

A case of mucormycosis causing acute pansinusitis with periorbital involvement in a severe case of COVID-19 pneumonia

^{1,2}Dana Crișan, ^{1,3}Lucreția Avram, ^{1,4}Bogdan Micu, ^{1,5}Mihaela Cociș, ⁶Alina B. Olar, ⁷Anda Gâța, ⁸Sergiu Văcăraș, ⁶Mihaela Coman, ^{1,5}Constantin Bodolea, ^{1,2}Sorin Crișan, ^{1,4}Călin Ionescu

¹ Clinical Municipal Hospital, Cluj-Napoca, Romania; ² Department of Internal Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ³ Department of Geriatrics and Gerontology, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁴ Department of Surgery, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁵ Department of Intensive Care Unit, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁶ Clinical Hospital of Infectious Diseases, Cluj-Napoca, Romania; ⁷ CF Clinical Hospital, Cluj-Napoca, Romania; ⁸ Clinical of Surgery Oral and Maxillofacial I, Cluj-Napoca, Romania; ⁹ Department of Intensive Care, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. The burden of COVID-19 is not only represented by pneumonia and acute respiratory failure, but also by its numerous complications, especially those unexpected or less reported. In view of this, we present the case of a 71 years old male patient admitted for severe acute respiratory failure and sudden alteration of the general condition who was tested positive for SARS-CoV-2 infection 12 day before. Native chest CT scan result was suggestive of a severe COVID-19 pneumonia. Shortly after admission, the patient accused persistent headache located in the right frontal area which evolved bilaterally and it associated periorbital edema later. Based on the cranial CT scan he was diagnosed with acute pansinusitis and periorbital cellulitis. Despite broad spectrum antibiotic and antifungal therapy the inflammatory syndrome was rising and his clinical condition was getting worse. Considering the inflammatory recurrence, his immunosuppressed status caused by COVID-19 and the corticosteroid therapy, his history of diabetes, the cranial CT scan and the extemporaneous histopathological examination, we suspected mucormycosis. So, the patient underwent surgical transosseus drainage of the right sinus and nasal endoscopy with further recommendation of functional endoscopic sinus surgery. The extemporaneous histopathological examination of the samples collected during surgery suggested a presumptive diagnose of mucormycosis. Although right after surgical debridement we started targeted antifungal therapy, his impaired condition required transfer to the intensive care unit.

Key Words: Covid-19, pansinusitis, mucormycosis

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Corresponding Author: L. Avram, e-mail: avram.lucretia9@gmail.com

Introduction

COVID-19 is a highly contagious infectious disease caused by the novel coronavirus - SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), firstly being responsible of acute respiratory infections. Along with SARS-CoV and MERS-CoV, it belongs to the family Coronaviridae. It emerged in 2019 as an outbreak of severe acute pneumonia of unknown etiology, shortly after being identified by genomic sequencing as a new coronavirus. The high contagiousness and the variability of its clinic forms contributed to the rapid and massive spread of the virus worldwide, causing important public health problems, health care system overload and economic imbalance. On March 2020, COVID-19 outbreak was declared a pandemic (Khan et al 2020). The heterogenous clinical presentation varies from asymptomatic forms to severe respiratory failure, characterized by unfavorable prognosis and potential evolution towards death. The extent of clinical presentation is strongly related to the magnitude of

the inflammatory syndrome and the expression of the cytokine storm, and also to patients' susceptibility to develop a severe form of disease. Despite its general receptivity, clinical presentation mainly depends on age and comorbidities, so the elderly are prone to develop a severe form of disease. The most common clinical manifestations are fever, chills, fatigue, headache, myalgia, sore throat, cough, anosmia and ageusia, but depending on the severity, there are other signs and symptoms associated with pneumonia, acute respiratory failure, acute respiratory distress syndrome and other non-respiratory complications related to SARS-CoV-2 infection.

