Pulmonary aspergillosis with in-situ pulmonary artery thrombosis: to anti-coagulate or not?

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Aspergillus is widespread in the environment and causes a variety of tracheobronchial and pulmonary disorders, depending upon the alterations of immune status of hosts.[1] Among the spectrum of pulmonary aspergillosis (PA), allergic bronchopulmonary aspergillosis, and most chronic pulmonary aspergillosis are considered as non-invasive diseases, whereas invasive pulmonary aspergillosis (IPA) and subacute invasive pulmonary aspergillosis (SAIA) may cause tissue invasion.

Blood vessel invasion, thrombo-mycotic occlusion, and hemorrhagic infarctions are characteristic pathological findings in angioinvasion pulmonary aspergillosis. In-situ pulmonary artery thrombosis (PAT) is a potentially life-threatening disorder, which is caused by inflammation and injury of pulmonary artery wall as well.[2] The therapy of PAT is similar with that of pulmonary thromboembolism (PTE), including thrombolyis and anti-coagulation, and hemoptysis is one of the most common complications. Anti-coagulation should be given or not, which may depend on different clinical situations.

Here we present three cases with different clinical outcome, which could be helpful to set the diagnosis and therapy strategy of PA with in-situ PAT.

Case 1. A 71-year-old man had a history of chronic obstructive pulmonary disease (COPD) and productive cough and dyspnea for 30 years. The symptoms exacerbated 15 days with edema of both lower extremities. Computed tomography pulmonary angiography (CTPA) [Figure 1A and 1B] showed cavity in right lobe and dorsal segment of lower lobe with fibrosis and pleural thickening. It also showed thrombosis in right main pulmonary artery, which was considered as in-situ PAT because of the close adjacent relationship between thrombosis and pulmonary lesion. He was treated with anti-coagulation. Then serum Galactomannan showed 1.11, sputum culture showed Aspergillus, which led to the diagnosis of IPA. With treatment of itraconazole, the patient improved then.

Case 2. A 75-year-old man had COPD had fever, chest pain for 15 days. The CT scanning [Figure 1C] showing maculas shadows in tip-posterior of left upper lobe. He was diagnosed as IPA with microbiology of Aspergillus and was treated with voriconazole. A CTPA [Figure 1D] showed a filling defect in artery supplying the left upper lobe. He was diagnosed as in-situ PAT instead of PTE because of the close relationship of artery and lung parenchyma lesions. After 10-day anti-coagulation, the patient had hemoptysis, and a follow-up chest CT [Figure 1E] showed a rapid deterioration in lung. Anti-coagulation was stopped for persistent hemoptysis and anti-fungal therapy was continued. The patient improved after several weeks and continued oral voriconazole after discharging.

Case 3. A 42-year-old woman, who got lung tuberculosis 12 years ago, with complaint of dyspnea and hemoptysis for 5 months, recurrence for 5 days. CTPA [Figure 1F and 1G] showed filling defect in right pulmonary artery, bronchiectasis, and cavities in multiple lobes. She was diagnosed as PTE and treated with warfarin, but stopped anti-coagulation because of hemoptysis. Four months later, CTPA [Figure 1H] showed serious local pulmonary fibrosis. Five days before admission, she had hemoptysis again. Chest CT [Figure 1I] showed cavity, formation of new nodules and progressive massive fibrosis, which clued the possibility of SAIA. Aspergillus immunoglobulin G antibody was positive and the diagnosis of SAIA was made. The pulmonary artery thrombotic lesion was diagnosed as in-situ PAT instead of PTE. Intra-venous itraconazole was used. At day 4 after admission, she suffered from fatal hemoptysis and died due to asphyxia.

These three cases were all diagnosed as PA with in-situ PAT. In vivo experiment showed that Aspergillus hyphae
stimulated tissue factor activity in vascular endothelial cell, revealing the potential mechanism of angioinvasion and thrombosis. In addition, in patients with underlying pulmonary diseases, because of the pulmonary vascular remodeling, blood flow vortex is another risk factor of thrombosis. CTPA should be taken into to identify PAT if necessary.

