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Case Report **Open Access**

Clinical neglect of aspergillosis in pulmonary tuberculosis co-infection: a case report of avoidable mortality in a resource-constrained setting

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Abstract:

Background: Pulmonary aspergillosis (PA) is common among patients with tuberculosis (TB). With both infections presenting with similar clinical and radiologic features, diagnosis of PA is often made too late or missed completely due to lack of clinical suspicion and poor diagnostic laboratory capacity for mycotic infections prevalent in our settings. We present a case of preventable mortality caused by delayed diagnosis and treatment of PA in a patient with pulmonary TB (PTB).
Case presentation: A 13-year-old female was diagnosed and treated for PTB, having received anti-TB regimen for 8 months in a mission hospital from where she was referred due to worsening cough, chest pain and progressive breathlessness. The patient was re-assessed and investigated, with GeneXpert detecting *Mycobacterium tuberculosis*, susceptible to rifampicin. Diagnosis of pulmonary tuberculosis complicated by right pneumothorax was made indicating an emergency thoracotomy and chest tube insertion and continuation of the first line anti-TB regimen. At about 2 weeks into admission, patients had features of superimposed acute bacterial sepsis with fever becoming high grade, marked neutrophilia with toxic granulation and elevated sepsis biomarker, and this necessitated empiric antibiotic treatment with parenteral meropenem and vancomycin. However, the patient only had mild clinical improvement following which there was progressively worsening respiratory symptoms and massive haemoptysis. Result of sputum fungal study was available on admission day 20 and revealed a growth of *Aspergillus flavus*. Treatment with intravenous voriconazole was however commenced rather late when the fungal respiratory disease could no longer be remedied. The patient died on admission day 23.
Conclusion: Diagnosis of PA in patients with background TB is often made too late to guarantee timely and effective antifungal treatment with negative consequences on patients' outcomes. Improving clinical and laboratory capacities is essential to reducing mortality from PA in healthcare facilities.

Keywords: pulmonary aspergillosis; tuberculosis; co-infection; voriconazole

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Négligence clinique de l'aspergillose dans la co-infection tuberculeuse pulmonaire: à propos d'un cas de mortalité évitable dans un contexte de ressources limitées

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Résumé:

Contexte: L'aspergillose pulmonaire (AP) est fréquente chez les patients atteints de tuberculose (TB). Les deux infections présentant des caractéristiques cliniques et radiologiques similaires, le diagnostic d'AP est souvent posé trop tard ou complètement manqué en raison d'un manque de suspicion clinique et d'une faible capacité de diagnostic en laboratoire pour les infections mycotiques prévalentes dans nos contextes. Nous présentons un cas de mortalité évitable causée par un diagnostic et un traitement tardifs de l'AP chez un patient atteint de tuberculose pulmonaire (TBP).
Présentation de cas: Une femme de 13 ans a été diagnostiquée et traitée pour une TBP, après avoir reçu un traitement antituberculeux pendant 8 mois dans un hôpital de mission d'où elle a été référée en raison d'une aggravation de la toux, de douleurs thoraciques et d'un essoufflement progressif. Le patient a été réévalué et investigué, GeneXpert détectant *Mycobacterium tuberculosis*, sensible à la rifampicine. Le diagnostic de tuberculose pulmonaire compliquée d'un pneumothorax droit a été posé indiquant une thoracotomie d'urgence et l'insertion d'un drain thoracique et la poursuite du traitement antituberculeux de première intention. À environ 2 semaines après l'admission, les patients présentaient des caractéristiques de septicémie bactérienne aiguë superposée avec une fièvre devenant de haut grade, une neutrophilie marquée avec une granulation toxique et un biomarqueur de septicémie élevé, ce qui a nécessité un traitement antibiotique empirique avec du méropénème parentéral et de la vancomycine. Cependant, le patient n'a présenté qu'une légère amélioration clinique, suivie d'une aggravation progressive des symptômes respiratoires et d'une hémoptysie massive. Le résultat de l'étude fongique des expectorations était disponible au jour 20 de l'admission et a révélé une croissance d'*Aspergillus flavus*. Le traitement par voriconazole par voie intraveineuse a cependant été commencé assez tardivement lorsque la maladie respiratoire fongique ne pouvait plus être soignée. Le patient est décédé le jour 23 de l'admission.
Conclusion: Le diagnostic d'AP chez les patients atteints de tuberculose de fond est souvent posé trop tard pour garantir un traitement antifongique rapide et efficace avec des conséquences négatives sur les résultats des patients. L'amélioration des capacités cliniques et de laboratoire est essentielle pour réduire la mortalité due à l'AP dans les établissements de santé.

