

Case Report

Primary tracheobronchial amyloidosis: a case report and literature review

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Abstract: Objective: Tracheobronchial amyloidosis (TBA) is a rare disease involving localized amyloid deposits within the lower respiratory tract. There are no specific treatments for TBA. Some patients can be observed and others can be treated using bronchoscopic techniques or chemotherapy, depending on their symptoms. Methods: We present a 28-year-old woman with fever, cough, sputum, and dyspnea. Results: Bronchoscopy showed multiple nodules in the bronchi, and further diagnostic efforts confirmed TBA by positive staining with Congo red. Owing to reproductive requirements, she was observed in the outpatient department after the infection was brought under control, without recurrence of fever accompanied by shortness of breath sometimes during the follow-up. Conclusions: In patients with refractory asthma or chronic cough of unknown etiology, bronchoscopy should be performed to obtain biopsy samples for definitive diagnosis of rare diseases, including TBA. There are no specific treatments for TBA. Patients who have reproductive requirements can be observed if their symptoms are minor, such as mild obstructive pulmonary ventilation dysfunction.

Keywords: Amyloidosis, clinical symptoms, bronchoscopy, histopathology

Introduction

Primary tracheobronchial amyloidosis (TBA) is a rare disease, occurring as a localized process restricted to the lung or as a part of systemic infiltration. Berraondo first observed amyloidosis localized to the respiratory tract in 1877 [1, 2]. Many TBA patients have respiratory symptoms such as progressive dyspnea, productive cough and breathlessness [3]. TBA treatment focuses on bronchoscopic techniques [4], but symptomatic treatment is also very common in clinical practice.

We report herein a case of a patient with primary TBA confirmed by positive staining with Congo red, who was observed rather than actively treated because of her reproductive status.

This report was approved by the Institutional Review Board of Gansu Provincial Hospital. Informed consent was obtained from all individual participants included in the study.

Case presentation

A 28-year-old woman from northern China was transferred to our hospital because of fever, cough, sputum, and dyspnea. She was admitted after being diagnosed with chronic bronchitis or asthma over a period of 3 years in other hospitals, and had previously been treated with bronchodilators and anti-infection measures for numerous times (specific type unknown). This patient had no history of smoking and no other medical history. Physical examination showed wheezing breath sounds on both sides of the lungs. The laboratory results were as follows: a blood workup was routine, and auto-antibodies, tumor markers and arterial blood gas (while breathing room air) showed no abnormal values. A T-SPOT assay was within normal limits. Tests for liver function, renal function and coagulation profile were normal. Tests for kappa and lambda were within normal limits. Tests for acid-fast bacilli and fungi in three sputum samples were negative. Chest computed tomography (CT) showed 1) triangular high-

