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Lethal breath

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Have you even thought that just a breath can kill you? No, we don't, as a healthy individual. However, for a particular group of patients, a breath can kill. That is aspergillosis.

There is such a patient. Mr. X, aged 63, was a chronic smoker and drinker. He had poorly controlled diabetes mellitus, old stroke, hypertension, history of pulmonary tuberculosis in 2013 and chronic hepatitis B. He firstly presented to us in June 2015 with on and off mild hemoptysis. Chest-X ray (CXR) at that time showed right upper zone haziness which was similar to post-TB treatment CXR taken in 2014. Repeated bronchoscopy showed no endo-bronchial lesion and bronchial aspirate showed negative growth of acid fast bacilli. Computed Tomography (CT) thorax done in 2015 showed bronchiectasis with superimposed infective/inflammatory change in right upper and middle lobes. The patient refused further investigation and was happy with transamin. The patient presented to us again in early Jan 2017 for massive hemoptysis requiring intubation, mechanical ventilation and placement of endobronchial blocker. Bronchial artery embolization (BAE) was done to stop bleeding. CXR on admission showed right upper zone and mid-zone opacities. CT thorax showed typical signs of chronic aspergillosis – 'air crescent sign'. Subsequently sputum found A.fumigatus and blood tests for 1-3 beta D glucan and galactomannan were positive. The patient was started voriconazole for chronic pulmonary aspergillosis. In view of having life threatening haemoptysis, he was referred to cardiothoracic surgical unit for consideration of surgical treatment. However, he refused lung resection.

There are several hundred species in Genus Aspergillus but only 40 species can cause human infection (1). The most common one is *A. fumigatus*, followed by *A. flavus*, *A. niger* and A. *terreus.* Although they like aerobic area and carbon rich area, their spores can be everywhere. A normal human being can inhale over hundreds to thousands of fungal spores every day. It will be fine for healthy individual. However, for patients with chronic lung

diseases or cavitary lung diseases, or who are immunocompromised, the sequalae can be very severe or even fatal. That's why we call it lethal breath.

There are acute (invasive), chronic and allergic form of pulmonary aspergillosis. We would focus on the chronic pulmonary aspergillosis (CPA) in this article.

CPA has many subtypes, including chronic necrotizing pulmonary aspergillosis (CNPA) [other names are sub-acute invasive aspergillosis (SAIA) or semi-invasive pulmonary aspergillosis]; chronic cavitary pulmonary aspergillosis (CCPA); chronic fibrosing pulmonary aspergillosis (CFPA); aspergilloma and aspergillus nodule (2,3). The chronic pulmonary aspergillosis is chaotic because there are overlaps among different subtypes and different subtypes are inter-changeable. They can change from one subtype to others when there is a change in patient's immune status, lung condition, or it is just due to disease progression. We call that 'the disease spectrum'.

The patients always have some form of prior or current lung diseases, such as previous treated pulmonary tuberculosis, atypical mycobacterial infection, chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis, sarcoidosis, thoracic surgery, cystic fibrosis, radiation therapy etc. Among them, pulmonary tuberculosis is the most common risk factor. The prevalence of post pulmonary tuberculosis associated CPA can be up to 20-30% in some localities, so you can see that CPA is an underdiagnosed condition (4). One of the reasons is due to the nonspecific symptoms. Thus, when a patient with underlying risk factors presents with persistent chest symptoms and progressively worsening CXR (with or without cavities) but repeated sputum specimens show negative AFB smear and culture, we should suspect CPA.

Chronic necrotizing pulmonary aspergillosis (CNPA) [Other names are sub-acute invasive aspergillosis(SAIA) or (semi-invasive pulmonary aspergillosis)]

For CNPA, patients always have mild degree of immunosuppression (e.g. AIDS, prolonged corticosteroid treatment, DM, alcoholism, chronic liver disease, malnutrition, chronic obstructive lung disease, or connective tissue diseases). It progresses over weeks to months with chronic pulmonary or systemic symptoms. There is local chronic invasion of hyphae into the lung tissue, but little or no angioinvasion. Radiological features are variable including nodules, consolidation, cavitary lung lesion with evidence of para-cavity infiltrate or expansion of cavity size over time. It is more likely to have detectable aspergillus antigen in blood and

isolation of Aspergillus spp. from pulmonary or pleural cavity.

Chronic cavitary pulmonary aspergillosis (CCPA)

For CCPA, it is slowly evolving, with at least 3 months period with chronic pulmonary symptoms or chronic illness or progressive radiological abnormalities. There may have detectable aspergillus IgG antibody in the blood. Patients usually have no or minimal immunocompromised, with one or more underlying pulmonary disorders.