Over time, along with the attempt to prevent the virus spreading, many efforts were made in order to develop a treatment targeted on both the etiological agent and its pathogenic mechanisms, but also on different complications. Till now, several complications were reported, such as venous thromboembolism, cardiovascular, neurological and gastroenterological complications,

acute renal failure, acute liver failure, autoimmune hemolytic anemia, immune thrombocytopenia, disseminated intravascular coagulation, pancreatic injury etc. Moreover, these patients are immunocompromised not only because of the SARS-CoV-2 infection, but also because of the immunosuppressive medication such as corticosteroids and monoclonal antibodies. Therefore, associating different bacterial and/or fungal infections is an important consequence of COVID-19 (Hu et al 2020). These can be classified as co-infections or secondary infections, the last having a higher prevalence among SARS-CoV-2 patients. Both are associated with unfavorable course including increased mortality. Consequently, in case an additional infection is suspected, a rigorous infectious disease screening is required in order to have an accurate therapeutic approach. Most studies have focused on respiratory infections and bacteremia, having *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Acinetobacter spp*, *Haemophilus influenzae* and other gram negative bacteria as the main bacterial etiologic agents and among fungi, *Aspergillus* and *Candida spp* are mentioned (Russell et al 2021; Musuuzza et al 2021; Song et al 2020). When it comes to severely ill patients, clinicians should equally focus on patients' fungal and bacterial infections in COVID-19 patients (Song et al 2020). An increasingly reported fungal infection in COVID-19 patients is mucormycosis, a high mortality infection (~54%) (Roden et al 2005) caused by Mucormycetes (Rudrabhatla et al 2021). Among the most common underlying diseases in mucormycosis are diabetes mellitus, immunosuppressive therapy –including corticosteroids, malignancies, prolonged neutropenia, malnutrition, iron disequilibrium, endothelial injury, hypoxia, transplant recipients (Rudrabhatla et al 2021; Prakash et al 2019). Because some of these risk factors are also described in severe forms of COVID-19, screening for fungal infections should be considered.

Certain less frequent clinical characteristics of COVID-19 that are reported in the literature can suggest either respiratory bacterial superinfection or manifestations of COVID-19. Sino-nasal signs and symptoms, such as rhinorrhea and nasal congestion, are rarely described compared to those related to the respiratory tract and the constitutional ones (Gengler et al 2020). Nevertheless, there is an increased prevalence in olfactory dysfunction, as a part of the superior respiratory tract manifestations (Speth et al 2020). Up to this time, most of the studies that examined any possible rhinosinusal complications referring to COVID-19, are isolated cases of acute sinusitis. As far as ophthalmic pathology is concerned, xerophthalmia, blurred vision, foreign body sensation and conjunctival congestion are most commonly described (Chen et al 2020), with potential progress to more severe complications as periorbital cellulitis (Carvalho et al 2021). Referring to mucormycosis infection mentioned above, the most common clinical form is the rhino-orbito-cerebral one (Rudrabhatla et al 2021). COVID-19 associated mucormycosis usually affects paranasal sinuses and it often manifests as sinusitis, periorbital cellulitis, facial numbness, impaired vision, soft tissue swelling, persistent headache and nasal obstruction and unusual nasal discharge (Rudrabhatla et al 2021).

In the following, we will discuss 2 infrequent sites of secondary COVID-19 infections: sino-nasal (ENT) and ophthalmic. We will present the case of a 71 years old man being diagnosed with SARS-CoV-2 infection, severe form of COVID-19 pneumonia

and acute respiratory failure, complicated by acute pansinusitis with periorbital involvement.

Case report

A 71 years old male patient with a previous history of primary arterial hypertension, developed a 2 weeks history of asthenia, fatigue, myalgias and loss of appetite, progressively aggravated by the further association of dyspnea, low peripheral oxygen saturation (73% at rest in ambient air) and sudden alteration of the general condition up to obtundation. It is worth mentioning that 12 days before admission to the hospital he was tested positive for SARS-CoV-2.

The physical examination revealed a conscious and cooperative patient, having a slightly altered general state, increased vesicular breath sounds and crackles at auscultation of the thorax, moderate respiratory effort, tachypnea (RR=35 bpm), SpO₂=90-92% - 15 LPM of additional oxygen being delivered using a non-rebreather mask.

