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Cryptococcal Pneumonia in an Elderly Patient Without Classical Immunosuppression

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Abstract

Cryptococcosis is an invasive fungal infection caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. Although classically associated with advanced immunosuppression, it is increasingly reported in people without these risk factors. Pulmonary disease can closely mimic lung cancer, so it is easily mistaken for malignancy, and the diagnosis can be missed in patients who lack classical risk factors.

We report an 83-year-old man with type 2 diabetes mellitus and a previous ICU admission requiring dialysis, but with no HIV infection, transplantation, or immunosuppressive treatment, who presented with a three-month history of lethargy and non-productive cough. Imaging showed a perifissural nodule with consolidation and a small left pleural effusion, and the radiologist was suspicious for malignancy. Pleural fluid cytology showed no malignant cells. CT-guided lung biopsy showed intracellular organisms with lymphoplasmacytic inflammation and foreign body giant cells, staining positive on periodic acid-Schiff (PAS) and Grocott stains. Bronchoalveolar lavage was positive for cryptococcal antigen; culture/PCR identified *Cryptococcus neoformans*, and serum cryptococcal antigen titre was low positive (1:16). Lumbar puncture was not performed, so central nervous system involvement was not formally excluded. After intolerance of fluconazole, he completed six months of itraconazole, with symptomatic and radiological resolution on chest X-ray.

This case is a reminder that a lung nodule with pleural effusion that looks like cancer may be fungal, including in older patients without classical immunosuppression, and that diabetes and a previous critical illness may be relevant risk factors. It shows how tissue histology with special stains, lavage antigen, serum antigen, and culture/PCR together can establish the diagnosis, and that a patient with mild pulmonary disease and a low antigen titre recovered on oral therapy. It also illustrates a decision that readers should consider the omission of lumbar puncture, which guidelines recommend, carefully. Recognising this presentation may avoid delay, further invasive investigation, and unrecognised dissemination.

Categories: Pulmonology, Epidemiology/Public Health, Infectious Disease
Keywords: community-acquired pneumonia (cap), fungal pneumonia, immuno-competent host, infectious diseases epidemiology, pulmonary cryptococcal infection

Introduction

Cryptococcosis is an invasive fungal infection caused predominantly by *Cryptococcus neoformans* and *Cryptococcus gattii*. It has traditionally been regarded as an opportunistic infection of people with advanced immunosuppression, particularly those with HIV/AIDS or solid organ transplants, but it is increasingly recognised in people without these classical risk factors [1,2]. Infection is acquired by inhalation of fungal spores, so the lungs are often the first site involved. Radiological appearances range from diffuse infiltrates to solitary nodules that can closely mimic malignancy [3,4].

Diagnosis can be difficult, particularly when classical risk factors are absent, because clinical and imaging features are often nonspecific [2]. A missed or delayed diagnosis may lead to unnecessary invasive investigations and to dissemination, most often to the central nervous system [5].

We report an 83-year-old man without classical immunosuppression (HIV-negative, non-transplant) but with type 2 diabetes and a previous ICU admission requiring dialysis. He presented with a lung nodule and pleural effusion that were suspicious for malignancy on CT. Pulmonary cryptococcosis was diagnosed by CT-guided biopsy, bronchoalveolar lavage, and culture/PCR, and he recovered on oral antifungal therapy. We describe his work-up and its limitations, including that lumbar puncture was not performed, and discuss when fungal infection should be considered in patients with atypical lung lesions.

Case Presentation

Our patient, an 83-year-old male, presented with a three-month history of lethargy and non-productive cough but otherwise felt well and had no shortness of breath. He had no haemoptysis, weight loss, fevers, or

night sweats. Physical examination was unremarkable with clear heart and lung sounds. This prompted a chest X-ray from his GP (Figure 1), and subsequent referral for a suspicious-looking nodule in his left lower lung zone to investigate for malignancy.