Mots clés: aspergillose pulmonaire; tuberculose; co-infection; voriconazole

Introduction:

Aspergillus is a saprophytic ubiquitous mould, acquired and spread by inhalation of aerosolised spores with conidia invading and destroying host tissues. It causes a spectrum of pulmonary infections which is principally determined by virulence of the pathogen, underlying lung disease and host immunity (1). As an opportunistic pathogen, it commonly affects immunocompromised patients or immunocompetent patients with underlying respiratory tract diseases (2). Patients with background pulmonary tuberculosis (PTB) are also particularly prone to pulmonary aspergillosis (PA) resulting from associated generalised debility from impaired immunity and reduced macrophage functions (3). PA commonly complicates but often co-infects with tuberculosis (TB) especially in low socioeconomic environment with inherent insufficient capacities for diagnosis and treatment (4,5).

Global epidemiological data revealed that of the approximately 3 million people suffering from chronic pulmonary aspergillosis (CPA), 1.2 million cases are associated with PTB (2). Annual prevalence of co-infection varies but is pronounced globally, estimated at 145,372 in South-East Asia and 98,551 in Africa (6). PA lacks definite pathognomonic clinical syndrome and co-infection with PTB often reduces tendencies for detection because of similarities in clinical features especially in settings where diagnosis of fungal pathogens is still rudimentary (7). About 2 million new cases of non-bacteriologically diagnosed PTB were reported by WHO in 2015 and a proportion of these patients probably had undiagnosed chronic pulmonary aspergillosis (CPA) (8). Five-year estimated prevalence rates of chronic PA among patients with PTB vary globally ranging from 0.4 to 51 per 100,000 population; developing countries are more affected with Nigeria having a high rate of 42.9 per 100,000 population (6).

Information about fungal infections is sparse in Africa; available data from 15 of 57 African countries revealed that estimated 1.7 million people suffer from serious and life-threatening fungal diseases including PA with key factors influencing management outcomes being availability of appropriate diagnosis and promptness of treatment. This duo has been greatly challenged in Africa and other resource-limited countries which do not only have high burden of infections by these opportunistic fungi but also basically deficient in advanced fungal diagnostics and mycologic experts (9,10). Missed clinical diagnoses of PA in patients with background PTB coupled with unavailability of rapid, sensitive and reliable laboratory capacity for fungal infections is a great challenge to early commencement of appropriate antifungal drug therapy, access to which is rather poor in Nigeria and most of other countries in sub-Saharan Africa, and all

these have led to high mortality (11-13). We report a case of avoidable mortality resulting from late diagnosis of PA in a patient with TB co-infection.

Case presentation:

A 13-year-old female referred from a faith-based specialist hospital where she had presented with a low-grade fever and chronic productive cough. Patient had positive sputum GeneXpert (Xpert 2110 polymerase chain reaction) results as well as chest radiographic features of PTB for which she had been on treatment for 8 months at the referral hospital. The patient was commenced on another course of anti-tuberculosis drugs (still first line regimen) having completed an initial 6-month course with no improvements in clinical symptoms and signs with persistence of radiologic features of PTB.