The peripheral blood count indicated leukocytosis, neutrophilia, lymphopenia, inflammatory syndrome based on elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH), impaired renal function based on elevated serum creatinine and urea (creatinine clearance =55 ml/min/1.73 m²), hepatocytolysis, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) elevated, hyperglycemia. As we were planning to administer steroidal anti-inflammatory medication in a patient who presented with hyperglycemia, we monitored his glycemic profile. The glycosylated hemoglobin test showed a level of 7.1g%. Our patient was newly diagnosed with type 2 diabetes mellitus. In order to assess lung damage, our patient was evaluated using native chest CT scan which showed extended interstitial ground glass opacities and some bilateral basal parenchymal bands, suggestive of COVID-19 pneumonia with a TSS severity score of 17/20. Further follow up showed no moderation of its severity, on the contrary, lung abnormalities had the tendency to turn into retractile atelectasis that distorts the lung parenchyma (Figure 1).

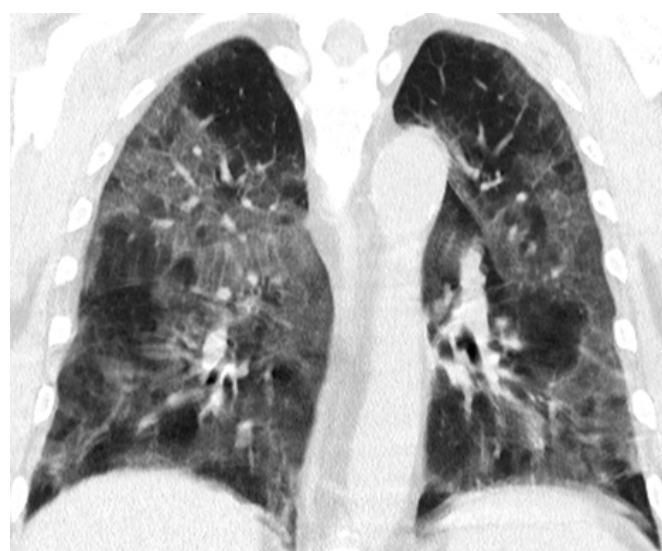


Figure 1. Chest CT scan- Coronal lung window- Extensive confluent bilateral ground glass opacities which associates interlobular septal thickening, related to COVID-19 pneumonia.

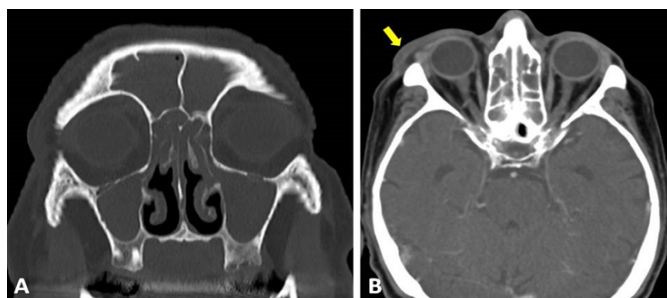


Figure 2. Cranial CT scan with contrast- Image A (Bone window, oblique reconstruction) showed heterogeneous filling of all anterior paranasal sinuses, that suggested acute pansinusitis. Image B (axial plane, after contrast enhancement) showed edematous densification of the right periorbital soft tissues (arrow) and swelling-right periorbital edema.

Case management was according to the national guideline for COVID-19 treatment, except for antiviral therapy which was no longer considered beneficial, given the fact that the disease onset exceeded 10 days. As far as respiratory parameters were concerned, peripheral oxygen saturation was stabilized by high-flow oxygen therapy, using AIRVO. Inflammatory syndrome had a sinusoid follow-up, initially decreasing and increasing afterwards. Consequently, a bacterial superinfection resistant to Ceftriaxone was suspected so we changed the antibiotic therapy to Piperacillin/Tazobactam.