Chronic fibrosing pulmonary aspergillosis (CFPA)

CFPA is often a result from untreated CCPA. There is extensive fibrosis with fibrotic destruction of at least two lobes of lung complicating CCPA, leading to a major loss of lung function. The fibrosis is usually solid in appearance, but large or small cavities with surrounding fibrosis may be seen. One or more aspergillomas may be present.

Aspergilloma

Aspergilloma is a fungal ball containing fungal hyphae and extra-cellular matrix. The most common species is A.fumigatus. Patients are mostly asymptomatic, if do symptomatic, they may have mild hemoptysis, cough, dyspnea and severe hemoptysis can occur. In CXR, there may be a mass in in a pre-existing cavity, which is mobile with air crescent in periphery. Sometimes there can be change in position of the fungal ball between supine and erect position. In CT, air crescent sign presents. There should be no radiological progression over at least 3 months of observation and patient is not immunocompromised.

Aspergillus nodule

Aspergillus nodule is usually an incidental finding on CT scan, which shares a high similarity to malignant lesions, tuberculoma or coccidioidomycosis and other diagnoses. It can only be definitively diagnosed after excision biopsy. Patient should not receive antifungal therapy unless symptomatic.

The diagnosis of chronic cavitary pulmonary aspergillosis (CCPA) requires: (i) 3 months of chronic pulmonary symptoms or chronic illness or progressive radiographic abnormalities, with cavitation, pleural thickening, pericavitary infiltrates, and sometimes a fungal ball; (ii) Aspergillus IgG antibody elevated or other microbiological data; and (iii) no or minimal immunocompromise, usually with one or more underlying pulmonary disorders (5-7). The most sensitive microbiological test is blood for aspergillus specific IgG. Other investigations include serum galactomannan, specimens (esp. broncho-alveolar lavage) for aspergillus culture or polymerase chain reaction (PCR) or antigen test and biopsy (transbronchial,

percutaneous or open-lung) for histological assessment. We may perform imaging such as CXR or CT thorax to look for consolidation, new or expansion of cavities, variable wall thickness, pleural thickening, parenchymal destruction, fibrosis, air-crescent sign for aspergilloma, nodule(s) with spiculated borders.

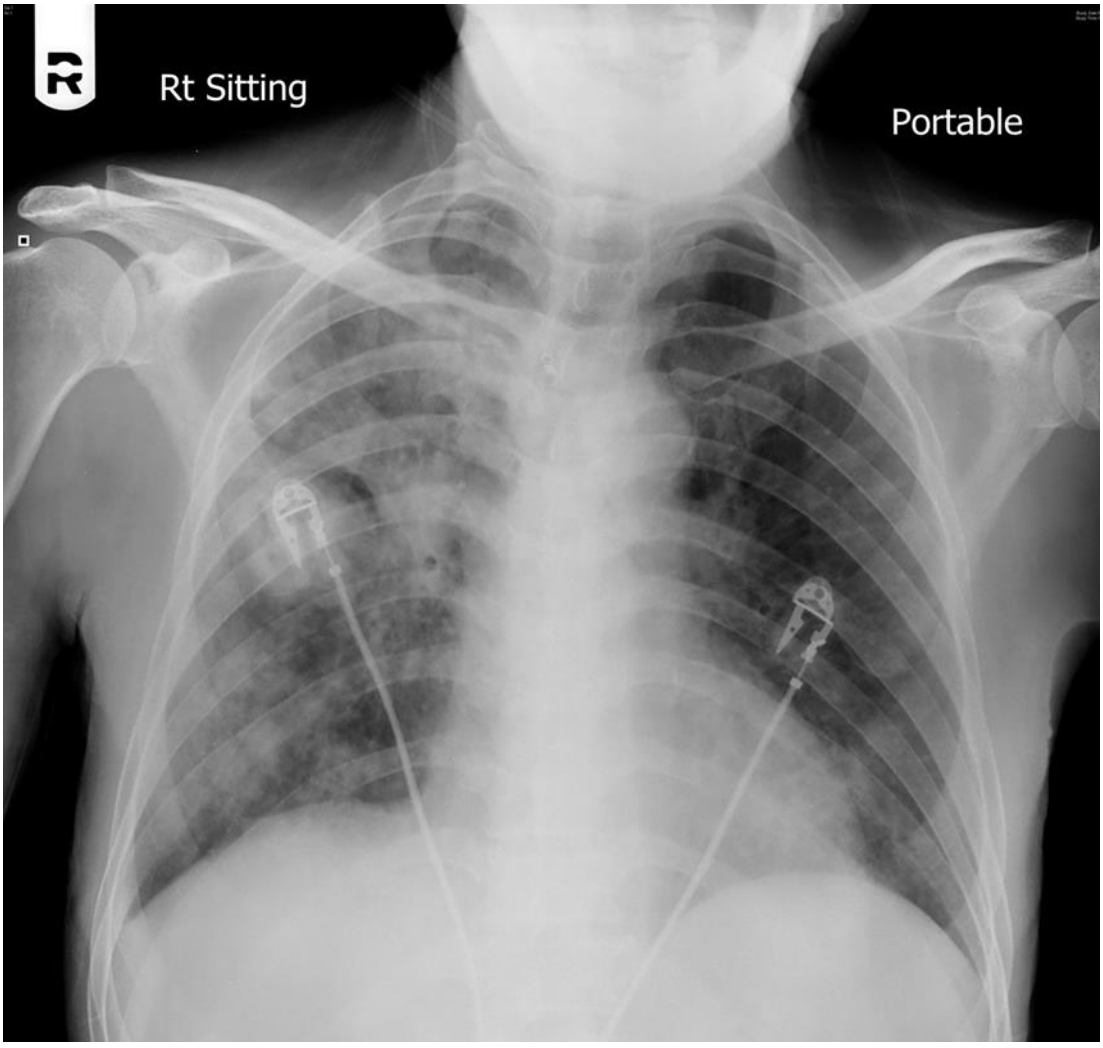
Triazoles with a minimum of 6 months are preferred agents for treatment of CPA. The first line treatment is oral itraconazole or voriconazole, while posaconazole remains as third line treatment. Triazole antifungal agents contribute to various important toxicities and drug–drug interactions that may limit therapy. For example, combined use of voriconazole, posaconazole, isavuconazole, or itraconazole with rifampin/
rifabutin should generally be avoided. In those who fail triazole therapy, develop triazole resistance or are intolerable to triazoles, we may use intravenous echinocandins (e.g. micafungin, caspofungin) or amphotericin B. Although a minimum of 6 months of antifungal therapy is suggested in responding case or stable case, the exact duration depends on the patient's response (clinical, radiological, serological, and microbiological areas). In some CCPA and CFPA patients, even long term anti-fungal treatment with continual monitoring for toxicity and resistance may be needed for stabilization, preventing hemoptysis, reducing further fibrosis, improving quality of life, and control of infection. Haemoptysis may be managed with oral tranexamic acid (for mild cases), BAE (for severe or life-threatening bleeding) or antifungal therapy to prevent recurrence. Patients failing these measures may require surgical resection.

