Response to reviewers' comments

Dear Editor,

Thank you very much for your positive comments on our manuscript (ID: 86214). We are honored to have the opportunity to publish this case report in your esteemed journal. To address the critiques of the reviewers, we have extensively revised the manuscript according to all the comments. Moreover, we invited two experts to proofread and improve the language. Attached please find the revised version (all changes are marked in yellow) for your kind consideration. We would like to express our great appreciation for the comments on our paper.

Looking forward to hearing from you.

Kind regards.

Tao Wang

9-Aug 2023

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Point-by-point response to:

Reviewer 1

1.In this article the authors present a rare case of bronchial Dieulafoy's disease. My criticism is minor.

Reply: We appreciate your positive comments on our manuscript. Thank you very much.

2.In the abstract, the abbreviation needs to be written after first term–line 13 IPA.

Reply: We are sorry for this oversight. We have made the correction to define the abbreviation “IPA” (marked in yellow), and reviewed the full text again to ensure that the "*Abbreviations must be defined upon first appearance*" requirement is met.

3.Sentences in the line 13-14 and 20-22 are the same.

Reply: Thank you for your comment. We have made the necessary changes to the sentences (marked in yellow).

4.This is a quality case report and I recommend it for publishing.

Reply: We would like to express our great appreciation for your positive comments on the paper.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Point-by-point response to:

Reviewer 2

1.Title. The title reflects the primary aspect but probably should be shortened.

Reply: Thank you very much for your helpful suggestion. We reconsidered the topic, and simplified the title to “Recurrent Hemoptysis in Pediatric Bronchial Dieulafoy's Disease with Inferior Phrenic Artery supply", which is more concise and reflects the core content.

2.Abstract. The abstract summarizes the case well but needs improvement regarding the English language and the use of abbreviations.

Reply: We are sorry for the language quality and abbreviations. We have made the corresponding corrections to the abbreviations (marked in yellow), and reviewed the full text again to ensure that the "*Abbreviations must be defined upon first appearance*" requirement is met. Moreover, we invited two experts to proofread and improve the language.

3.Key Words. The keywords reflect the focus of the manuscript, but there is no need to include case-report as it is the style of the article and not a word regarding the paper's content. I would change the order and also child instead of pediatrics.

Reply: Thank you for your constructive comments. Accordingly, we carefully considered the topic of the article, and revised the keywords to "Hemoptysis, Child, Bronchial Dieulafoy's disease, Inferior phrenic artery, Interventional Treatment".

4.Background. The authors correctly describe the field of BBD. They could combine the data from line 3 (only few cases) with the following data from line 10 (only 2 children). Also, do not use numerals under five.

Reply: Thank you for your comments. According to your suggestions, we have revised the statements for better coherence (marked in yellow).

5.Clinical data–case report: The clinical, diagnostic and therapy presentation could be improved. The figures are well presented and important to the readers.

Reply: Thank you for your positive comments. Accordingly, we revised this section, and revised the language to make the content more concise. Also, we invited native English experts to review our manuscript.

6.Discussion. The authors interpreted their findings on managing this case adequately and highlighted the critical points for the readers. The discussion is relevant to the clinical practice in such cases. The final paragraph could be separated as Conclusions.

Reply: We appreciate your positive comments. We have included the final paragraph as the Conclusions section in the revised version.

7.References. The authors seem to cite the essential references appropriately.

Reply: Thank you very much for your positive comments.

8.Quality of manuscript organization and presentation. The manuscript is generally well and coherently organized, but the style, language and grammar should be rechecked and corrected. Also, abbreviated words and numerals must be verified and improved.

Reply: We are sorry for the language and grammatical errors. We have reviewed the full text again to ensure that the style, language, grammar and abbreviation requirements are met (all revisions are marked in yellow). Moreover, we invited two experts to proofread and improve the language.

9.Research methods and reporting. There is no mention that the paper was prepared according to BPG's standards for manuscript type: CARE Checklist (2013) - Case report. I think it would be better to include a figure with the timeline of the events.