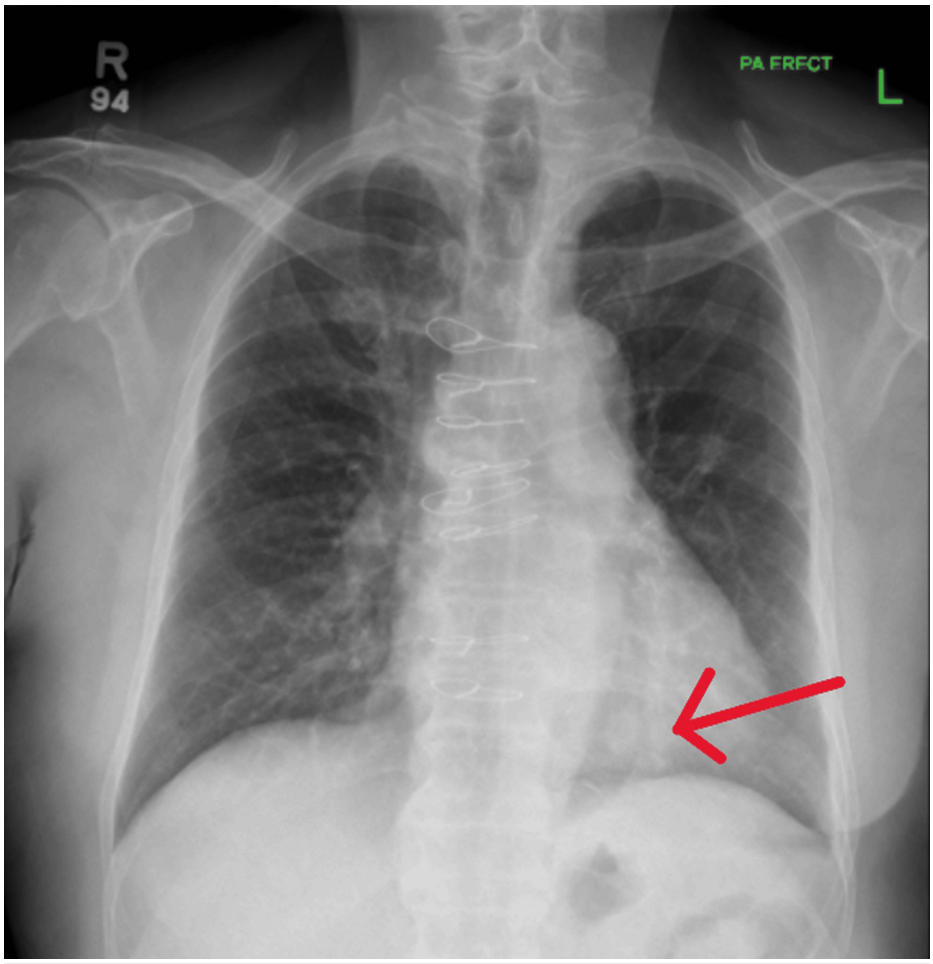


FIGURE 1: Initial chest X-ray

Posteroanterior erect chest X-ray at presentation, requested by the patient's GP. The arrow indicates a nodular opacity in the left lower zone. There is no other focal abnormality.

His past medical history included type 2 diabetes mellitus (HbA1C 50mmol/mol), cataracts, and a coronary artery bypass graft (CABG) procedure performed three years prior, complicated by a postoperative ICU admission and temporary dialysis. He had no previous history of HIV, malignancy, or previous transplantation, and no known bird contact. He has no known allergies, was an ex-smoker but stopped smoking 50 years ago, does not drink alcohol and previously worked as a builder. He emigrated from Myanmar to the UK in 1995 and lives with his son but reported frequent return visits to Myanmar, where he mainly resided in urban areas near the China border. His last visit was in 2018, when he stayed in Myanmar for two to three months, and he denied any known tuberculosis (TB) exposure or history, although TB prevalence is high in that region.

Initial blood work demonstrated mild anaemia and raised HbA1c but was otherwise unremarkable, with normal inflammatory markers, as well as negative HIV serology (Table 1). CT thorax revealed a left pleural reaction with a small effusion, atelectasis and consolidation and a perifissural nodule within the same lobe (Figures 2, 3). There were post-sternotomy changes and no aggressive bone lesion. The radiologist considered an infective or inflammatory process (including TB pleuritis) but also suspected malignancy (provisional staging Tx N0 M1a), and recommended pleural aspiration or biopsy. For chronology, his symptoms began at the end of April, and a chest X-ray requested by his GP in June showed a left lower zone nodule. CT showed a left pleural reaction with a perifissural nodule, and CT-guided biopsy histology, reported later that month, showed intracellular yeast forms. Both of these investigations were performed within a two-week wait period from reporting of the chest X-ray due to suspicion of malignancy.