For asymptomatic single aspergilloma without progression over 5-24 months, it is suggested to keep observation. Surgical resection is for symptomatic patient with hemoptysis. BAE is for life saving and bridging to definitive surgery. The recurrent rate of haemoptysis is 30 – 50% over 3 years for BAE alone. Please refer to the summary prepared by our guest speaker Dr Lo, a cardiothoracic surgeon from Queen Elizabeth Hospital, for a more detail discussion on surgical management of chronic aspergillosis.

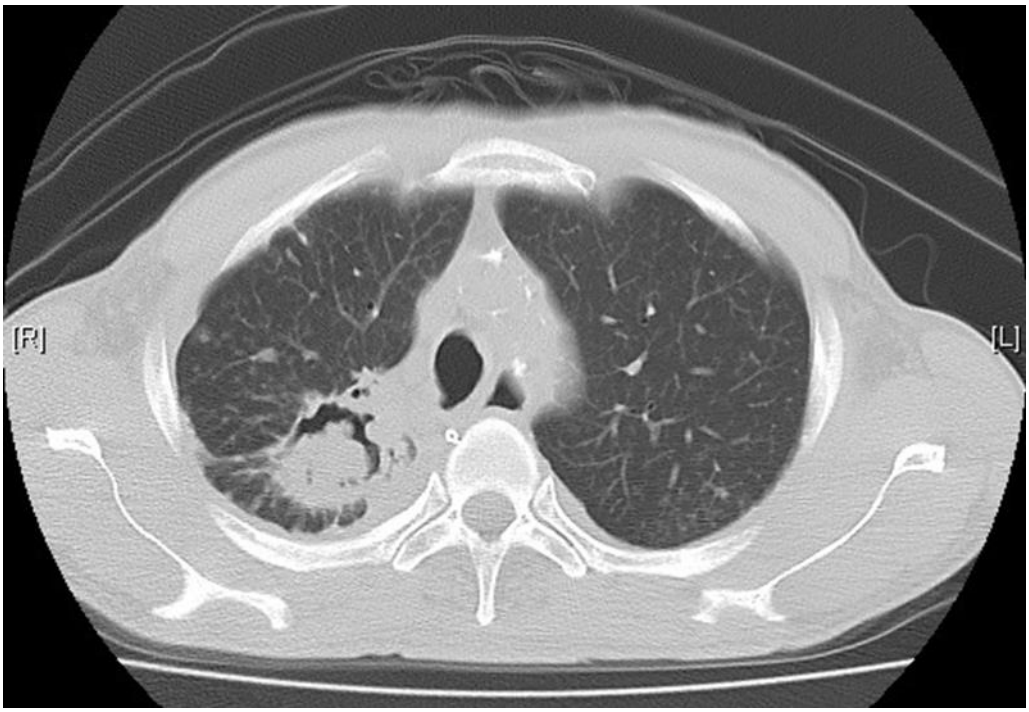
If the patient is symptomatic, or having radiologic progression or a need for concurrent immunosuppression and also unable to undergo surgery, antifungal therapy and/or catheter instillation of antifungal drug may be considered.

