

Otitis with *Aspergillus niger* in a patient with SARS-CoV-2 and multiple comorbidities

Andreea Florentina Stoenescu^{1,2}, Geta Vancea^{1,2}, Dana Ispas¹, Nicoleta Voicu-Pârvu¹, Nicoleta Tudor¹, Gabriela Precup¹, Gabriela Scurtu¹, Sebastian Alexandru Pișcu¹, Andreea Popica¹, Raluca Bontea¹, Claudia Chirilă¹, Elena Sandu¹, Diana Potârniche¹, Octavian Tăbăcaru¹, Daniela Mischie¹, Andreea Toderan¹, Emanoil Ceaușu^{1,2,3}, Simin-Aysel Florescu^{1,2}

¹ „Dr. Victor Babes” Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania

² „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

³ Academy of Medical Sciences, Romania

ABSTRACT

Introduction. COVID-19 is associated with a significant incidence of bacterial and fungal superinfections and with the exacerbation of pre-existing infections, representing a diagnostic and therapeutic challenge.

Case presentation. A 64-year-old woman, confirmed with COVID-19 by the SARS-CoV-2 antigen test, is hospitalized accusing fatigue, nausea, watery stools, cough and vertigo started 10 days ago, aggravated 4 days before the presentation. It also reports recurrent episodes of otalgia and otorrheic pluriantibiotic treatment in the last 2 months. From the personal pathological antecedents we remember: hypothyroidism, dyslipidemia, hypertension, ischemic heart disease, history of deep vein thrombosis (DVT) and secondary pulmonary thromboembolism, in chronic anticoagulant treatment. Pathological clinical signs at admission: bilateral basal crackling rales. Biologically, inflammatory syndrome is detected, and radiologically, interstitial-alveolar infiltrates in the lower lung fields. On day 3 of hospitalization, the patient shows purulent secretion in the right external auditory canal and the ENT consultation confirms chronic suppurative otitis media in acute onset. Bacteriological examination of otic secretion reveals *Aspergillus niger*. Antiviral treatment with Remdesivir is initiated, antibiotic therapy initiated at home with Azithromycin is continued for one day, then escalated to Ceftriaxone i.v. (in the context of clinical-paraclinical aggravation), systemic corticotherapy, anticoagulation with Dalteparin in the prophylactic regime of DVT, systemic treatment with Voriconazole p.o. (according to the antifungal program) and topical (local) with a slow favorable evolution.

Conclusions. The association of COVID-19 with otitis with *Aspergillus* is a rare and particular clinical picture.

Keywords: COVID-19, *Aspergillus niger*, otitis

Abbreviations

COVID-19 = coronavirus disease 2019

SARS-CoV-2 = severe acute respiratory syndrome coronavirus

DVT = deep vein thrombosis

ENT = ear-nose-throat, otolaryngology

Rt-PCR = real time polymerase chain reaction

Corresponding author:

Andreea Florentina Stoenescu

E-mail: andreeastoenescu0193@gmail.com

Article History:

Received: 16 September 2021

Accepted: 22 September 2021

INTRODUCTION

With the appearance of atypical cases of pneumonia at the end of 2019, the new coronavirus (SARS-CoV-2) was identified, and the disease caused by it, COVID-19, spread rapidly worldwide, generating the COVID-19 pandemic, also present in 2021 (1-3).

In the management of COVID-19 disease, an important aspect is the occurrence of SARS-CoV-2 coinfection and other viruses, bacteria or fungi (4,5). Co-infection with fungi such as *Candida*, *Aspergillus*, *Cryptococcus*, *Mucorales* has been reported less frequently (4,6). Among fungi, coinfection with *Candida* and *Aspergillus* ranks first (7,8), with an increasing frequency, having a severe evolutionary potential, even fatal in some cases (7,9).