Reply: In the revised version, we have mentioned that the manuscript was prepared in accordance with BPG's standards for manuscript type. We have also added a timeline chart (Figure 4) of the events according to your comments. The timeline chart clearly shows the characteristics of the case.

10. Ethics statements. There is a mention regarding the informed consent for the publication of the case.

Reply: We have strictly adhered to academic norms and ethics, and obtained informed consent from the patient's parents.

Recurrent Hemoptysis in Pediatric Bronchial Dieulafoy's Disease with Inferior Phrenic Artery Supply

Running title: Recurrent Hemoptysis in Pediatric BDD

Abstract

Background: Bronchial Dieulafoy's disease (BDD) is characterized by the erosion of an anomalous artery in the submucosa of the bronchus. The etiology of pediatric BDD is mainly congenital dysplasia of bronchus and pulmonary arteries, which is different from chronic inflammatory injury of the airway in adult patients. The internal thoracic artery, subclavian artery and intercostal artery are known to be involved in the blood supply to the BDD lesion in children.

Case presentation: We reported a case of BDD in a 4-year-old male with recurrent hemoptysis for one year. Selective angiography showed dilated right bronchial artery, and anastomosis of its branches with the right lower pulmonary vascular network. Bronchoscopy showed nodular protrusion of bronchial mucosa with local scar. Selective embolization of bronchial artery was performed to stop bleeding. One month after the first intervention, the symptoms of hemoptysis recurred. A computed tomography angiogram (CTA) showed another tortuous and dilated feeding artery in the right lower lung, which was an abnormal ascending branch of the inferior phrenic artery (IPA). The results of angiography were consistent with the CTA findings. IPA was found to be another main supplying artery, which was not considered during the first intervention. Finally, the IPA was also treated with microsphere embolization combined with coil interventional closure. During the one-year follow-up, the patient never experienced hemoptysis.

Conclusion: The supplying arteries of the bleeding lesion in children with BDD may

originate from multiple different aortopulmonary collateral arteries, and IPA should be considered to reduce the missed diagnosis. CTA is a noninvasive radiological examination for the screening of suspected vessels, which shows high coincidence with angiography, and serves as the first choice for the diagnosis of BDD.

Keywords: Hemoptysis, Child, Bronchial Dieulafoy's disease, Inferior phrenic artery, Interventional Treatment

Introduction

Bronchial Dieulafoy's disease (BDD) is a type of tortuous malformation of submucosal artery of bronchial wall, which may spontaneously rupture under the action of external factors, resulting in acute lumen hemorrhage with massive hemoptysis. To the best of our knowledge, there are more than 70 cases of BDD reported to date in the literature, of which only two have been reported in children (eight months and 13 years old, respectively) [1]. The etiology and pathogenesis of BDD remain unclear, but may be related to congenital vascular dysplasia or chronic inflammatory injury of pulmonary vessels [2]. BDD is an important cause of pulmonary hemorrhage with massive hemoptysis. Most of the auxiliary examinations performed show normal results, and the chest imaging does not show any specific findings, which may lead to misdiagnosis of cases. There is no consensus on the diagnosis and treatment of BDD. Selective embolization of bronchial artery is considered to be an effective method to stop bleeding. However, 52.6% of patients with bronchial artery embolization required surgical intervention because of embolization failure or recurrent bleeding [3]. Collectively, all these reports indicate the need to optimize the diagnosis and treatment of BDD through further exploration.

Clinical data

A 4-year-old male was admitted to the hospital with a history of "cough for two years, recurrent hemoptysis for one year, and massive hemoptysis once". The child suffered from recurrent coughing after birth, and was hospitalized for pneumonia with bronchiectasis 3-5 times every year. After hospitalization, the bronchoscopy performed during initial episodes of bronchiectasis showed chronic endobronchial inflammation. One year ago, the child suffered from recurrent hemoptysis symptoms, and was treated

with anti-hemostasis and anti-infection therapies, but the condition continued to deteriorate. Massive hemoptysis occurred one hour before admission, with about 100 ml of blood loss. There was no history of tuberculosis (TB) or any contact with TB patients. The patient had shortness of breath, with positive three concave sign of nails and mild clubbing of the toes. The respiratory sounds of the right lower lung were weak, and no dry and wet rales were found. Routine blood tests, biochemical function, electrolyte levels, bleeding and coagulation related indicators were not abnormal.

