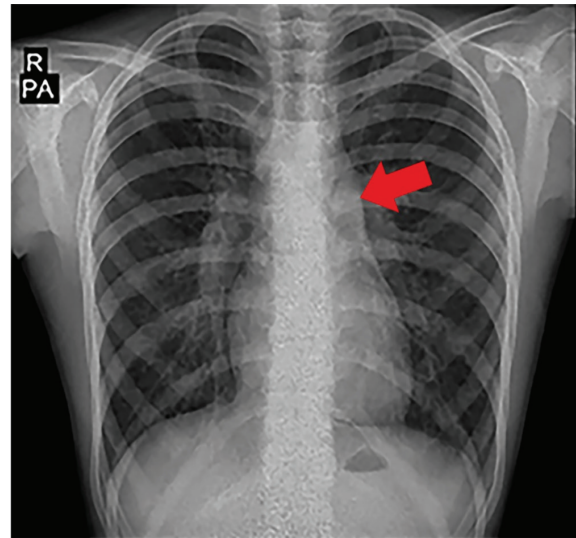
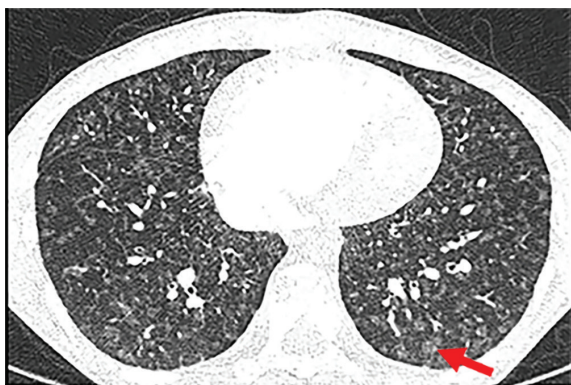


Figure 1: The arrow in this chest radiograph shows rigorous dilatation of the main pulmonary artery.



Figure 2: The arrow on this thoracic CT scan of the patient indicates dilatation of the main pulmonary artery and branches.



**Figure 3:** The arrow on the patient's lung CT scan shows centriacinar ground-glass opacities in nodular patterns diffused throughout the lungs.

Ultrasonography of the abdomen and lower extremities revealed no particular abnormalities. The laboratory assessment revealed no significant findings in the patient's blood and urine indices. After starting the vasodilator, the patient developed pulmonary edema, and his symptoms worsened. Therefore, it was discontinued immediately. The patient was stabilized after receiving the appropriate treatment, which included diuretics. The CT scan findings, together with the patient's worsening condition, after beginning the vasodilator, raised the possibility of PCH in our patient. DNA extraction was performed using an in-house salting-out method. The whole exome sequencing (WES) was performed on the proband, and raw data (fastq file) was analyzed by the Cardiogenetic Research Center at the Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences (Tehran, Iran). The library was prepared, and the reads were sequenced using the Illumina NovaSeq6000 platform. The reference genome (hg19) was used for the reads alignment using the burrows-wheeler Alignment (BWA) algorithm. Variants were identified and annotated using the GATK and ANNOVAR software, respectively. Then, the pathogenicity of the detected variants was evaluated using some predictive tools. Pathogenic biallelic EIF2AK4 mutations, affecting entire exomes, were discovered. With the diagnosis of PCH, the patient was scheduled for a lung transplant. Moreover, it is necessary to emphasize that the case is alive and currently is listed on the lung transplant waiting list.

The present study was conducted in accordance with the ethical guidelines outlined by Iran University of Medical Sciences (Tehran, Iran). The study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (code IR.IUMS.REC.1402.941). Besides, written informed

consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

## Discussion

A 13-year-old boy with worsening shortness of breath and chest pain underwent different clinical tests, which revealed pulmonary hypertension. Vasodilator medication exacerbated his condition, prompting physicians to suspect a rare cause, known as PCH, which was confirmed by genetic testing.