Patient was referred to the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria on the 3rd January 2020 as a result of progressively worsening cough associated with dull aching non radiating chest pain, and difficulty with breathing. Initial examination revealed chronically ill-looking patient, febrile (temperature of 37.9^0C), mildly pale, stage III finger clubbing, tachypnoeic (respiratory rate of 84 cycles per minute), in respiratory distress with intercostal and sub-costal recessions and pectus escavatum, reduced chest expansion in the left hemithorax. Percussion notes were dull in the left middle and lower lung zones but hyper-resonant in the right lung fields with increased tactile fremitus and vocal resonance in the left middle and lower lung zones, reduced air entry in the right lung zones as well as left middle and lower lung zones, There were widespread bilateral crepitations and oxygen saturation of 78% (at room air), The patient was tachycardic (pulse rate of 148 beats per minute), blood pressure was normal and jugular venous pressure was not raised, apex beat was however displaced to the 6th left intercostal space in the anterior axillary line (non-heaving, non-tapping) and heart sounds were normal with no murmur. There was mild tender hepatomegaly (liver was 4 centimetres below the right costal margin).

Complete blood count showed packed cell volume of 33%, white cell count of 9200/mm^3 with neutrophil and lymphocyte proportion of 54% and 46% respectively, and platelet count of 316,000/mm^3. Chest radiograph showed features of PTB including cavitatory lesions within both upper lung zones with adjacent reticular and patchy opacities (Fig. 1). Sputum by GeneXpert detected *Mycobacterium tuberculosis*, not rifampicin-resistant. Erythrocyte sedimentation rate (ESR) was elevated at 117mm/hour (Westergreen method). Further investigations revealed negative results for retroviral screening, hepatitis B surface antigen and anti-hepatitis C antibody, and blood culture yielded no growth of bacteria.

Abdominal and chest ultrasonography revealed no abnormality. Plasma blood glucose, serum electrolytes, and renal and liver function tests gave parameter values that were within normal range. In addition to features of TB, the patient also had radiographic features of right sided pneumothorax and was consequently placed on intranasal oxygen (2-3 litres per minute) with first line anti-tuberculosis drugs. She immediately had right-sided thoracotomy and chest tube insertion with post intubation chest radiograph showing satisfactory lung re-expansion, and subsequently had right pleurodesis post extubation.

The clinical condition mildly improved until 2 weeks into admission when patient developed high-grade continuous fever with worsening cough, productive of copious blood-stained sputum and an associated worsening respiratory distress. A new set of laboratory investigations ordered at this time included another set of blood culture which yielded no bacterial growth, sputum bacteriological culture which yielded no growth of pathogen, packed cell volume of 35%, leukocytosis (total white cell count of 21,600/mm^3) with neutrophilia (neutrophil count of 19,872/mm^3 with toxic granulations) and normal platelet count (335,000/mm^3), and serum procalcitonin level >10 ng/ml (confirming bacterial sepsis). Additional diagnosis of bacterial sepsis was made and the antibiotic treatment was escalated to intravenous meropenem and vancomycin.

Twenty days into admission, result of sputum fungal study revealed fungal hyphae on direct microscopy (Fig. 2) and *Aspergillus flavus* on culture (Figs 3 and 4). A new diagnosis of pulmonary aspergillosis (possibly chronic pulmonary aspergillosis) was made necessitating request for computerized tomographic (CT) scan of the chest and commencement of intravenous voriconazole. At that time, the patient's clinical conditions had deteriorated, with cough and respiratory distress becoming very severe, and the patient had haemoptysis lasting for about 2 hours. The clinical condition continued to take a turn for the worse despite aggressive resuscitation. There was cessation of breathing and the patient was confirmed dead on admission day 23.