Fiberoptic bronchoscopy showed multiple nodular protrusions in the right middle and lower lobar bronchial mucosa, local scar formation, rough and pale surface, and easy bleeding of mucosa (Fig. 1a). Partial bronchial branch openings were deformed, with sputum thrombus and old bleeding (Fig. 1b). Computed tomography (CT) showed uneven thickening of the bronchial wall of the basal segment of the right lower lobe, which was partially protruding into the lumen. The right bronchial artery was tortuous and thickened, and branched into a descending vessel, which was obviously dilated at the distal end and anastomosed with the vascular network of right lower pulmonary artery (Fig. 2a). Selective angiography showed dilated right bronchial artery, and anastomosis of its branches with the right lower pulmonary vascular network. The diameter at the beginning was 2.7 mm, and 2.6 mm at the entrance to the lung (Fig. 2b). The patient was clinically diagnosed as BDD.

First, 500 μ polyvinyl alcohol (PVA) particles were injected through a 2.7F microcatheter, and then 3-3 coils were inserted through a 4F cobra catheter to embolize the vessels of each branch (Fig. 2c). Selective embolization of bronchial artery was performed to stop bleeding. However, one month after the first intervention, the symptoms of hemoptysis recurred.

A computed tomography angiogram (CTA) showed another tortuous and dilated

feeding artery in the right lower lung, which was an abnormal ascending branch of IPA. The IPA originated from the abdominal aorta celiac trunk, which moved along the right upper diaphragm and anastomosed with the vascular network of right lower pulmonary artery (Fig. 3a). The blood vessels responsible for hemoptysis were suspected to be the branches of right bronchial artery and IPA.

The abnormal branch of IPA moved along the right upper diaphragm (Fig. 3b). A 2.7F microcatheter was injected with 500 μ PVA particles, and a 3-3 coil was inserted through a 4F cobra catheter to embolize the abnormal branch vessels (Fig. 3c). No residual shunt was detected after intervention. After one-year follow-up, the growth and development of the patient were normal, and he had no episodes of recurrent hemoptysis (Fig. 4).

Discussion

BDD is very rare among children, and the youngest patient reported with BDD is eight months old. Normally, the disease is considered in heavy smokers when recurrent massive hemoptysis is present without any other abnormal findings, or in patients with chronic respiratory diseases. Congenital vascular dysplasia may be considered in pediatric patients with such findings. Smith et al. speculated that the disease was caused by the failure of the submucosal artery with constant diameter to branch into capillaries [4]. Stoopen et al. suggested that the variations in right bronchial artery during embryonic development might cause an increased risk of abnormal right vessels [5]. Most of the abnormalities in arteries reported in BDD cases originated from branches of the right bronchial artery, which accounted for about two-third of all cases. Relative to adults, BDD in children is rare, which is mainly considered to be associated with congenital vascular malformations. In the present case, the pulmonary hemorrhagic

lesion had two supplying arteries, in addition to the abnormal right bronchial artery branch, also a branch from IPA, which was involved in pulmonary hemorrhage. If IPA is ignored, it may lead to treatment failure in patients with BDD. Importantly, for BDD related to congenital angiogenesis, it is necessary to consider the ectopic origin of the supplying vessels such as IPA, which has not yet been reported.