Investigation	Result	Reference range	Timing
Blood			
Haemoglobin (Hb)	12.2 g/dL (mildly low)	13.0–17.0 g/dL	Presentation
White cell count	9.4 x10⁹/L	4.0–11.0 x10⁹/L	Presentation
Eosinophil count	Normal (no eosinophilia)	0.0–0.4 x10⁹/L	Presentation
C-reactive protein (CRP)	2 mg/L	<5 mg/L	Presentation
Glycated haemoglobin (HbA1c)	50 mmol/mol	<42 mmol/mol (non-diabetic)	Presentation
Estimated glomerular filtration rate (eGFR)	84 mL/min/1.73 m²	>90 mL/min/1.73 m²	Presentation
HIV serology (fourth-generation antigen/antibody)	Negative	Negative	Presentation
Serum cryptococcal antigen (CrAg) titre	1:16 (low positive)	No antigen detected	Pre-treatment
Pleural fluid (20 mL, clear, blood-stained)			
Cytology	Paucicellular; slightly increased lymphocytes, occasional neutrophils; no malignant cells	No malignant cells	Diagnostic work-up
Microscopy and culture (direct and enrichment)	No organisms seen; no bacterial growth	No growth	Diagnostic work-up
Bronchoalveolar lavage (BAL)			
Cryptococcal antigen	Positive	Negative	Diagnostic work-up
Fungal culture/PCR	*Cryptococcus neoformans* isolated	No growth	Diagnostic work-up
Tuberculosis testing	Negative (by AFB smear + culture/PCR)	Negative	Diagnostic work-up
Lung biopsy (CT-guided)			
Histology and special stains	Intracellular yeast forms, PAS- and Grocott-positive, with narrow-based budding; Ziehl-Neelsen-negative; no malignancy	No organisms	Diagnostic work-up

TABLE 1: Summary of laboratory investigations carried out (all taken before antifungal treatment)

PCR - polymerase chain reaction; AFB - acid-fast bacilli; PAS - periodic acid-Schiff

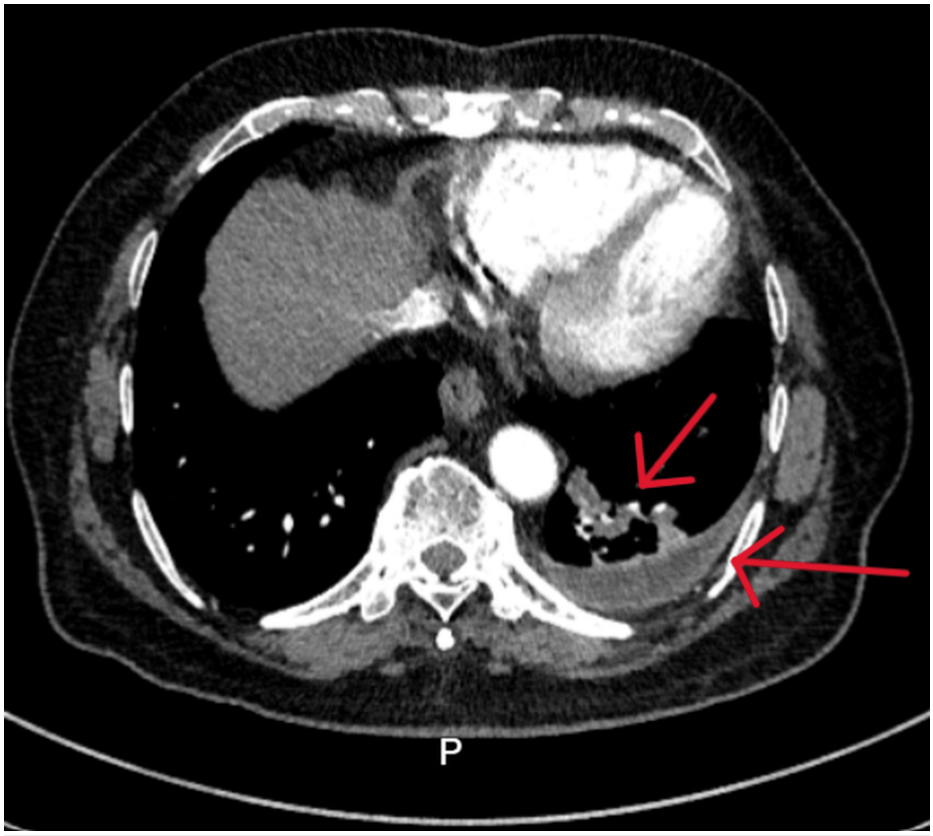


FIGURE 2: Axial contrast-enhanced CT thorax, soft-tissue window

The upper arrow shows an area of consolidation with some internal air-containing spaces in the left lower lobe. The lower arrow shows an associated left pleural effusion with adjacent atelectasis.