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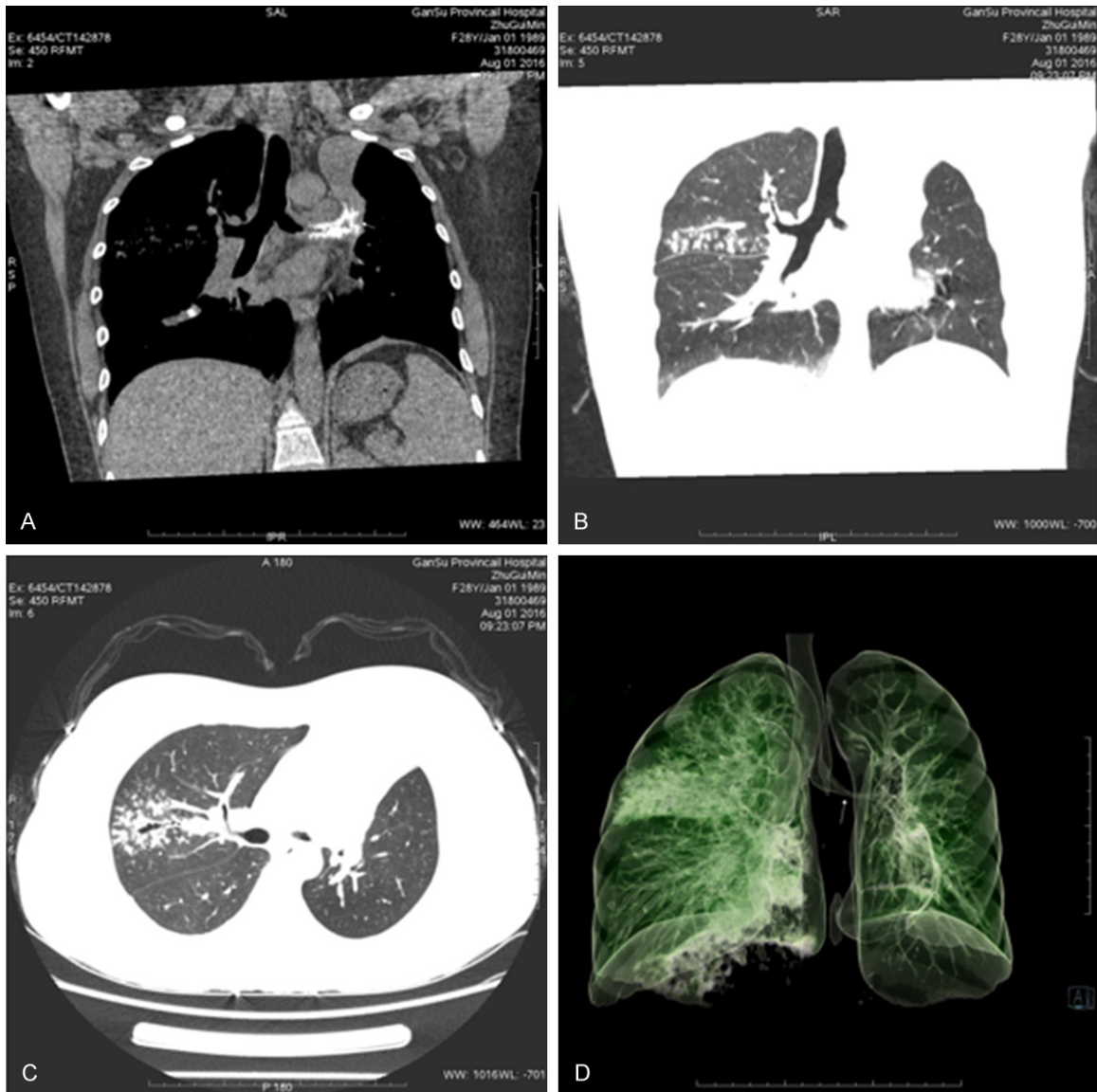


Figure 1. Chest CT of 28-year-old woman. Chest computed tomography (CT) showing (A) triangular high density foci in the left lobe of the lungs, stenosis and partial occlusion in upper left lung bronchi; (B) Mediastinum slightly shifted to the right; (C) Diffuse shadows with uneven density in the front and right lower lobe puncta; (D) Swollen lymph nodes in the mediastinum and bilateral paratracheal lymph nodes associated with calcification. Magnification: $\times 200$.

density foci in the front portion of the left lung lobe, stenosis and occlusion in the upper left lung bronchi; 2) mediastinum shifted slightly to the right; 3) diffuse shadows with uneven density in the right front and lower lobe; 4) swollen lymph nodes in the mediastinum, with bilateral paratracheal lymph nodes associated with calcification (**Figure 1A-D**). When this patient experienced relief from shortness of breath after 3 days treatment by bronchodilation, she underwent bronchoscopy, which revealed nodules in the left main bronchus and

right basal branch with significant swelling and hypertrophy (**Figure 2A-D**). Further diagnosis from tissue biopsy showed chronic mucosal inflammation and amyloid deposition, and Congo red staining was positive (**Figure 3A-D**). There was no evidence of extrapulmonary organ involvement in amyloidosis. Based on this comprehensive evaluation, a diagnosis of primary TBA was established. The treatment consisted of antibiotics and phlegm reduction, because this patient refused invasive bronchoscopic treatment and refused chemotherapy

