Scientific Research Publishing

Case Reports in Clinical Medicine, 2024, 13, 147-154
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

A Bronchopulmonary Onset of Candidemia Revealing a Granulomatosis with Polyangiitis

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How to cite this paper: Zeroual, C., Moudatir, M., Echchilali, K., Barakat, L. and El Kabli, H. (2024) A Bronchopulmonary Onset of Candidemia Revealing a Granulomatosis with Polyangiitis. *Case Reports in Clinical Medicine*, **13**, 147-154.
https://doi.org/10.4236/crcm.2024.135016

Received: March 25, 2024
Accepted: May 5, 2024
Published: May 8, 2024

Abstract

Candidemia is defined as being a yeast infection confirmed by the presence of at least one positive *Candida* blood culture. It is a life threatening infection causing high mortality. The clinical signs are generally compatible with the causative agent (whether there is a deep venous catheter or not). On the other hand and according to the 2012 *Revised Chapel Hill Classification*, granulomatosis with polyangiitis GPA is classified as a vasculitis associated with antineutrophil cytoplasmic antibodies ANCA. It is a systemic disease characterized by the anatomopathological aspect of granuloma. We report the case of a patient who presented an atypical and a very rare revealing mode of GPA which was a bronchopulmonary candidiasis complicated by candidemia. Despite its controversy, the combination in the acute phase of antifungal treatment based on intravenous voriconazole and glucocorticoid therapy has made it possible to control candidemia and calm vasculitis.

Keywords

Candidemia, *C. glabrata*, Pulmonary Candidiasis, Vasculitis, Immunodepression, Granulomatosis with Polyangiitis, Cavitary Lesions, Antifungal Therapy, Immunosuppressants

1. Introduction

In contrast to bacterial and viral diseases, invasive human fungal infections are rarely communicable. Thus, we have relatively little information on the incidence and prevalence of mycoses [1].

Although *C. albicans* is most often blamed for candidiasis, other species are beginning to be involved such as *C. glabrata*. Being able to spread by hematogenous route or by oral-esophageal colonization, bronchopulmonary candidiasis is an infection that appears most often on a site of immunosuppression and

which can be the cause of candidemia [2].

The selection criteria for antifungal therapy in pulmonary fungal diseases have changed over time. Thanks to its clinical efficacy and safety, voriconazole has become the treatment of choice for most pulmonary mold diseases [3]. The prognosis can be poor in the absence of early and effective management.

Granulomatosis with polyangiitis GPA was formerly called *Wegener*'s disease. Dr. Friedrich Wegener is a German pathologist who described in 1936 the clinical and histopathologic findings of three patients having GPA. It is a necrotizing vasculitis of small and medium vessels associated with antineutrophil cytoplasm antibodies ANCA. It is characterized by the inflammatory involvement of several organs such as the lungs, the ENT sphere, the kidneys... The evolution depends on the organs affected and the therapeutic adherence.

We report a significant and novel intersection of bronchopulmonary candidiasis and GPA, offering unique insights into the diagnosis and management of a patient with both conditions.

2. Case Report

She is a 54-year-old patient who was admitted to the internal medicine department for suspected candidemia on primary ANCA-associated vasculitis AAV type GPA.

The patient's family reported that the symptomatology began 2 weeks ago with epistaxis, alternation of dry and productive cough, low abundance hemoptysis and dyspnea grade 4 mMRC. The clinical signs were enriched one week after by a sudden decrease in left visual acuity, all evolving in a context of fever at 39˚C and deterioration of general condition (asthenia, anorexia and non-quantified weight loss).The patient complained of left ear hearing loss associated to very disturbing tingling of the upper and lower extremities.

At admission, the patient was drowsy with *Glascow Coma Scale* GCS at 14/15, pale, febrile at 39.5˚C, *Body Mass Index* BMI at 16.2 kg/m^2, hypotensive at 10/6 cmHg, tachypneic at 26 breaths/min, tachycardia at 103 beats/min with SaO_2 of 86% on room air and 96% under a high concentration mask. The fasting blood sugar was normal at 86 mg/dl.

On ENT examination, she had a saddle nose, left hypoacusis and an oropharyngeal mycosis. During mycological sampling, the yeast *C. glabrata* was isolated. The audiogram objectified a mixed hearing loss in the left ear.

Multiple chorioretinal foci on the left were visualized in the fundus oculi and on retinal angiography (**Figure 1**).