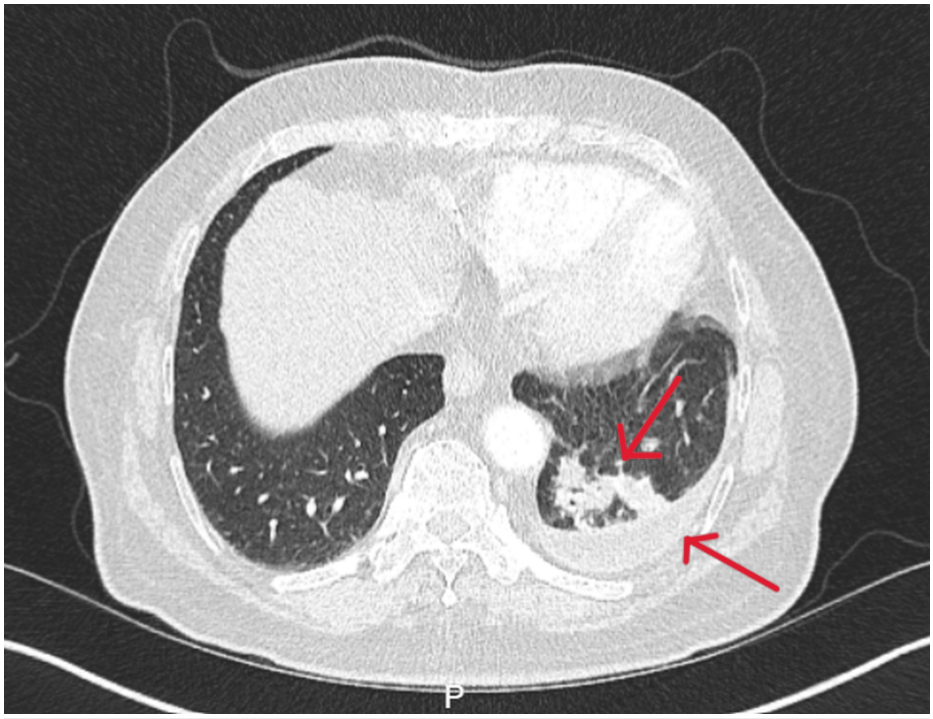


FIGURE 3: Axial CT thorax, lung window

The upper arrow shows the patchy, irregular left lower lobe opacity with internal air lucencies. The lower arrow shows the adjacent left pleural effusion. The right lung is clear.

Pleural fluid analysis demonstrated 20 mL of clear, blood-stained fluid. Cytological examination revealed a paucicellular sample with slightly increased lymphocytes and occasional neutrophils. No malignant cells were seen. No organisms were identified on microscopy, and both direct and enrichment cultures demonstrated no bacterial growth. CT-guided core biopsy of the left lower lobe lesion showed distorted lung parenchyma with loose fibrosis, lymphoplasmacytic inflammation and foreign body giant cells. Within the giant cells and intercellular spaces were rounded, refractile organisms of variable size, about the size of a red blood cell or slightly larger, many with a central hyperchromatic nucleus-like structure (Figure *4*). They stained with PAS and Grocott (Figures *5*, *6*) (some with narrow-based budding) and partly with Masson-Fontana, and were negative on Giemsa, Ziehl-Neelsen and Wade-Fite. Direct microscopy of the Grocott slide showed large numbers of budding yeast cells. The histological differential was cryptococcosis, histoplasmosis and pneumocystis, with blastomycosis also considered. No malignancy was seen.