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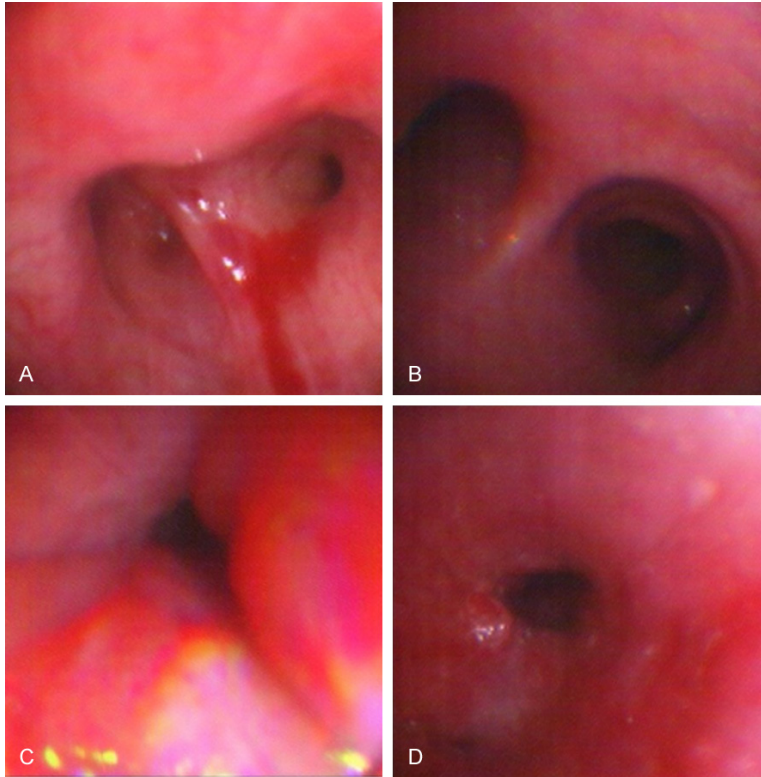


Figure 2. Bronchoscopy of 28-year-old female patient. A. Normal knuckle. B. Nodules visible in left main bronchus, local hyperemia, and luminal stenosis. C. Nodules visible in right upper leaves of the front inside tracheal cavity. D. Nodules visible in right basal branch nodular creatures. Magnification: $\times 200$.

due to reproductive requirements. Because of minor symptoms consisting of dyspnea and a productive cough, she was observed in the outpatient department. Recurrence of fever was not observed, although the patient experienced shortness of breath occasionally during a follow-up of 10 months after her discharge.

Discussion

Amyloidosis is characterized by the deposition of a histochemically specific substance—an inert, eosinophilic, proteinaceous material usually recognized by its staining reaction with Congo red. The types of respiratory amyloidosis have been classified as: 1) tracheal bronchus amyloidosis, 2) diffuse alveolar septal amyloidosis, 3) nodular amyloidosis, 4) lymph node amyloidosis, 5) pleural amyloidosis, 6) laryngeal amyloidosis, 7) diaphragm amyloidosis. Tracheal bronchus amyloidosis is the most common form of respiratory amyloidosis, while local lymph node amyloidosis is relatively rare [2, 5-7].

The common clinical symptoms are breathing difficulty or cough, hemoptysis, and hoarseness [8]. The most common clinical manifestations in TBA patients are breathing difficulty and coughing. Bronchial obstruction can cause atelectasis, and as a result, shortness of breath and breathing difficulty. In some cases it is possible to observe a cough with yellow sputum, fever, and increased white blood cells due to secondary infection caused by secretion retention as a result of airway stenosis [9-11].

Our patient presented with symptoms of cough and shortness of breath. Before visiting our clinic, this patient had a long disease course, and had been misdiagnosed for three years with chronic bronchitis or asthma. There were several reasons for the misdiagnosis. First, the patient was not diagnosed in a timely

fashion because of limited health care resources, and lung CT scans and bronchoscopy were not available; consequently, the patient was misdiagnosed with chronic bronchitis or asthma due to the results observed on a bronchial challenge test. Second, the clinicians were not acquainted with or knowledgeable about TBA. Third, the medical staff did not perform further examinations for histologic diagnosis.

A chest CT of amyloid can show mesh nodular infiltrates, diffuse and irregular thickening of the airway wall with calcification, luminal stenosis and pleural plaques. Tracheal bronchus amyloidosis is characterized by airway stenosis or obstructive atelectasis. Alveolar septum amyloidosis is characterized by interlobular septal thickening, diffuse interstitial and alveolar infiltration, and occasionally the appearance of nodules. Lymph node amyloidosis manifests as enlargement of mediastinal lymph nodes or lung lymph nodes, with punctate calcifications [12-16]. A CT scan of our patient showed trian-