Cardiac, abdominal, musculoskeletal and neurologic exams were normal.

On pleuro-pulmonary examination, rhonchi and crackling rales were found on auscultation of the pulmonary bases.

Computed tomography CT scan of the chest showed bilateral excavated lung lesions (**Figure 2**).

Additionally, the bronchoscopy revealed:

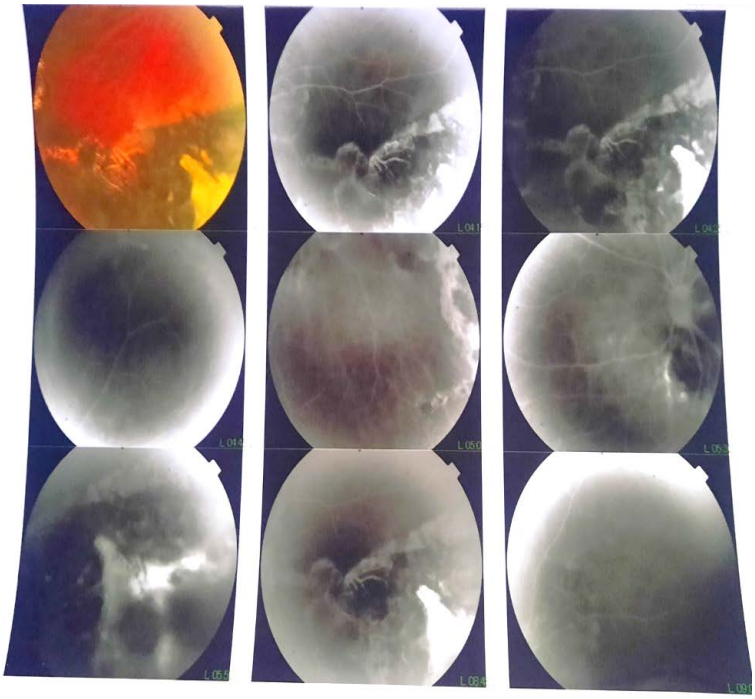

Figure 1. Retinal angiography objectifying multiple chorioretinal foci in the left eye.

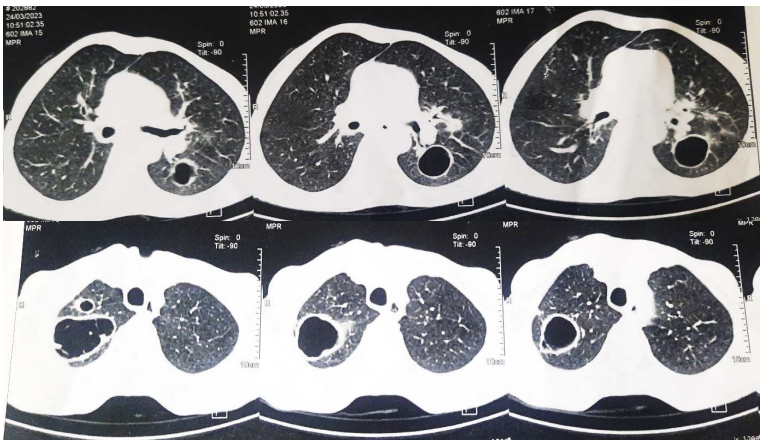

Figure 2. Cross sections of the lung CT scan objectifying bilateral excavated lung lesions.

- Macroscopically, a diffuse second-degree inflammation with pale mucous membrane and the presence of mucopurulent secretions.
- On mycological examination of bronchial aspiration, *C. glabrata* >10^4 UFC/ml on the culture media.
- On cytobacteriological examination, a cloudy appearance with T leukocytes >25 elements/field and epithelial cells <10/field.
- A negative *GeneXpert* in the bronchoalveolar fluid.
- On parasitological examination, there were no parasites, no *Echinococcus granulosus* scolex or hooks.

It should be noted that the patient had negative aspergillar and toxoplasmic serologies (IgM and IgG) and did not present a retroviral infection.

The patient had a very significant inflammatory and infectious syndrome made of leukocytosis at 22,000/mm^3 with neutrophilic polynucleosis at 12,000/mm^3, hyperfibrinogenemia at 7 g/L, C-Reactive Protein CRP at 171 mg/L and procalcitonin at 1.6 ng/ml. Besides, one blood culture was positive for *C. glabrata*.