COVID-19 can lead to acute respiratory distress syndrome, and in the case of diffuse alveolar involvement with the appearance of inflammatory exudate, patients diagnosed with COVID-19 have a degree of immunosuppression by decreased CD4 + and CD8 + T lymphocytes (10). Patients with a critical form of the disease, admitted to the intensive care unit, requiring mechanical ventilation and a prolonged period of hospitalization have a greater predisposition to develop fungal co-infections (11). These aspects suggest that patients, especially those with severe forms of the disease, may develop fungal infections in the middle of the disease course or in the more advanced stage (12).

AIM

The aim of the paper is to emphasize the importance of early diagnosis of a fungal infection in a patient diagnosed with SARS-CoV-2 infection. The informed consent of the patient was obtained.

CASE PRESENTATION

Presenting concerns

We present the case of a 64-year-old woman confirmed with COVID-19, who was hospitalized for chills, watery stools, fatigue, cough, started 10 days before and worsened 4 days prior the admission. She reports recurrent episodes of otalgia and otorrhea pluriantibiotic treated in the last 2 months.

The patient comes from a family outbreak and is known to have high blood pressure, hypothyroidism, dyslipidemia, ischemic heart disease, a history of deep vein thrombosis (DVT) and secondary pulmonary thromboembolism, in chronic anticoagulant treatment (Xarelto) and antihypertensive treatment (Nebilet).

Clinical findings

Clinical examination at admission revealed a patient with mediocre general condition, afebrile (36

degrees C), G = 82 Kg, normally colored skin and mucous membranes, post-thyroidectomy anterior cervical scar, left lower limb swelling, impalpable superficial ganglion system, system normotonous, normokinetic muscle, apparently intact morpho-functional osteo-articular system, dry cough, bilateral vesicular murmur present, bilateral crackling rales, rhythmic heart sounds, apparently without valvular murmurs, SpO₂ = 96% in aa, AV = 85 bpm, TA = 125/71 mmHg, abdomen relaxed by volume through adipose tissue, mobile with breathing, painless spontaneously or on palpation, liver with lower edge at costal rim, impalpable spleen, intestinal transit present, watery stools, normal urination affirmative, bilateral negative Giordano, conscious, cooperative, temporally-spatially oriented, with no signs of meningeal irritation.

Diagnostic focus and assessment

Biologically, inflammatory syndrome is detected (CRP = 2.54 mg/dl, fibrinogen = 505 mg/dl) and radiologically infiltrated interstitial-alveolar in the lower 1/3 of the right lung field and in the lower 1/2 of the left lung field that associates small foci of condensation.

On day 3 of hospitalization, the patient presents with purulent secretion in the right external auditory canal and the ENT consultation confirms chronic suppurative otitis media in acute onset.

Otic secretion is taken and bacteriological examination and mycological examination are performed, being isolated in culture *Aspergillus niger*. Subsequently, antifungigram is performed. Biologically, on day 3 of hospitalization, leukocytosis (15,700/ μ l) and neutrophilia are detected (13,500/ μ l).

Therapeutic focus and assessment

During hospitalization he received antiviral treatment with Favipiravir 3.2 g/day on the first day po, then replaced with Remdesivir 200 mg iv on the first day, then 100 mg/day, iv on days 2-5, antibiotic treatment with Ceftriaxone (Cefort) 2 g/day, iv, for 8 days, systemic corticosteroids in decreasing doses, iv, anticoagulant treatment with Dalteparin (Fragmin) 5000 IU/day sc, antitussive (Bromhexin), anti-diarrheal (Tasectan), gastric protector (Famotidine), symptomatic and background treatment administered for known pathologies.

Because *Aspergillus niger* was isolated in the culture of otic secretion, treatment with Voriconazole 800 mg/day p.o. was instituted on day 1, then 400 mg/day, in the following days p.o, according to antifungigram. Under treatment the evolution was favorable with the progressive remission of the symptomatology.

Follow-up and monitoring

The patient was monitored by the family doctor and ENT doctor.

DISCUSSION

The COVID-19 pandemic is currently one of the most important health problems globally. The clinical picture is vast and includes asymptomatic, mild, moderate, severe and critical forms of the disease. The most common manifestations are fever, cough, dyspnea, rhinorrhea, myalgia, nausea, vomiting, watery stools, headache (13,14). Regarding the case presented, the patient had a disease-specific symptomatology.