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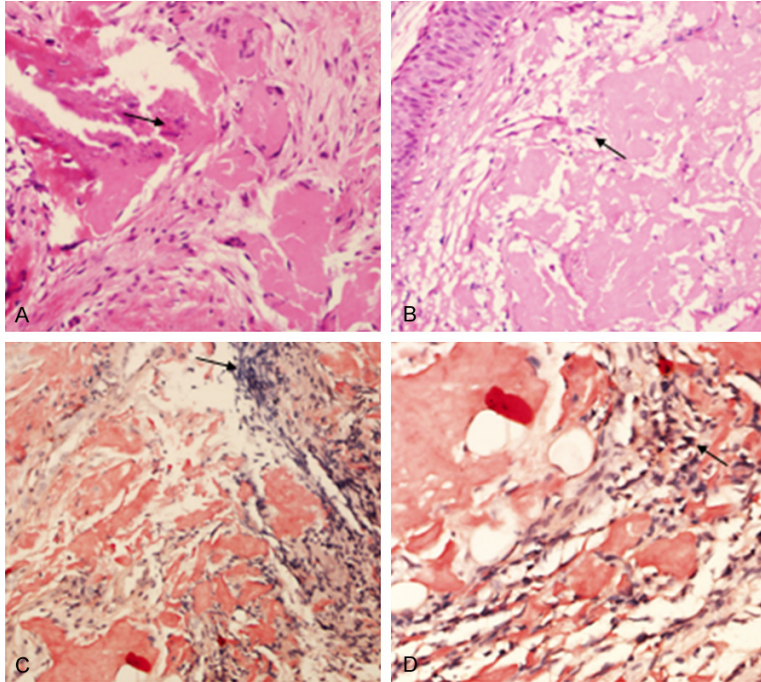


Figure 3. Pathological appearance of tissue biopsy. Biopsy specimens showing tissue surface erosion, an area of coated ciliated columnar epithelium, no obvious abnormally formed cells. A and B. The submucosa showed a wide-flaked red dye deposit structure and scattered infiltration of small lymphocytes, without abnormal cells, granulomatous lesions, or fungus. C and D. Congo red staining was positive. Magnification: $\times 200$.

gular high-density foci in the lung lobes, bronchial stenosis with patchy calcification, occlusion, a mediastinal shift, lower lobe puncta, lymph nodes, and bilateral paratracheal lymph node calcification.

Bronchoscopy in TBA patients can show visible gas wall deformation, multifocal or single focal uplift, common hypertrophy, or luminal stenosis. The uplift is smooth without pedicle nodules, at scales up to 1 cm, to the full cover pale epithelium. In some cases, lesions caused by luminal stenosis are prone to bleeding [4]. Because amyloid deposition does not produce consistent morphological changes, histopathology is the gold standard in the diagnosis of amyloid. Inflammatory cells are generated by a granulomatous reaction involving plasma cells and lymphocytes, and sections stained with Congo red reveal greenish birefringence under polarized-light microscopy [17, 18]. Bronchoscopy of our patient revealed nodules in left main bronchus, right upper bronchi, the front inside pipe cavity, and right basal branch nodular creatures.

There is no specific treatment for TBA. The nodular form of TBA is generally asymptomatic and can be managed by observation. Local bronchoscopic treatment with balloon dilation, stent placement, laser surgery, or radiation may be indicated [2]. Chemotherapy using melphalan, thalidomide, bortezomib, lenalidomide or bendamustine in combination with dexamethasone could be a treatment choice in some patients, and in some cases, even high-dose chemotherapy combined with autologous stem cell transplantation could be used [19, 20]. In general, the choice of treatment in TBA depends on the symptoms. However, the efficacy of the treatments listed above is uncertain in the long term, and consequently, other possibilities need to be explored. Our patient refused invasive bronchoscopic treatment be-

cause she was fearful of massive hemoptysis. She also refused chemotherapy and radiation therapy due to reproductive requirements. Due to minor symptoms of mild obstructive pulmonary ventilation dysfunction, we decided to treat this patient by observation in the outpatient department after controlling her infection. Recurrence of fever was not observed, although the patient experienced shortness of breath occasionally during the follow-up of 10 months after her discharge.

The clinical symptoms and signs of TBA are nonspecific. Knowledge about the pathology of this disease is important. Histopathology remains the gold standard for diagnosis. For patients with refractory asthma or chronic cough of unknown etiology, bronchoscopy should be performed to obtain biopsy samples for definitive diagnosis of rare diseases, including TBA. There are no specific treatments for TBA, and patients who have reproductive requirements can be treated with observation if their symptoms are minor, such as mild obstructive pulmonary ventilation dysfunction.

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Disclosure of conflict of interest

None.