Shortly after, the patient accused headache located in the right frontal area, partially alleviated by analgesic therapy. It soon became persistent and it started to spread bilaterally. At first, we took into consideration the continuous high-flow oxygen therapy as a possible cause of the headache, but due to its unilateral location, other etiologies came into question. Local physical exam revealed high sensitivity in palpation of the superior anterior point of the orbit. A cranial CT scan was performed that suggested acute pansinusitis with quasi-complete opacified sinus cavities (Figure 2). Taking into account the initial drop of the inflammatory syndrome during Piperacillin/Tazobactam antibiotic therapy, further treatment was not reconsidered.

Even though laboratory analysis seemed to improve, clinically speaking the frontal headache persisted and it associated right periorbital edema 2 days after, which also had the tendency to spread bilaterally (Figure 3). No nasal discharge was available for culture. There was a significant growth in the inflammatory markers after 5 days of antibiotic therapy. So, we were facing a patient diagnosed with acute pansinusitis and the suspicion of periorbital cellulitis.

Therefore, an ENT workup was requested, which recommended a new assessment of inflammation of sinuses using contrast-enhanced CT scan and the switch of antibiotic therapy to Meropenem and Fluconazole. Imaging reassessment revealed the progression of the previously described pansinusitis, all sinus cavities being completely filled with fluid, as well as edema of the sinus mucosa. Moreover, at the anterior frontal level to the base of the nasal pyramid, periorbital on the left and diffuse on the right, there was described edematous-inflammatory densification of subcutaneous fatty tissue. No inflammatory infiltration or collections were displayed in the intraorbital fatty tissue (Figure 2).



Figure 3. Bilateral periorbital edema, especially on the right side

Despite the systemic and local therapy, biological and clinical evolution were unfavorable, so we asked for a consultation at Oral and Maxillofacial Surgery Clinic. Our patient underwent surgical transosseous drainage of the right sinus through an incision in the right upper vestibule and antiseptic lavage using the drainage tube. Afterwards, the clinical exam showed persistent periorbital edema which had extended to the right mandible and jaw. There was no purulent discharge through the oral cavity after the drainage, so a microbiological analysis was not possible. Nasal endoscopy was performed and purulent collection could be seen through the transparency of the right middle meatus, for which further functional endoscopic sinus surgery was recommended. Vancomycin was added to the therapeutic regimen. Taking into account the improvement in our patient's clinical condition and laboratory tests, the surgery was temporized. In regard to the periorbital edema, an ophthalmological consultation was requested which recommended to follow on the antibiotic therapy and to apply nasal spray containing xylometazoline chlorhydrate. Driven by a slightly increase of the inflammatory syndrome, we performed infectious disease screening tests that identified non-albicans *Candida* in oral and pharyngeal swabs for which was administered Voriconazole. After that, in the following week, our patient had a promising progress, the inflammatory syndrome remitted and the periorbital edema was significantly reduced up to the point where we could notice only minimal edema on the right side.

After 5 days of normal inflammatory profile, the patient had a new increase in CRP and white blood cells (WBC). We decided to repeat the infectious disease screening tests, and the cranial CT scan which showed slightly improved modifications compared to the previous CT scan: partially pneumatization of the maxillary sinuses and the right sphenoid sinus, decreased inflammation in the left sphenoid mucosa and constant modifications in the frontal and ethmoidal sinuses.

After a few days, our patient complained about nasal obstruction and breathing difficulties. Physical examination showed the relapse of bilateral periorbital edema.

Based on the clinical and paraclinical relapse, we reconsidered oral and maxillofacial surgery consultation which suggested that the patient should undergo functional endoscopic sinus surgery (FESS). We consulted with ENT specialist who suspected mucormycosis of the nose and sinuses based on patient's history

of diabetes mellitus, his immunosuppressed status caused by COVID-19 and the recent intake of Dexamethasone, and agreed with performing FESS. During surgical intervention, the macroscopic examination revealed pale mucosa and bare bone in the ethmoid bulla, suggestive of invasive fungal sinusitis. The following surgical interventions were performed: uncinectomy followed by right maxillary anthropotomy, right maxillary sinus suction, right anterior ethmoidectomy, partial mucotomy of the left middle nasal concha followed by the same procedures performed on the right side. The extemporaneous histopathological examination of the polypoid and bone tissue removed suggested a presumptive diagnose of mucormycosis. Samples for microbiological investigations were collected as well. Postoperative antibiotic therapy consisted of Meropenem, Clindamycin, Voriconazole and Isavuconazole. The drug of choice for initial therapy of mucormycosis would have been Amphotericin B, but it was unavailable in our country so we had to switch the treatment to the second-line therapy - Isavuconazole.