Dating back to 1978, Wagenvoort and colleagues introduced PCH as one of the rare causes of pulmonary hypertension.<sup>9</sup> The primary mechanism of this disorder is extensive alveolar capillary proliferation with infiltration of capillaries into the pulmonary interstitium, alveolar septae, and pulmonary vasculature. Vessels develop due to the proliferation of bleed easily which lead to the accumulation of macrophages loaded with hemosiderin in the alveolar region. This disease is still rare, with less than 100 cases reported in the literature. PCH incidence pattern is sporadic, and familial occurrence is extremely rare. Other clinical diseases associated with PCH include hypertrophic cardiomyopathy, systemic lupus erythematosus, Kartagener's syndrome, and Takayasu arteritis.<sup>4</sup>

Due to the rarity of PCH, epidemiological information regarding this condition is relatively scarce. The sex distribution of PCH was reported to be equal. Anazawa and colleagues reported a male/female ratio of 1:1.2.<sup>5</sup> The age of onset in PCH varied greatly in the literature, ranging from 2 to 72 years.<sup>10</sup> However, the majority of reported cases were diagnosed between 20 and 40 years of age.<sup>10</sup>

The primary symptoms of PCH include pulmonary hypertension features and worsening dyspnea (which typically begins with exertional dyspnea). Other much less prevalent features are pleural effusion, hemoptysis, and right heart failure.<sup>2, 9</sup> The clinical distinction between PCH, PVOD, and IPAH is critical because the administration of pulmonary vasodilators enhances IPAH but leads to damaging results such as hemothorax, hemoptysis, and pulmonary edema in PCH and PVOD cases.<sup>4</sup> This differentiation is also mandatory for the timely planning of lung transplantation. In 1989, the first radiologic profile of PCH cases was published.<sup>11</sup> According to the findings, the majority of PCH patients exhibited diffuse bilateral reticulonodular patterns in their chest X-rays. In the following years, HRCT was used as a more precise and comprehensive modality



for the assessment of these conditions. Several reports revealed that the main CT findings suggestive of PCH were centrilobular ground-glass opacities, septal lines, and lymph node enlargement.<sup>5</sup> However, different studies proposed diverse features for ground-glass opacities, such as nodular pattern, diffuse and bilateral distribution, and absence of peripheral involvement. Previous research mentioned that PCH was a highly probable diagnosis whenever centrilobular nodular ground-glass opacities existed in conjunction with enlargement of the main pulmonary artery. In a study on 26 PCH cases, 92% of patients had ground-glass opacities with 88% nodular pattern, and only 4% indicated bat-wing pattern. Septal lines and lymph node enlargement were also seen in 19% and 12% of patients, respectively. Other less prevalent characteristics were pleural effusion (8%), pericardial effusion (12%), emphysema (8%), and pulmonary fibrosis (4%).<sup>5</sup>

The main characteristic of PCH is the infiltration of capillary vessels into other pulmonary structures. However, in PVOD, venous occlusion is the most prominent feature, and no infiltration of other pulmonary structures is observed.<sup>12</sup> Additionally, PCH involves two layers of vessels, whereas, in PVOD, there is a single-layer angioproliferation.<sup>7,12</sup> Radiologically, all three main features of PCH in CT scan (centrilobular ground-glass opacities, septal lines, and lymph node enlargement) can also be observed in PVOD. However, the presence of lymph node enlargement and septal lines is less common in PCH than in PVOD.<sup>10</sup> In addition, the nodular pattern of ground-glass opacities suggests PCH, whereas ground-glass opacities in PVOD range from a minimal patchy appearance to a widely diffuse distribution.<sup>5</sup> Besides, some reports stated that the size of ground-glass opacities in HRCT was larger in PCH than in PVOD cases. Thus, patients suffering from pulmonary hypertension and have large and nodular ground-glass opacities without the presence of septal lines and lymph node enlargement, are more likely to have PCH.

Due to the rarity of PCH and its epidemiological features, its natural course is not well-established. However, the patient's survival rate in almost all cases is less than 5 years. According to a previous report, family cases of PCH and the presence of EIF2AK4 altered the onset and progression course of PCH.<sup>13</sup> Thus, variability in the PCH course is evident, and factors influencing its course are yet to be investigated further.

Pharmacologic treatment of PCH is not very effective, and lung transplantation is the

preferred therapeutic option in these cases.<sup>10</sup> Some medications, such as calcium channel blockers or epoprostenol, can cause serious complications, including pulmonary edema in PCH cases. However, few studies stated the beneficial effects of parenteral prostanoids in patients suffering from PCH. Moreover, angiogenesis inhibitors, such as imatinib, doxycycline, and interferon alfa-2a, were found to cause promising results.<sup>14</sup>

## Conclusion

Diagnosing the cause of PPH is critical for effective treatment. This case report discussed the difficulty of diagnosing a rare cause of PPH and PCH, in a young patient. Although the symptoms were widespread, a negative reaction to medication and genetic testing pointed towards PCH. The present case highlighted the significance of using a combination of approaches to diagnose PCH, as well as further research for better treatment options.