Hematoxylin & Eosin stain x 100 magnification

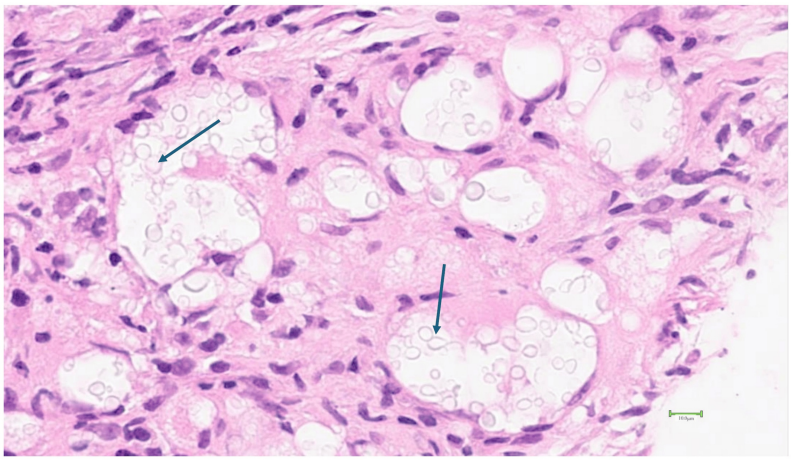


FIGURE 4: Haematoxylin and eosin stain

×100 magnification (scale bar 10 µm). Macrophages with expanded, vacuolated cytoplasm contain numerous small, round, pale, yeast-like organisms (arrows), giving a "soap bubble" appearance. The surrounding stroma has a mild inflammatory infiltrate.

PAS stain x 40 magnification

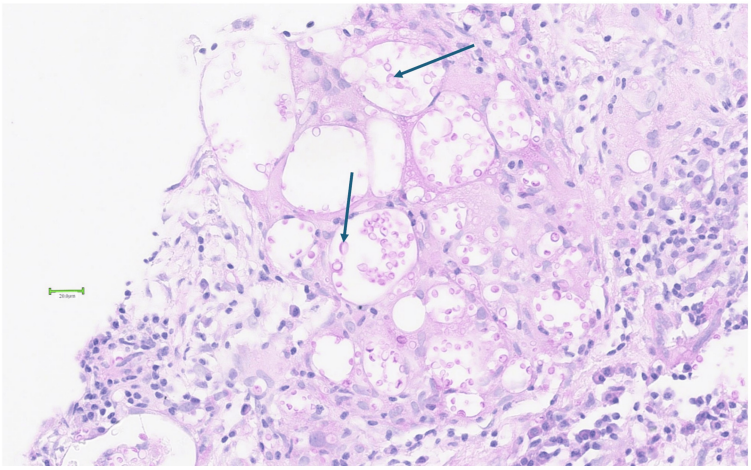


FIGURE 5: Periodic acid-Schiff (PAS) stain

Periodic acid-Schiff (PAS) stain, ×40 magnification (scale bar 20 µm). The yeast forms stain magenta (arrows) and lie within distended macrophages. Several show narrow-based budding. The surrounding tissue has a mixed inflammatory infiltrate.

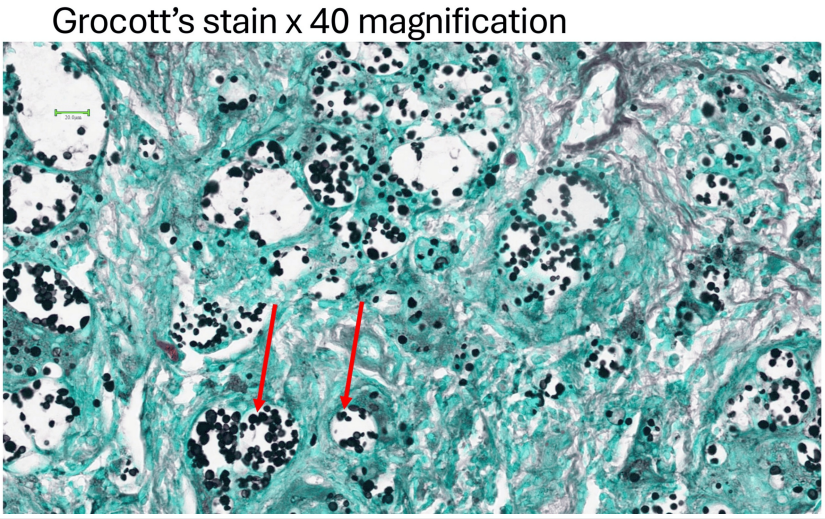


FIGURE 6: Grocott's methenamine silver stain

Grocott's methenamine silver stain, ×40 magnification (scale bar 20 µm). Abundant round yeast forms stain black against a green background (arrows) and fill the macrophages. Their size varies, and some are budding. The silver stain shows the full burden of organisms more clearly than the H&E.