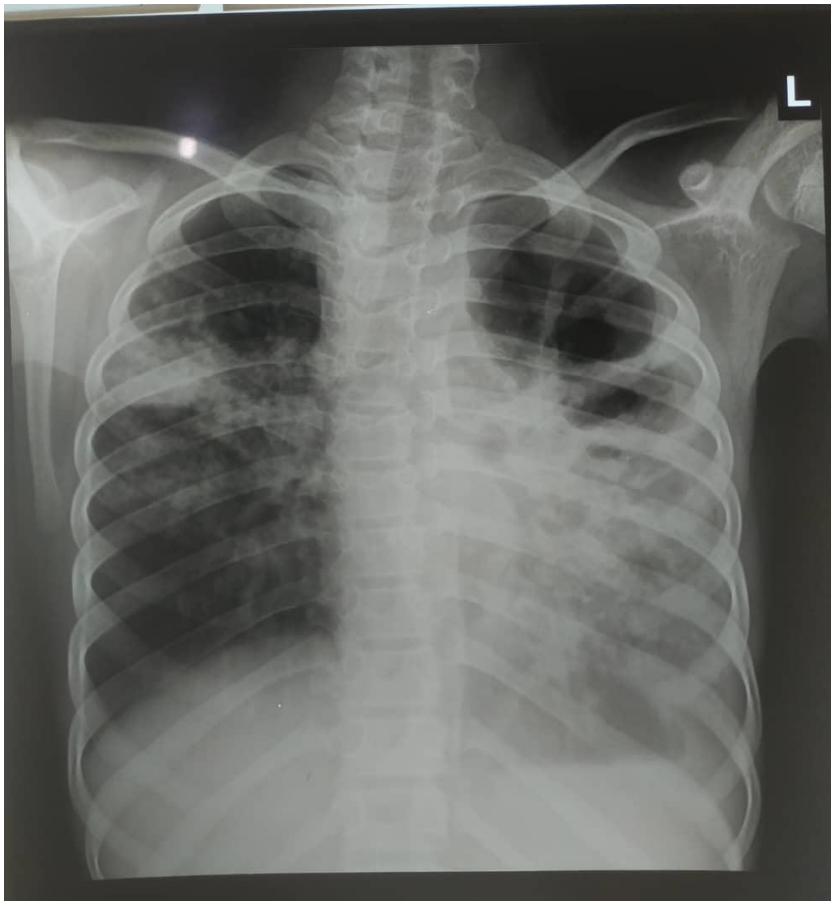

Fig. 1: Chest radiograph showing cavitatory lesions within both upper lung zones with adjacent reticular and patchy opacities It also shows homogeneous opacification of the left middle and lower lung zones with obliteration of the left cardiac silhouette, diaphragmatic outline and costophrenic angle in keeping with pleural effusion with ipsilateral mediastinal shift.

Fig. 2: Direct microscopy (wet mount) with lactophenol cotton blue stain showing septate fungal hyphae

Fig 3: Darkish green cottony colonies of *Aspergillus flavus* on Saboraoud dextrose agar