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References

- [1] Lu J, Yu Y, Zhu I, Cheng Y and Sun PD. Structural mechanism of serum amyloid A-mediated inflammatory amyloidosis. *Proc Natl Acad Sci U S A* 2014; 111: 5189-5194.
- [2] Berraondo J, Novella L, Sanz F, Lluch R, de Casimiro E and Lloret T. Management of tracheobronchial amyloidosis with therapeutic bronchoscopic techniques. *Arch Bronconeumol* 2013; 49: 207-209.
- [3] Ding L, Li W, Wang K, Chen Y, Xu H, Wang H and Shen H. Primary tracheobronchial amyloidosis in China: analysis of 64 cases and a review of literature. *J Huazhong Univ Sci Technol Med Sci* 2010; 30: 599-603.
- [4] Alloubi I, Thumerel M, Bégueret H, Baste JM, Velly JF and Jougon J. Outcomes after bronchoscopic procedures for primary tracheobronchial amyloidosis: retrospective study of 6 cases. *Pulm Med* 2012; 2012: 352719.
- [5] Renapurkar RD and Kanne JP. Metabolic and storage lung diseases: spectrum of imaging appearances. *Insights Imaging* 2013; 4: 773-785.
- [6] Howard S, Jagannathan J, Krajewski K, Giardino A, Zukotynski K, O'Regan K, Ghobrial I and Ramaiya N. Multimodality imaging in amyloidosis. *Cancer Imaging* 2012; 12: 109-17.
- [7] Zhang LQ, Zhao YC, Wang XW, Yang J, Lu ZW and Cheng YS. Primary localized tracheobronchial amyloidosis presenting with massive hemoptysis: a case report and literature review. *Clin Respir J* 2017; 11: 122-125.
- [8] Lu X, He B, Wang G, He B, Wang L and Chen Q. Bronchoscopic diagnosis and treatment of primary tracheobronchial amyloidosis: a retrospective analysis from China. *Biomed Res Int* 2017; 2017: 3425812.
- [9] Daniels JT, Cury JD and Diaz J. An unusual cause of postobstructive pneumonia. *Chest* 2007; 131: 930-933.
- [10] Serraj M, Kamaoui I, Znati K, Kouara S, Sahnoune F, Amara B, El Biaze M, Tizniti S, Amarti A and Benjelloun MC. Pseudotumoral tracheobronchial amyloidosis mimicking asthma: a case report. *J Med Case Rep* 2012; 6: 40.
- [11] Kavita V, Raiyani PD and Vyas SS. Tracheobronchial amyloidosis-a series of two cases. *J Clin Diagn Res* 2014; 8: FD09-10.
- [12] Chung MJ, Lee KS, Franquet T, Müller NL, Han J and Kwon OJ. Metabolic lung disease: imaging and histopathologic findings. *Eur J Radiol* 2005; 54: 233-245.
- [13] Gilad R, Milillo P and Som P. Severe diffuse systemic amyloidosis with involvement of the pharynx, larynx, and trachea: CT and MR findings. *AJNR Am J Neuroradiol* 2007; 28: 1557-1558.
- [14] Chu H, Zhao L, Zhang Z, Gui T, Yi X and Sun X. Clinical characteristics of amyloidosis with isolated respiratory system involvement: a review of 13 cases. *Ann Thorac Med* 2012; 7: 243-9.
- [15] Ozer Simsek Z, Oymak FS, Tutar N, Canoz O and Demir R. A rare cause of diffuse parenchymal lung disease together with granulomatous reaction: pulmonary amyloidosis. *Case Rep Pulmonol* 2013; 2013: 837190.
- [16] Graham CM, Stern E, Finkbeiner WE and Webb WR. High-resolution CT appearance of diffuse alveolar septal amyloidosis. *AJR Am J Roentgenol* 1992; 158: 265-267.
- [17] Torres PPTES, Rabahi M, Pinto SA, Curado KCMA and Rabahi MF. Primary tracheobronchial amyloidosis. *Radiol Bras* 2017; 50: 267-268.
- [18] Howard ME, Ireton J, Daniels F, Langton D, Manolitsas ND, Fogarty P and McDonald CF. Pulmonary presentations of amyloidosis. *Respirology* 2001; 6: 61-64.
- [19] Mahmood S, Palladini G, Sanchorawala V and Wechalekar A. Update on treatment of light chain amyloidosis. *Haematologica* 2014; 99: 209-221.
- [20] Raschle J, Banz Wälti Y, Suter T and Pabst T. A single-centre cohort of patients with systemic light chain AL-amyloidosis treated with conventional chemotherapy or with high-dose chemotherapy and autologous stem cell transplantation. *Swiss Med Wkly* 2014; 144: w13922.