In summary, chronic pulmonary aspergillosis mostly occurs in patients with previous tuberculosis. Patients usually present with constitutional symptoms and chest symptoms which are similar to other chronic lung diseases such as bronchiectasis, so it is always underdiagnosed. Therefore, if patients with old

TB or other risk factors have symptoms, progressive radiological changes (e.g. cavities, consolidation, fibrosis) and negative acid-fast bacilli smear and culture, it should arise the suspicion of aspergillosis. Serum aspergillus IgG is the most sensitive microbiological test to pick up this infection. Prolonged course of triazoles (>/= 6 months) is usually needed and some patients may require lifelong treatment. We should be aware of the significant drug-drug interaction and the drug toxicity. Surgical resection is an option for selected patients. Careful risk assessment prior to surgery is required.



CXR showing “air crescent” sign



CT thorax showing “air crescent” sign

Surgical management of chronic aspergillosis

Surgery is reserved for symptomatic chronic aspergillosis while surgery for asymptomatic aspergillosis is controversial. Although symptoms range from productive cough to life-threatening hemoptysis, hemoptysis is the most common reported symptoms in surgical series (8).

The prime importance in the management of acute massive hemoptysis secondary to chronic aspergillosis is to maintain airway patency and avoid soiling uninvolved lung. These are achieved by double lumen endotracheal intubation or endobronchial blocker because site of bleeding can usually be identified on chest X-ray or CT scan. Flexible or rigid bronchoscopy is reserved for removal of blood clot in case of difficult ventilation or instillation of medications. Bronchial artery embolization should be arranged once patients are stabilized because surgery is now no longer considered as first line treatment especially in emergency setting (9,10). Immediate success rate in control of hemoptysis after bronchial artery embolization ranged from 80-99% (11). In acute massive hemoptysis, emergency surgery is difficult and carries higher risk than elective surgery because of difficulty in single lung ventilation during surgery and soiled uninvolved lung. In addition, both mortality and morbidity after surgery are high when compared with bronchial artery embolization. Under these circumstances surgery is usually deferred to allow time for patients to recover from acute insult, and for accurate assessment of their pulmonary function.

The source of bleeding in aspergillosis comes from systematic arteries rather than pulmonary artery. In the presence of chronic inflammation as in aspergillosis and tuberculosis, constriction of pulmonary artery leads to release of inflammatory markers (12). Neovascularization and hypertrophy of bronchial artery happen. Usually less than 1% pulmonary arterial supply come from systemic arteries but in chronic inflammation 5% or more come from systemic arteries. However thin-walled pulmonary vasculature cannot stand with high systematic blood pressure and may rupture easily. Recurrent rubbing of exposed bronchial arteries by fungal ball and coexisting bacterial infection may aggravate the condition.

Bronchial artery embolization may be a temporarily measure and sometimes is regarded as definitive treatment. There are four different bronchial artery anatomy with variation in numbers of bronchial arteries on each side and origins (11). In acute management, sometimes only one bronchial artery is embolized due to unstable hemodynamic condition, maximal dose of contrast medium given, and unfavourable anatomy. In addition, systemic arterial supply to the lung may come from intercostal artery, branches from subclavian artery, internal mammary artery and pericardiophrenic artery. Escaped systematic arteries may contribute to recurrence after bronchial artery embolization. Rarely recannulation of previous embolized artery may happen. About 10-30% of patients have recurrence that may require second or more embolization procedures (11). Liaison with radiologist is important to look for any residual arteries. There is no consensus about timing for second or further embolization if needs. Some prefer to have next session once patient recover from the first insult because life-threatening hemoptysis may occur at any time. But some prefer when second episode occurs.

Nowadays surgery is reserved for those who failed bronchial artery embolization, and have symptoms other than hemoptysis. Lobectomy and occasionally pneumonectomy through open thoracotomy approach require. Minimal invasive surgery and sub-lobar resection are often not possible due to complexities from fused pleural space, inflamed frozen hilum, and nutritionally depleted patients. Although mortality after surgery for chronic aspergillosis improves over decades, morbidity is still high compared with surgery for lung cancer in same extent (13). Cavernostomy is indicated for those who are unfit for pulmonary resection. The goal of cavernostomy is to remove the culprit lesion (aspergilloma) by opening up the cavity and plication of communicating bronchioles without any pulmonary resection, together with thoarcoplasty or myoplasty to obliterate the cavity.

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