In the literature, manifestations belonging to the ENT sphere have been described, such as the presence of acute otitis media, hearing dysfunction, altered taste and smell, oral manifestations, mumps (15).

The SARS-CoV-2 receptor is known to be the angiotensin II converting enzyme (ACE II). The virus enters the body airborne and attaches to ACE II (16). This attachment is also mediated by cytosolic pH, which is reduced in the elderly and facilitates the production of a more severe form of the disease (16,17). The case presented is an elderly patient, known with chronic otitis, COVID-19 infection having a role in exacerbating otitis.

Aspergillus infection is more common with *Flavus* and *Fumigatus* species and can manifest as invasive aspergillosis. This is a serious complication of severe forms of pneumonia and has been present in the 2003 SARS epidemic. A series of autopsies

performed on 20 deceased SARS patients showed that 10% of them (2/20) had an invasive infection suggestive of aspergillosis (18).

Most patients who develop severe forms of COVID-19 have at least one associated pathology such as diabetes, high blood pressure, chronic kidney disease, chronic obstructive pulmonary disease (19). In severe forms of COVID-19, the lungs are affected due to viral replication, cytokine storm and complex inflammatory processes, favoring the occurrence of fungal superinfections (20). A study conducted in France, on a group of 106 patients diagnosed with severe COVID-19, admitted to the intensive care unit, found the presence of *Aspergillus* in 19 cases (17.9%). Of these, *Aspergillus fumigatus* was isolated in 14 cases (21). In our case, although the patient was known to have high blood pressure, ischemic heart disease and was hospitalized on day 10 of evolution, she did not have a severe form of the disease. The isolated species of *Aspergillus* was *Aspergillus niger*, known in the literature for otic impairment. Early detection and established antifungal treatment allowed the control of otic fungal infection by preventing a possible spread of it, including lung.

CONCLUSIONS

Aspergillus-associated fungal infections associated with COVID-19 are more common in patients with severe forms of the disease and admitted to intensive care units. Although a less common species in SARS-CoV-2 infection, *Aspergillus niger* should not be overlooked.

REFERENCES

1. WHO. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*. 2020 Mar;55(3):105924.
3. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents*. 2020 Apr;55(4):105946.
4. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect*. 2020 Aug;53(4):505-512.
5. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. 2020 Aug;81(2):266-275.
6. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, Zhu F, Zhu B, Cui L. Co-infection with respiratory pathogens among COVID-2019 cases. *Virus Res*. 2020 Aug;285:198005.
7. Hoenigl M. Invasive Fungal Disease complicating COVID-19: when it rains it pours. *Clin Infect Dis*. 2020 Sep 5;ciaa1342.
8. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, et al.; COVID-19 Researchers Group. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect*. 2021 Jan;27(1):83-88.
9. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. 2020;81(2):266-275.
10. Yang W, Cao Q, Qin L, Wang X, Cheng Z, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J Infect*. 2020 Apr;80(4):388-393.
11. Yang X, Yu Y, Xu J, Shu H, Xia J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020 May;8(5):475-481.
12. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: We should be prepared. *J Mycol Med*. 2020 Jun;30(2):100971.
13. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.

14. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020 Apr 7;323(13):1239-1242.
15. Zahran M, Ghazy R, Ahmed O, Youssef A. Atypical otolaryngologic manifestations of COVID-19: a review. *The Egyptian Journal of Otolaryngology*. 2021;37(1):5.
16. Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol*. 2020 Jul;92(7):726-730.
17. Cure E, Cumhuri Cure M. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during COVID-19 pandemic. *Diabetes Metab Syndr*. 2020 Jul-Aug;14(4):349-350.
18. Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Mod Pathol*. 2005 Jan;18(1):1-10.
19. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. 2020 May 12;323(18):1775-1776.
20. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020 Mar 28;395(10229):1033-1034.
21. Dupont D, Menotti J, Turc J, et al. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). *Med Mycol*. 2021;59(1):110-114.