Bronchoalveolar lavage was positive for cryptococcal antigen; culture/PCR isolated *Cryptococcus neoformans*, and TB testing was negative. Serum cryptococcal antigen titre was low positive (1:16).

Our patient had no headache, neurological symptoms and a normal neurological exam (no meningism, no cranial nerve pathology, normal reflexes and power in all four limbs, no gait abnormalities or ataxia). Due to these findings, a low antigen titre and the patient's preference, a lumbar puncture was not performed, and the patient was not started on intravenous therapy. Our patient was treated with oral fluconazole but was unable to tolerate this after two weeks of treatment due to gastrointestinal intolerance, so was switched to oral itraconazole 200 mg twice daily for six months. At the six-month follow-up, his symptoms had resolved, and his chest X-ray showed resolution of the left lower zone lesion (Figure 7). Following this, our patient was provided with a patient-initiated follow-up appointment, which he did not utilise, as there was no relapse of symptoms.

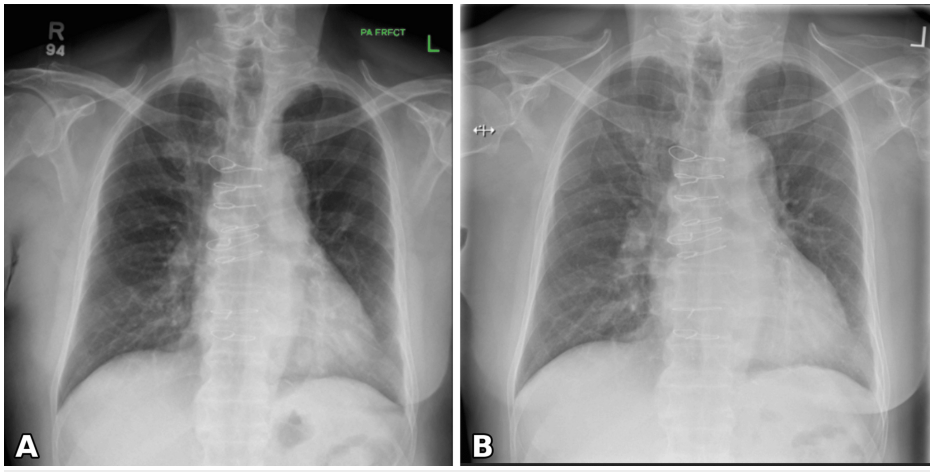


FIGURE 7: Chest X-ray before and after antifungal treatment

Posteroanterior chest X-ray at presentation, showing a nodule in the left lower zone (A). Posteroanterior chest X-ray at follow-up (six months after starting itraconazole), showing resolution of the left lower zone lesion, with clear lungs and no visible pleural effusion (B).

Discussion

This patient presented with a lung nodule and pleural effusion that the radiologist considered suspicious for malignancy (provisional staging Tx N0 M1a), which is a recognised way for pulmonary cryptococcosis to

present [3,4]. The diagnosis was established by CT-guided biopsy showing intracellular yeast forms, a positive bronchoalveolar lavage (BAL) cryptococcal antigen, and culture/PCR identifying *Cryptococcus neoformans (C. neoformans)*. No malignant cells were seen in the biopsy or in the pleural fluid cytology. The histological differential included histoplasmosis, pneumocystis, and blastomycosis. Narrow-based budding, partial Masson-Fontana positivity, and the culture/PCR result favoured cryptococcosis. Pneumonia is the most common clinical manifestation associated with respiratory fungal pathogens. While pulmonary cryptococcosis often requires T-cell dysfunction and granulomatous inflammation to occur, as often seen in HIV/AIDS, it is increasingly reported in phenotypically immunocompetent patients or those without classical immunosuppression [1]. Risk factors in this cohort include severe viral infections, ICU admission, systemic corticosteroids and diabetes (especially diabetic ketoacidosis) [1]. Our patient was HIV-negative and had no history of transplantation or immunosuppressive treatment, but he was 83 and had type 2 diabetes (HbA1c 50 mmol/mol) and a previous ICU admission with dialysis after CABG, all of which are recognised risk factors for cryptococcosis [1]. We therefore describe him as having no classical immunosuppression, rather than being immunocompetent. The history identified risk factors but no specific exposure. He reported no bird contact and no other known source. He had worked as a builder and made regular visits to urban areas of Myanmar, most recently in 2018. The place and time of acquisition cannot be determined from this case. Identification of cryptococcal infection with laboratory tests such as BAL, fungal cultures and antigen testing is important in helping establish diagnosis, facilitating early treatment with a reduction in complications and improved patient outcomes [2]. Our patient was initially being investigated for suspected malignancy, so CT thorax and biopsy were carried out within a two-week wait period.