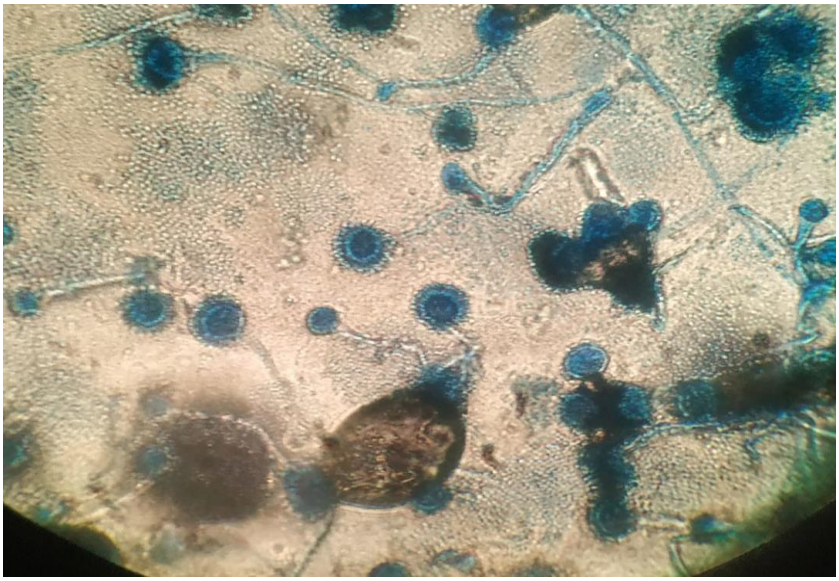

Fig 4: Lactophenol cotton blue preparation of colony showing microscopic morphology of *Aspergillus flavus* with conidia heads which are radiate and split to form loose columns, biseriate but some heads have phialides borne directly on the vesicles. Conidiophores are hyaline and coarsely roughened and more noticeable near the vesicles. Conidia are globose and conspicuously echinulated. Note that each metula covers three-quarter of circumference (25)

Discussion:

We report a case of PA co-existing with rifampicin-susceptible PTB in a 13-year-old female who initially presented in a health-care facility with low grade fever and productive cough, confirmed to be PTB by positive GeneXpert assay on sputum sample. She had first line anti-tuberculous drugs for six months without improvement in the presenting symptoms. A repeat sputum examination by GeneXpert was positive for rifampicin susceptible *Mycobacterium tuberculosis* that necessitated commencement of another course of first line anti-tuberculous drugs. Patient was referred to our facility after two months into the second cycle of anti-tuberculosis drugs when there was worsening clinical condition due to the primary chest infection which was complicated by right sided pneumothorax. We made a diagnosis of co-infection of PTB and PA 20 days into admission in our facility, late enough for the patient's clinical condition to have become worse with marked respiratory distress and haemoptysis. For the patient, presence of pulmonary cavitatory TB lesion with persistence of symptoms of chronic lung infection for many weeks and positive sputum culture for *Aspergillus*, coupled with absence of pronounced angio-invasive symptoms (i. e haemoptysis lasing for few hours) suggests a possibility of CPA (14).

Co-existing PTB and pulmonary fungal infections is common yet usually not looked for in patients (5). The burden of co-infection is substantial particularly in low-resourced countries. According to a systematic review and meta-analysis of studies in Asia, prevalence of co-infections varied between 12.3-68.8% (combined prevalence of 17.4%) with *Aspergillus* being among the major fungal isolates and *Candida* the most predominant (15). A separate report from Africa showed that pooled prevalence of *Aspergillus* co-infection among patients with PTB was 17.7% with individual country rates varying from 5.2% in Kenya, to 24% in Egypt and 25.4% in Cameroun. According to the report, co-infection occurs at all ages but particularly higher above 40 years, and cases in those above age 50 are largely due to recurrent TB, immunosuppression and prolong anti-tuberculosis therapy in a background of active PTB (16). A more recent multicentre study gave an overall prevalence of aspergillosis to be 8.7% among TB cases in Nigeria. It further revealed that PA is a neglected disease found among both HIV positive and negative patients, and among TB smear negative individuals (17). Neglect of PA among TB patients is also underscored in a French study in which 35.7% (50/140) of cases of TB had concomitant positive culture for *Aspergillus* among which only 6% received treatment for PA (18).

In sub-Saharan Africa, the burden of TB is enormous, however, clinical and radiological criteria for diagnosis of other chronic chest infections such as chronic PA are non-discriminatory and often identical with those of PTB. Diagnosis of PA is mostly challenging and often made late especially in settings of low index of suspicion like in this case precluding timely laboratory testing and appropriate antifungal treatment. This problem is made worse by decoy from clinical symptoms of the co-infecting chronic lung infection like

TB. Defining cases of PA therefore requires specific testing for *Aspergillus* (19). However, it is often impossible to identify pulmonary fungal infection objectively without a good clinical awareness and laboratory diagnostic capacity which are not optimal in our environment (9). Recent revolution in non-culture diagnostic techniques across the world is yet to be popular in African countries and there is near total reliance on the less efficient, laborious and time-consuming microscopy and culture methods with unfavourable consequences on patient outcomes (9).