The next day after surgery, our patient presented dyspnea, tachypnea and sudden oxygen desaturation (SpO₂=75-80%) despite oxygen therapy, so we had to switch to noninvasive ventilation CPAP (FiO₂=100%). Soon after that the patient became feverish, so a pulmonary X-Ray was performed which showed signs of pulmonary infiltrate. He was transferred to the intensive care unit where, after several episodes of acute pulmonary edema and the association of large pleural collections, invasive ventilation was necessary. He also developed acute renal failure that implied 3 weeks of dialysis, which was interpreted as an acute tubular necrosis. His condition was also aggravated by stress ulcer manifested as upper gastrointestinal bleeding, stage 4 bed sore, post-extubation dysphagia that required a temporary nasogastric tube and *Clostridium Difficile* infection. He experienced recurrent transudative pleural effusion associated with severe hypoproteinemia, that involved continuous drainage and protein substitution. After remitting the protein malnutrition, pleural effusion was significantly reduced.

Furthermore, the patient became emotionally unstable, expressing depression and insomnia, alleviated by psychiatric treatment. After 4 months of hospitalization the patient was discharged, being hemodynamically stable, still requiring low flow oxygen, with small bilateral pleural effusion.

Discussions

We decided to present this case for several reasons. First of all, as far as SARS-CoV-2 infection is concerned, our patient had an atypical evolution. Considering the average incubation time of about 5 days, the onset of the pneumonia and the severe respiratory symptoms after more than 10 days after the infection and the small chance to develop a severe form at this stage of the disease, we notice that laboratory tests predicted the possibility of a cytokine storm despite the late onset of the symptoms (more than 14 days) (Hu *et al* 2020; Cheng *et al* 2021; Caricchio *et al* 2021; Melo *et al* 2021). Besides, our patient needed a relatively high amount of oxygen intake throughout the whole hospitalization period. The association between this and lung fibrosis and atelectasis sequelae suggests a possible post-COVID-19 syndrome.

The main feature of this case is the presence of a less common superinfection in a COVID-19 patient, leading to diagnostic

difficulties. This triple association (COVID-19, sinusitis and periorbital cellulitis) has been studied in literature before, but having a different chronology of the events, i.e some of the patients were tested positive for COVID-19 as part of the perioperative protocol and did not develop any COVID-19 symptoms (Turbin *et al* 2020). In a study focused on invasive fungal sinusitis, the majority of the patients were in the recent post COVID-19 infection period (El-Kholy *et al* 2021). Therefore, we can notice the fact that in other cases these complications were not related to a critical form of the illness or to an active disease, so it is questionable to what extent this association is caused by SARS-CoV-2 infection or by COVID-19 and by default the pathogenic mechanisms that lead to local and/or systemic inflammation. A local dysmicrobism, probably triggered by SARS-CoV-2 virus, may result in less predictable infections (Shires *et al* 2021). Given the anatomical proximity between the sinus cavities and the orbital/periorbital region, we could consider the periorbital cellulitis as a direct extension of the acute sinus infection (Carvalho *et al* 2021). Another evidence would be the fact that in case of unilateral sinusitis, the periorbital cellulitis was located on the same side (Turbin *et al* 2020; El-Kholy *et al* 2021; Shires *et al* 2021). It is also supported by other studies that have described this pathological mechanism apart from COVID-19 (Sijuwola *et al* 2007; Chang *et al* 2017) or as part of mucormycosis natural course (Prakash *et al* 2019). On account of the alteration of all sinuses, the presence of pre-existing inflammatory changes of chronic sinusitis might be disputed. In this case, it is proven by the fact that our patient had later stated to have a history of chronic sinusitis. In the context of the relationship between SARS-CoV-2 infection and acute sinusitis, which could possibly favor each other, it is important to note that nasal congestion encountered in COVID-19 and the consequent obstruction of the sinus orifices may cause subclinical inflammation of the mucosa. Yet nasal congestion and the consequent obstruction related to COVID-19, explored by cranial CT scan, does not correlate with the opacification of paranasal sinuses (Sumi *et al* 2021). An argument that supports the hypothesis of a possible preexisting condition that could be decompensated by COVID-19 is the case of a patient diagnosed with unilateral sinusitis, with a negative outcome even though the treatment was according to the antibiogram. It turned out to be caused by an underlying autoimmune cause, named IgG4 syndrome (Harb *et al* 2021).