CTA and angiography can clearly show the tortuous and dilated bronchial artery in BDD patients [6]. The blood vessels of BDD lesions traverse through the bronchial mucosa and could pass through the bronchial cartilage ring. The diameter of the diseased artery is significantly increased and remains constant, which is called "constant diameter artery". The bronchial artery suddenly disappears at the point of entering the pulmonary segment, showing a "truncated" change. Part of the tortuous and dilated artery extends into the bronchial lumen, forming local protuberant lesions or small nodules covered with normal mucosa, and these signs could be easily detected by CTA and bronchoscopy. Bronchoscopy is an important method to detect BDD, where the typical microscopic lesions are manifested as nodular lesions protruding into the lumen. The surface mucosa of the lesions is normal and complete, which is usually misdiagnosed as tumor or tuberculosis. If biopsy is performed for confirmation due to misdiagnosis as tumor, it may result in massive hemorrhage with profuse and fatal hemoptysis. A retrospective study analyzed 73 BDD patients reported worldwide from 1995 to 2019. Among them, 19 underwent bronchoscopy, 17 suffered from bleeding and six patients died [2]. Hence, CTA is recommended as a low-risk noninvasive method, which can be used as the preferred diagnostic method for suspected cases of BDD.

At present, there is no consensus or guidelines for the accurate diagnosis and treatment of BDD. The two reported pediatric BDD cases were characterized by recurrent

hemoptysis. Among them, one female developed pulmonary hemorrhage at the age of eight months, and was diagnosed as BDD at the age of five years. The lesion was located in the upper right bronchus. The pulmonary hemorrhage did not improve after two bronchial artery embolizations, and the right lung upper lobotomy was subsequently performed [7]. The other case was a 13-year-old boy with recurrent hemoptysis three months after bronchial artery embolization, who subsequently underwent lobotomy. Both patients had no symptoms of hemoptysis after surgery [8]. Selective bronchial artery embolization is considered to be an effective way to prevent bleeding and reduce the mortality rate. However, studies have found that 52.6% of patients with bronchial artery embolization require surgical intervention because of embolization failure or recurrent bleeding, which may be due to local tissue revascularization and neovascularization, as well as the proliferation and expansion of adjacent vascular system [3]. We believe that the vascular network is very rich in BDD, with many collateral branches. Microsphere embolization is recommended as the first choice for the surgical intervention of BDD. Consequently, selective occlusion of the main feeding arteries with coils can significantly reduce the risk of local rebleeding. A few patients with uncontrollable bleeding or failed arterial embolization may require further surgical treatment. In our case, the two supplying arteries responsible for hemoptysis were treated with microsphere embolization combined with coil interventional closure. After one-year follow-up, the patient had no recurrent hemoptysis, indicating that the combined intervention was effective.

Conclusions

The supplying arteries of the bleeding lesion in children with BDD may originate from multiple different aortopulmonary collateral arteries, and IPA should be considered to reduce the missed diagnosis. CTA is a noninvasive radiological examination for the

screening of the suspected vessels, which shows high coincidence with angiography, and serves as the first choice for the diagnosis of BDD.

The manuscript was prepared in accordance with BPG's standards for manuscript type: CARE Checklist (2016) - Case report.