Serologic testing for PA is simple but are still largely unavailable in our hospitals, and this is responsible for under-diagnosis of chronic PA both at initial presentation and during treatment and follow-up for TB (6,15). Serum galactomannan assay has been widely used for rapid detection of *Aspergillus* in body fluid, especially in bronchioalveolar lavage to diagnose CPA with high sensitivity and specificity (20). In addition, specific radiologic imaging including CT scan and magnetic resonance imaging (MRI) is essential for precise diagnosis and determining the spectrum of PA, however these are not accessible to patients in the low- and middle-income countries (21). Furthermore, shortage of experts in mycology is also a major impediment to prompt review and diagnosis of cases (10). All these setbacks make Africa not to have in place a robust network for providing the required platform for increasing consciousness on mycological infections (9).

PA is an under-rated and often neglected disease of global health impact (2), especially in more chronic forms, it is associated with slow but progressive lung destruction leading to increased morbidity and mortality (22). Apart from failure to make definitive diagnosis early enough to really be useful in patients management, promptness of determination of extent of tissue invasion by *Aspergillus* is another major problem in patients. Performing invasive procedures to obtain biopsy specimens for microbiological and histological examination is a difficult decision in majority of patients who have often been overwhelmed by the co-existing diseases and whose clinical conditions are too critical to cope with such procedures. For this patient, diagnostic biopsy was requested but her clinical condition was not good enough for the procedure to be carried out. Lateness of diagnosis of PA has been reportedly linked to unprecedented mortalities; even upon treatment, short-term mortality of chronic PA could be as high as 33% (6). It is worthy of note that lateness in the definitive diagnosis and treatment of the pulmonary fungal infection in the index case gave room for major complications such as pneumothorax with severe respiratory distress, lung destruction with cavitations and haemoptysis which were responsible for the poor treatment outcome. A review of some recent publications highlighted pulmonary factors such as shortness of breath, cavitary lung disease, and pleural involvement as predictors of mortality from chronic PA (2). In another systematic review of 50 studies involving 1941 patients, an overall PA case fatality rate of 58% was reported a proportion of which were due to pulmonary complications from PTB co-infection (23).

In this case, persistence of clinical features attributable to PTB coupled with a repeat GeneXpert positivity gave an impression of persistent infection that further obscured the possibility of pulmonary fungal infection in the patient. Although patients with persistent infection have repeat sputum nucleic acid amplification testing coming out positive, it is well known that the sputum test can remain positive even after successful treatment of PTB especially when there are lung cavities, and this is attributable to presence of residual mycobacterium nucleic acid as well as non-viable bacilli in the lower respiratory tract (24).

Conclusion:

PA is common among patients with TB but it is often missed due to poor clinical awareness and suboptimal laboratory capacity for diagnosing mycologic infections. The consequences of these deficiencies are much more pronounced in our environment which is already faced with problems of access to highly sensitive and specific radiologic imaging. There is therefore a crucial need for improved human and infrastructural capacities for diagnosing PA in our environment to enhance timely interventions and good outcomes in patients.

Authors' contributions:

ATA, TOO, SSE, AOI, EOI, AAA, ACA and AOA conceptualised and conducted the microbiological analyses; ATA, TOO, SEE, AOI, EOI, AAA, OAO, ACA, POO and AOA managed the patient; ATA, TOO and AOA prepared initial draft; ATA, TOO and AOA revised the manuscript and prepare the final draft.

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Consent for publication:

Written consent to publish this information was obtained from the patient.

Conflict of interest:

No conflict of interest is declared.

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