As previously mentioned, immunosuppressive drugs, including systemic corticosteroids, lead to increased risk of rare opportunistic infections. There is no evidence to claim that regular administration of intranasal corticosteroids, as part of the long-term treatment of chronic sinusitis, increases the risk of SARS-CoV-2 infection and the risk of developing a severe form of the disease. Contrariwise, giving up intranasal corticosteroids in these patients can lead to an unfavorable evolution of chronic sinusitis and trigger other diseases associated with COVID-19 impairment. Although there is yet not enough data, patients with a history of chronic sinusitis associated with chronic respiratory diseases could have a higher risk of SARS-CoV-2 infection and/or a higher chance of developing a severe form of the disease (Klimek *et al* 2021). This aspect could be enhanced by the prolonged viral shedding in upper respiratory tract in these situations (Recalde-Zamacona *et al* 2021). Concluding, acute

and/or chronic sinusitis and SARS-CoV-2 infection should not be considered a coincidental association.

In most cases of acute sinusitis linked to COVID-19 that were described in the literature, a common bacterial and/or fungal etiologic agent was not identified. In one case, microbiological analysis revealed microorganisms that were interpreted as normal microbial flora and Group-C beta-hemolytic *Streptococcus* (Turbin *et al* 2020). In another case, the swab test detected coronavirus, despite the purulent macroscopic appearance of the collected secretion (Carvalho *et al* 2021). Invasive fungal sinusitis, one of the most aggressive types of fungal sinusitis, identified *Mucor* species and *Aspergillus* as the main etiological agents (El-Kholy *et al* 2021). Taking into account that, at first, we could not determine a certain etiological agent, we approached a broad-spectrum antibiotic therapy. Considering the slow progress and the inflammatory recurrences during clinical and biological observation, infectious disease screening tests were repeated and it only identified *Candida albicans* and non-*albicans* which was properly treated afterwards. Although we had not received the results of the microscopic examination of the samples collected during surgery, the association among his clinical evolution, the CT scan and the extemporaneous histopathological examination lead to high suspicion for features of mucormycosis, so we decided that de proper management of the case was to start targeted antifungal therapy and to gradually reduce the corticosteroid dose. The therapeutic triad recommended for mucormycosis involves antifungal therapy, surgical debridement and reversed immunosuppression (Rudrabhatla *et al* 2021). When it comes to interventional treatment of acute sinusitis, it is worth mentioning that nasal endoscopy was a key element in the therapeutic strategy of the reported cases, so far. In patients with acute invasive fungal rhinosinusitis surgical debridement seems to be rather mandatory than reserved for isolated cases (El-Kholy *et al* 2021; Chauhan *et al* 2021). Because of the negative course of our patient's sinus infection, the risk of developing thrombosis (e.g. cavernous sinus thrombosis) would have been significantly high, as patients with COVID_19 are already having an increased risk of thrombotic events. Other studies bring forward some cases of cavernous sinus thrombosis related to severe pansinusitis (Ahmed *et al* 2021; El-Kholy *et al* 2021; Wang *et al* 2020). The majority had a positive outcome. In the circumstance of local thrombotic complications, other cases of acute sinusitis and thrombotic events involving the ophthalmic vein or the sphenopalatine artery had a negative outcome (Turbin *et al* 2020; Ahmed *et al* 2021). Being an angio-invasive fungal infection, in the course of rhino-orbitocerebral mucormycosis, thrombotic events can occur, particularly thrombosis, but it was not the case of our patient (Rudrabhatla *et al* 2021; El-Kholy 2021). Thus, confirmed cases should be assessed for cavernous sinus thrombosis.