References

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Figure legends

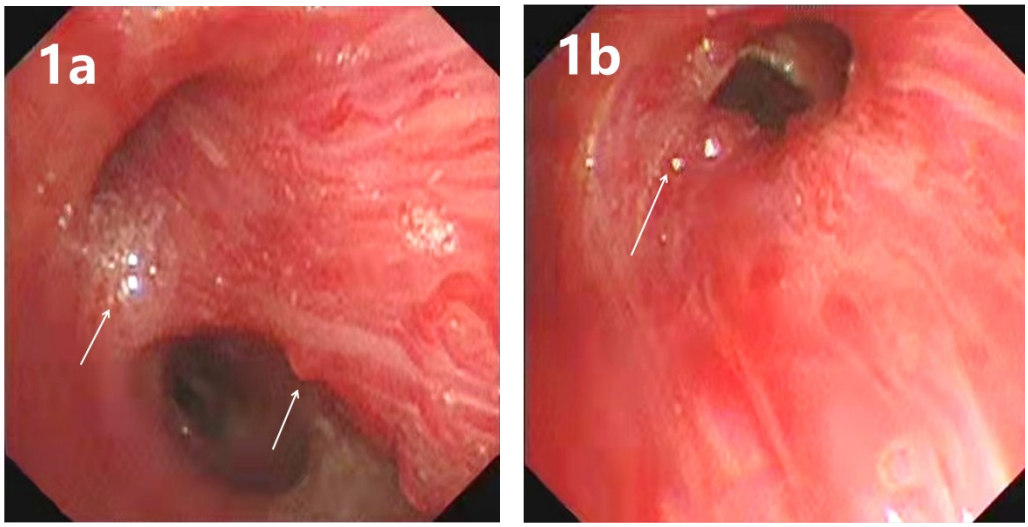


Figure 1. Fiberoptic bronchoscopy. (1a) Multiple nodular protrusions and scar formation in the right middle segment of bronchial mucosa (arrow); **(1b)** Nodular protuberances in the basal segment of the right lower lobe (arrow), where the mucosa could easily bleed.

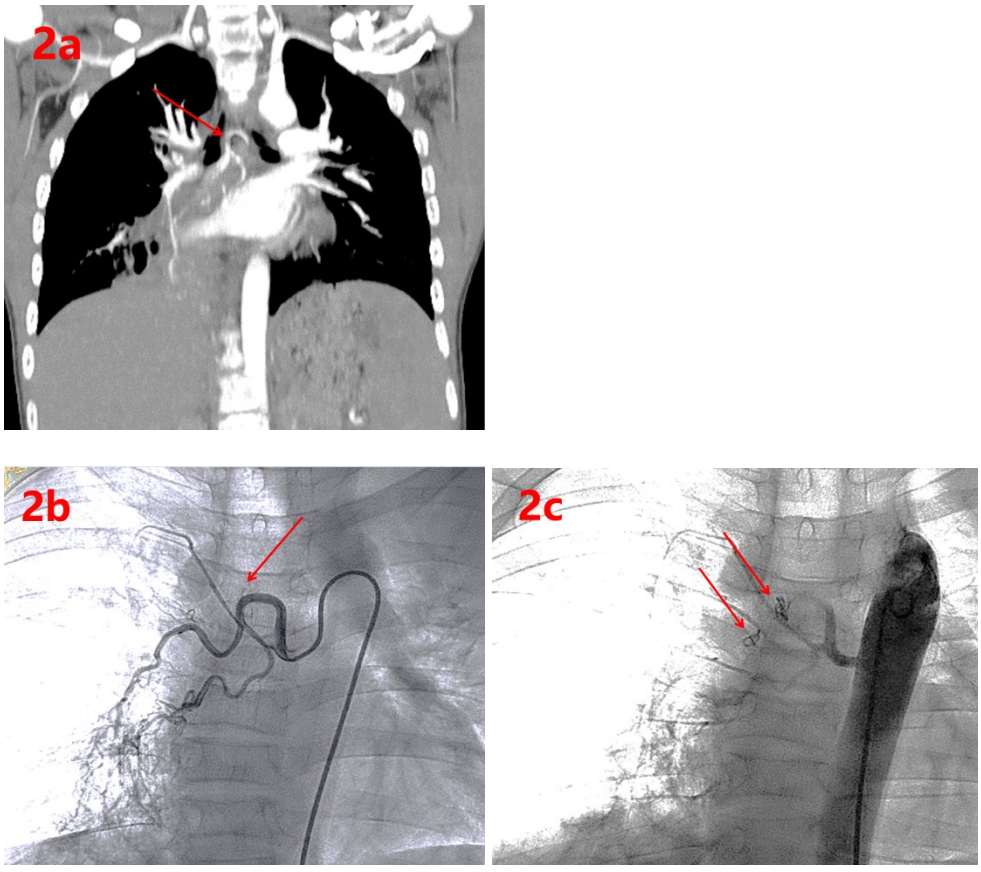
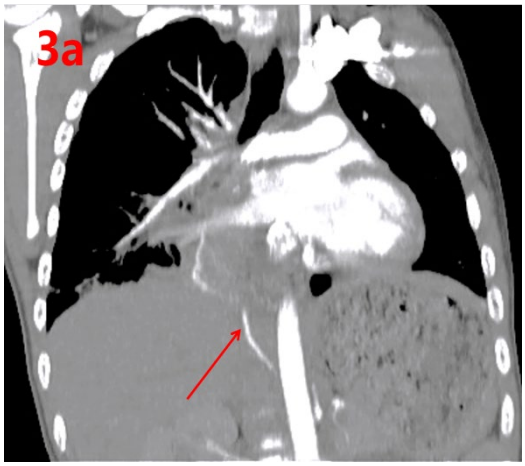
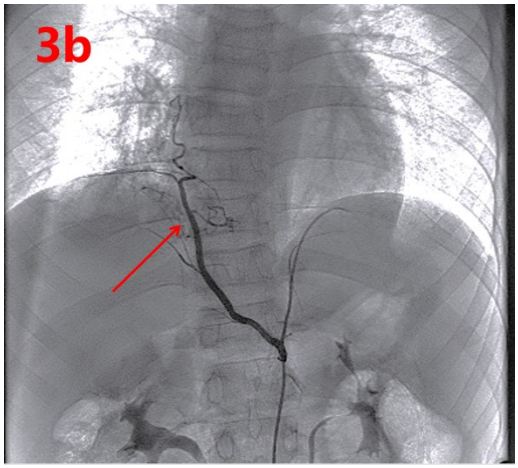