Moreover, an acute alteration of renal function was noted (glomerular filtration rate GFR at 53 ml/min /1.73m^2 vs 100 ml/min/1.73m^2) with a functional note (urea at 0.8 g/L). The vesico-renal ultrasound was without abnormalities. The cytobacteriological examination of urine CBEU showed a hematuria at 836,000/mm^3 and a leukocyturia at 138,000/mm^3. 24-Hour urine protein was at 1.7 g/24h.

The diagnosis of GPA was retained with a score of 15 points according to the 2022 *American College of Rheumatology ACR/European Alliance of Associations for Rheumatology EULAR*. The selected criteria were bloody nasal discharge, nasal crusting, cartilaginous involvement, conductive and neurosensorial hearing loss, very positive *anti-proteinase* 3 ANCA, pulmonary cavitations on chest imaging and epithelial-giganto-cellular granuloma in bronchoscopy and rhinocavoscopy.

Besides, both nephrological (proteinuria, hematuria, leukocyturia) and peripheral neurological disorders (tingling of lower and upper limbs with length-dependent sensitivomotor axonal polyneuropathy on the electroneuromyogram) were in favor of GPA.

Therapeutically, she was put on miconazole gel, chlorexidine oral rinse and intravenous voriconazole 200 mg/12h on the first day and then 100 mg/12h (with good intravenous rehydration) for 14 days, relayed orally. As an initial and intensive treatment for her AAV, a bolus of methylprednisolone 500 mg/day was administered for three days, followed by oral corticosteroid therapy at a full dose of 40 mg/d. Pregabalin at the dose of 150 mg twice a day (morning and night) was added for paresthesias.

The evolution was marked by the spectacular clinical, biological and endoscopic improvement.

The patient became neurologically more present GCS 15/15, apyretic at 37˚C with normalization of her vital signs.

The oropharyngeal candidiasis disappeared and the vision improved.

Biologically, there was a very significant decrease in CRP to 11 mg/L with negativation of procalcitonin and improvement in renal function.

At the bronchoscopic control, the cytobacteriological and mycological examinations returned sterile.

Additionally, she received an immunosuppressive treatment made of 6 cyclophosphamide's boli (vasculitis protocol) relayed by azathioprine 150 mg/d and *Pneumocystis jiroveci* prophylaxis with trimethoprim-sulfamethoxazole 160 mg/800mg three times per week.

3. Discussion

Among the 200 known *Candida* species, *C. albicans* is the most common. Other species that can be found in humans but to a lesser extent are *C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei* [4]. They are opportunistic yeasts that are capable of invading deep organs. Candidemia is currently emerging because of the rise in the rate of immunocompromised patients and the change in medical practice. However, *Candida*'s involvement in bronchopneumonia is a situation that is not at all frequent. Besides, its revealing mode of the GPA has never been reported until now. In GPA, the granulomatous inflammation of the upper respiratory tract facilitates pathogens's invasion by destroying the barrier function of the surfaces. The primary barrier deficiency seems to also contribute in the pathophysiology of GPA.

It seems necessary to distinguish primary pulmonary candidiasis from any secondary localization of hematogenous dissemination [5]. In our patient, there was a continuum between oral thrush and the bronchopulmonary involvement. A bronchopneumonia of adjacency was retained on the positivity of the endobronchial samples. Candidal uveitis, on the other hand, is a rare infectious disease, often secondary to candidaemia. It can manifest itself either by foci of chorioretinitis or by endogenous endophthalmia. At first, the infection reaches the choroid. It will then rupture the Bruch membrane to reach the retina. In case of diagnostic and therapeutic delay, the risk is the extension to the vitreous and therefore endophthalmos [6].

The management of candidemia requires prior knowledge of various parameters such as the gateway, the existence or not of neutropenia, the promoting factors (diabetes, immune deficiency, recent antibiotic therapy, tobacco...) and the species of *Candida*. When the diagnosis of candidemia is made late, there is a significant risk of secondary localizations that may appear in the weeks or months after. In our patient, several elements were confirming candidemia: the presence of *C. glabrata* on lung sampling, the positive blood culture, the candidal chorioretinitis, the malnutrition and her immunocompromising vasculitis. The start of the antifungal treatment was then indisputable (**Figure 3**) [7].