## Authors' Contribution

M.M., H.Sh., and M.Gh. performed the patient's diagnostic and therapeutic procedures, generated the idea of the case report, and edited the manuscript draft. S.H.M. prepared the draft of the manuscript, collected the data and images, followed the patient, and revised the final manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

## References

- 1 Maron BA. Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer. *J Am Heart Assoc.* 2023;12:e029024. doi: 10.1161/JAHA.122.029024. PubMed PMID: 37026538; PubMed Central PMCID: PMC6351336.
- 2 Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53. doi: 10.1183/13993003.01913-2018. PubMed PMID: 30545968; PubMed Central PMCID: PMC6351336.

- 3 Kobayashi H, Otsuki Y, Yamaguchi M, Ko K, Mizuno S, Ujita M, et al. An Autopsy Case of Pulmonary Capillary Hemangiomatosis with an Electron Microscopy Study. *Am J Case Rep.* 2019;20:1551-7. doi: 10.12659/AJCR.918375. PubMed PMID: 31636247; PubMed Central PMCID: PMC6818641.
- 4 Manjubashini D, Nagarajan K, Rajesh Kumar B. Pulmonary capillary hemangiomatosis: An unusual cause of primary pulmonary hypertension in a child with characteristic computed tomography imaging features. *Lung India.* 2019;36:157-9. doi: 10.4103/lungindia.lungindia\_122\_18. PubMed PMID: 30829252; PubMed Central PMCID: PMC6410579.
- 5 Anazawa R, Terada J, Sakao S, Shigeta A, Tanabe N, Tatsumi K. Features of radiological and physiological findings in pulmonary capillary hemangiomatosis: an updated pooled analysis of confirmed diagnostic cases. *Pulm Circ.* 2019;9:2045894019896696. doi: 10.1177/2045894019896696. PubMed PMID: 31908771; PubMed Central PMCID: PMC6935884.
- 6 Lefebvre B, Kyheng M, Giordano J, Lamblin N, de Groote P, Fertin M, et al. Dual-energy CT lung perfusion characteristics in pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (PVOD/PCH): preliminary experience in 63 patients. *Eur Radiol.* 2022;32:4574-86. doi: 10.1007/s00330-022-08577-x. PubMed PMID: 35286410.
- 7 O'Keefe MC, Post MD. Pulmonary capillary hemangiomatosis: a rare cause of pulmonary hypertension. *Arch Pathol Lab Med.* 2015;139:274-7. doi: 10.5858/arpa.2013-0500-RS. PubMed PMID: 25611112.
- 8 Park JE, Chang SA, Jang SY, Lee KS, Kim DK, Ki CS. Differential Diagnosis of Pulmonary Venous-Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis after Identification of Two Novel EIF2AK4 Variants by Whole-Exome Sequencing. *Mol Syndromol.* 2023;14:254-7. doi: 10.1159/000527524. PubMed PMID: 37323202; PubMed Central PMCID: PMC6810267509.
- 9 Wagenvoort CA, Beetstra A, Spijker J. Capillary haemangiomatosis of the lungs. *Histopathology.* 1978;2:401-6. doi: 10.1111/j.1365-2559.1978.tb01734.x. PubMed PMID: 730121.
- 10 Chaisson NF, Dodson MW, Elliott CG. Pulmonary Capillary Hemangiomatosis and Pulmonary Venous-occlusive Disease. *Clin Chest Med.* 2016;37:523-34. doi: 10.1016/j.ccm.2016.04.014. PubMed PMID: 27514598.
- 11 Faber CN, Yousem SA, Dauber JH, Griffith BP, Hardesty RL, Paradis IL. Pulmonary capillary hemangiomatosis. A report of three cases and a review of the literature. *Am Rev Respir Dis.* 1989;140:808-13. doi: 10.1164/ajrccm/140.3.808. PubMed PMID: 2675708.
- 12 Peacock AJ, Naeije R, Rubin LJ. Pulmonary Circulation: Diseases and Their Treatment. 4th ed. Florida: CRC Press; 2016. doi: 10.1201/9781315382753.
- 13 Best DH, Sumner KL, Austin ED, Chung WK, Brown LM, Borczuk AC, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. *Chest.* 2014;145:231-6. doi: 10.1378/chest.13-2366. PubMed PMID: 24135949; PubMed Central PMCID: PMC3921094.
- 14 Nayyar D, Muthiah K, Kumarasinghe G, Hettiarachchi R, Celermajer D, Kotlyar E, et al. Imatinib for the treatment of pulmonary arterial hypertension and pulmonary capillary hemangiomatosis. *Pulm Circ.* 2014;4:342-5. doi: 10.1086/675996. PubMed PMID: 25006453; PubMed Central PMCID: PMC4070788.