Figure 2. CT angiography and angiography of bronchial artery. (2a) The right bronchial artery was tortuous and thickened, branched into a descending vessel, and its distal end was obviously dilated (arrow); **(2b)** The bronchial artery near the lower end

of the left main bronchus was tortuous and thickened (arrow); **(2c)** The coil position was visible after the embolization, and no residual shunt was found (arrow).





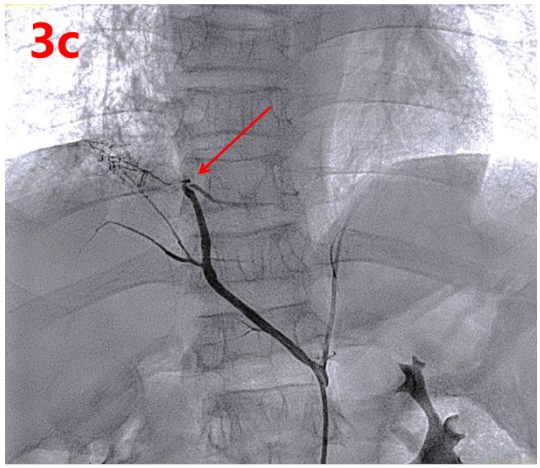


Figure 3. CT angiography and angiography of IPA. (3a) The abdominal aorta celiac trunk abnormally originated from a tortuous thickened artery and moved along the right upper diaphragm (arrow). **(3b)** An ectopic artery from the descending aorta under the diaphragm was anastomosed with the vascular network of the right lower pulmonary artery (arrow); **(3c)** The coil position could be observed after the embolization, and no residual shunt was found (arrow).

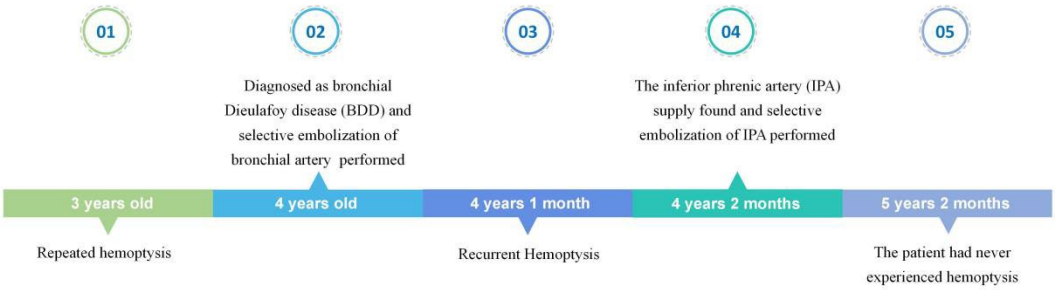


Figure 4. Timeline of the events in the present case.