Although fluconazole remains the first-line treatment for non-neutropenic patients, its uncertain sensitivity limits its use, in particular when it comes to the *C. glabrata* species. In this case, amphotericin B constitutes an excellent therapeutic alternative but with an increased risk of nephrotoxicity in the case of renal insufficiency which was pre-existing in our patient. On the other hand, voriconazole exhibits a powerful antifungal activity in vitro against *C. glabrata* isolates compared to fluconazole [8]. The appearance of resistance to voriconazole remains relatively rare. In large randomized trials, it is an effective and well-tolerated treatment in invasive candidiasis [9]. The oral route is to be preferred if the creatinine clearance is <50 ml/min/1.73m^2. However, the intravenous route remains the most effective in candidemia with close monitoring of creatinine figures. Voriconazole is associated with a lower incidence of serious systemic

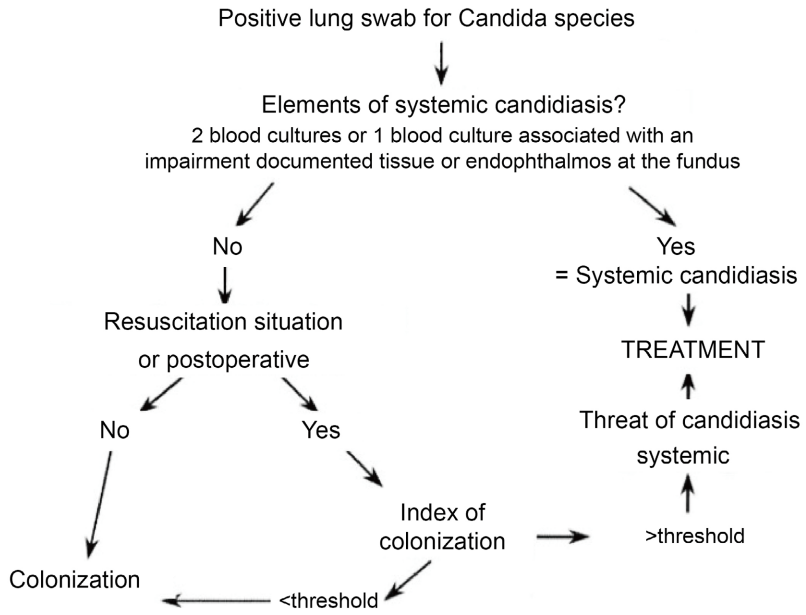

Figure 3. Medical attitude in positive lung swab for *Candida*.

adverse reactions compared to amphotericin B [10]. According to the guidelines of *the Infectious Diseases Society of America* IDSA, it should be dosed according to the patient's body weight (loading dose of 6 mg/kg/12h in intravenous infusion or 200 mg/12h per os for 24 hours followed by a maintenance dose of 4 mg/kg/12h in IV or 100 mg/12h per os [11]. Generally in candidaemia, antifungal treatment should be continued 14 days after negativation of the blood culture.

In our case, the use of two antagonistic treatments (agressive immunosuppressants in addition to antifungals) was a brave decision which the results were encouraging. No similar experience has been previously described in literature.

A regular follow-up in order to watch for the occurrence of any fungal infection is necessary. *Candida* infections of mucosal membranes are a frequent complication of glucocorticoid treatment. Whereas invasive candidiasis is very rarely found. All patients should be instructed to perform daily self-inspections of the mouth in order to detect mucosal candidiasis early [12]. Amphotericin B solution can be recommended in patients with long term glucocorticoid therapy >15 mg per day because of its efficacy and non-absorbance whereas the non-absorbable nystatin is not effective in avoiding fungal colonisation and cannot be recommended [13].

4. Conclusion

Bronchopulmonary candidiasis revealing GPA is a very rare situation whose mechanism is still unclear. Further researches are required to delve into the depths of pathophysiology and elucidate the trigger of the common cascade between both of them. Invasive fungal infections can also complicate either the vasculitis during its evolution or the disease's treatment. Although unknown and

neglected, all systemic diseases are immunosuppressive and should clearly figure in the list of predisposing factors to fungal infections. The concomitant management of an active GPA and candidemia is a real challenge. Sometimes in the acute phase, it is required to take bold therapeutic decisions (combining high doses of glucocorticoid with the antifungal) in order to save the patient's life. That's why in upcoming cases, we need treatment's codification while facing both conditions. The interest of anti-fungal chemoprophylaxis is also to be updated and clarified in medium and long term.

Informed Consent

The patient has provided informed consent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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