Cryptococcal pneumonia can present radiographically as solitary or multiple pulmonary nodules, often mimicking malignancy. The most common site of dissemination is the central nervous system (CNS); therefore, a comprehensive history and neurological examination to look for signs of dissemination is prudent and necessary. Patients with neurological symptoms warrant lumbar puncture and neuroimaging [3]. Opportunistic fungal infections should be considered as a differential in atypical presentations or unusual lesions seen on imaging, and a detailed history and examination should always be performed in conjunction with imaging and laboratory tests. Our patient did not have any neurological symptoms and had a normal neurological exam (no headache, no meningism, normal cranial nerve exam, normal power in all four limbs and no gait abnormalities or ataxia). Following shared decision-making conversations with the patient, the patient preferred not to go ahead with lumbar puncture. Therefore, CNS involvement was not formally excluded in this case. This case follows an individualised approach rather than supporting one, and it should be read as showing what was omitted, not as evidence that the investigation is unnecessary.

Global guidelines for the diagnosis and management of cryptococcosis recommend lumbar puncture with CSF microscopy and culture, alongside blood cultures, PCR, and blood and CSF antigen testing, as these provide information on diagnosis, severity, classification and prognosis [4]. Whether lumbar puncture should be mandatory in patients without HIV or transplantation has also been questioned [3]. Culture and PCR with species identification are desirable, because *C. neoformans* and *Cryptococcus gattii (C. gattii)* differ in their epidemiology, host susceptibility and potentially their treatment [5]. *C. neoformans* is predominantly associated with HIV, although it can also cause disease in hosts without classical immunosuppression, as in our patient. *C. gattii* is more often seen in phenotypically immunocompetent individuals, although an underlying risk factor or immune deficiency may remain undiagnosed and undetected by routine tests [5]. Geographically, *C. neoformans* is distributed worldwide, with most cases occurring in sub-Saharan Africa, reflecting the burden of HIV and AIDS, whereas *C. gattii* is less prevalent globally and occurs largely in tropical and subtropical regions [5].

Although first identified over a century ago, cryptococcosis has re-emerged in recent decades, driven by the HIV pandemic, increased organ transplantation, widespread use of immunosuppressive therapies, climate change and global migration [6]. HIV-associated cryptococcosis has declined in high-income settings, but increasing incidence has been reported in people without HIV. In Taiwan, for example, incidence rose from 1.48 to 2.76 per 100,000 between 2002 and 2015 [7], and the WHO ranks *C. neoformans* as a critical priority pathogen [8]. A single case cannot demonstrate a trend, but these data support considering the diagnosis in older patients with risk factors such as diabetes and prolonged hospital or ICU admission.

This report has important limitations. As a single case, its findings cannot be generalised. Lumbar puncture and CSF analysis were not performed, so CNS involvement was not formally excluded. Resolution was assessed clinically and on chest X-ray at six months, without measurement of the lesion, and no repeat CT was performed. Intravenous induction therapy was not given, so these findings may not apply to more severe disease.

Conclusions

This case describes pulmonary cryptococcosis presenting as a lung nodule with a pleural effusion, mimicking malignancy, in an 83-year-old man without classical immunosuppression (HIV-negative, non-transplant). His diabetes and previous ICU admission with dialysis may have contributed to his susceptibility. The diagnosis was established by CT-guided biopsy, BAL antigen and culture/PCR, with a low-positive serum antigen titre. He recovered clinically and radiologically after six months of oral itraconazole (200 mg twice daily), following intolerance of fluconazole. Lumbar puncture was not performed, so CNS

involvement was not formally excluded. Guidelines recommend it, and the decision should be individualised. Fungal infection should be included in the differential diagnosis of a lung nodule with pleural effusion, including in patients without classical immunosuppression.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Praneet Bolusani, Mahableshwar Albur

Acquisition, analysis, or interpretation of data: Praneet Bolusani, Mahableshwar Albur

Drafting of the manuscript: Praneet Bolusani

Critical review of the manuscript for important intellectual content: Praneet Bolusani, Mahableshwar Albur

Supervision: Mahableshwar Albur

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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