PAT is distinguished from PTE by pathophysiology and CTPA features. In PTE, thromboembolus migrates from venous of lower extremities to pulmonary artery, filling defects usually can be observed in bilateral pulmonary artery, whereas in-situ thrombus formation happens single often. In patients with PAT, it displays mural thrombus with obtuse angles with vessel wall, but not common in patients with acute PTE. In these three cases, radiology demonstrated that embolism was single and located in main pulmonary artery adjunct to the lung lesions, distal arteries were unobstructed, the lesions of pulmonary parenchyma and artery fit together, consistent with in-situ PAT. It is important to notice the correlation between PA and PAT rather than simply PTE due to the therapy is more than anti-thromboembolism.

There were only some sporadic cases of PA with PAT reported epidemiological data in population were not clear. IPA happened in both immunosuppressed and non-immunosuppressed patients. And thrombi in these cases were fungal thrombi proven by autopsy, among them, anti-fungal therapy was diverse, including triazole, Amphotericin B, and caspofungin. As for our cases, though there was no histopathology evidence, we supposed these thrombotic events were attributed to PAT according to clinical features. Anyway, anti-fungal therapy is essential, no matter for fungal thrombi or PA.

For example, case 3 suffered SAIA for 5 months speculated by previous CTs, without standard anti-fungal therapy, Aspergillus spoiled vascular, and fatal hemoptysis as a severe complication resulted in poor prognosis. Yet patients in case 1 and 2 received anti-fungal therapy in time and recovered. It speculates that early diagnosis and anti-fungal therapy are critical for patients with angioinvasion. Voriconazole is approved for first-line therapy in invasive aspergillosis according to guidelines, combination of anti-fungal drugs may help in immunocompromised or critical-ill patients.
The necessary of anti-coagulation therapy for PAT patients is unclear.2 Anti-coagulation should be personalized in PA with PAT. According to the recommendations of the American College of Chest Physicians guideline of antithrombotic therapy for venous thromboembolism (VTE) disease,3 bleeding estimation should be made in different anti-coagulation individuals. For example, the patient in case 2 was in high risk of bleeding with more than two bleeding risk factors, and got cessation of anti-coagulation after occurrence of hemoptysis. Anti-coagulation helped the improvement in case 1 while aggravated hemoptysis in case 3. The difference was decided by the treatment of underlying PA.

In summary, differential diagnosis of PTE and PAT should be conducted when the lesions of pulmonary parenchymal and artery fit together. Anti-fungal treatment is essential, slowing vascular invasion and avoiding fatal hemoptysis. Anti-coagulation depends on the evaluation of the risk-benefit ratio.

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**Conflicts of interest**

None.

**References**

1. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax 2015;70:270–277. doi: 10.1136/thoraxjnl-2014-206291.
2. Cha SI, Choi KJ, Shin KM, Lim JK, Yoo SS, Lee J, et al. Clinical characteristics of in-situ pulmonary artery thrombosis in Korea. Blood Coagul Fibrinolysis 2015;26:903–907. doi: 10.1097/MBC.0000000000000343.
3. Lopes Bezerra LM, Filler SG. Interactions of Aspergillus fumigatus with endothelial cells: internalization, injury, and stimulation of tissue factor activity. Blood 2004;103:2143–2149. doi: 10.1182/blood-2003-06-2186.
4. Kim SY, Seo JB, Chae EJ, Do KH, Lee JS, Song JW, et al. Filling defect in a pulmonary arterial stump on CT after pneumonectomy: radiologic and clinical significance. AJR Am J Roentgenol 2005;185:985–988. doi: 10.2214/AJR.04.1515.
5. Kirshenbaum JM, Lorell BH, Schoen FJ, Bettmann MA, Thompson GB. Angioinvasive pulmonary aspergillosis: presentation as massive pulmonary saddle embolism in an immunocompromised patient. J Am Coll Cardiol 1985;6:486–489. doi: 10.1016/S0735-1097(85)80191-1.
6. Landonso G, Novari A, Gargantini L, De Cataldo F, Oreste P. Pulmonary and myocardial infarction secondary to arterial occlusion by Aspergillus fumigatus in ANLL. Haematologica 1989;74:503–505.
7. Minhas HS, Jain G, Mangukia C, Goyal M. Pulmonary endarterectomy for saddle pulmonary embolism by Aspergillus fungus in an immunocompetent patient. Indian Heart J 2014;66:339–342. doi: 10.1016/j.ijhj.2014.08.008.
8. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141 (2 Suppl):e419S–e495S. doi: 10.1378/chest.11-2301.

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