It is worth mentioning that although in our case the disease was limited to rhino-orbito-sinus area, it can easily extend to the brain parenchyma, resulting in intracranial abscesses and neurological impairment (Rudrabhatla *et al* 2021; Prakash *et al* 2019; Shakir *et al* 2021; Sharma *et al* 2021). Several similar cases faced this complication and it lead to lower survival rate (El-Kholy *et al* 2021). It might be relevant to know if regular

imaging follow-up, regardless of the presence of any neurological manifestation, should be considered as a surveillance method for its extension.

Surprisingly, our patient's periorbital cellulitis was characterized by inflammation and edema, yet no purulent secretion was noticed. Rare cases quoted in literature having the same pathological triad have highlighted the pus-forming tendency of periorbital cellulitis which occurred in cases of sinusitis (Carvalho *et al* 2019). These required surgical drainage, with a favorable outcome. Up to this point, these cases that described sinusitis and periorbital cellulitis in relation to COVID-19, could not confirm a pathological mechanism of these associations. However, the recurrence of this pathological triad in different cases certifies the need for further studies focused on a possible etiological and pathogenic mechanism.

Diabetes mellitus is not only the most frequent underlying comorbidity for mucormycosis but also an independent risk factor (Jeong *et al* 2019). The fact that our patient developed a severe form of COVID-19, was given corticosteroid therapy and was newly diagnosed with type 2 diabetes, made him susceptible for mucormycosis. Nevertheless, the initial symptoms expressed by our patient were rather non-specific and they could have been easily attributed to COVID-19 and/or the continuous high-flow oxygen therapy. It made the diagnosis and the management of the case a laborious process that implied an interdisciplinary approach. This case also highlights the importance of a multidisciplinary team for an optimal management of a COVID-19 patient.

In order to maintain an adequate tissue oxygenation our patient required constant supplemental oxygen intake. During hospitalization he required high flow oxygen therapy and oxygen withdrawal was difficult. The fact that COVID-19 pneumonia was complicated by an acute sinusitis, brought into question whether the impairment of the sinus and nasal cavities might have a negative impact on respiratory gas exchange or not. In this regard, the small number of similar cases existing in the literature do not allow conclusions to be drawn, so it remains a hypothetical matter. Still, if we expand this theory to COVID-19 patients with a history of chronic sinusitis, we notice no statistically significant differences in the oxygen requirements of these patients (Wang *et al* 2020). Consequently, chronic sinusitis does not affect peripheral oxygenation, but patients with nasal polyposis seem to have a significantly lower blood oxygen level than those without (Bhattacharyya *et al* 2020).

We reported this case to draw attention to a rare but potentially severe complication of COVID-19. Although acute sinusitis can be considered a benign condition, easy to diagnose and treat, when associated to COVID-19, its proinflammatory and immunosuppressive status, and other additional immunosuppressive comorbidities can lead to severe consequences. In regard to this particular etiology, mucormycosis, we wanted to emphasize that early diagnosis is perhaps as essential as medical and surgical management in order to reduce mortality.

Conclusions

Mucormycosis, an invasive and life-threatening fungal infection, mainly associated with immunosuppression, is increasingly reported in COVID-19 patients. Our patient developed the most common clinical form of the disease- rhino-orbito-cerebral,

requiring both antifungal therapy and surgical debridement. A timely diagnose is of paramount importance to increase survival. Although we lacked microbiological evidence, the aggressive evolution of the disease required an early treatment decision. Considering that the risk factors for a severe form of COVID-19 and for mucormycosis seem to intercross, the possibility of a fungal superinfection in SARS-COV2 should not be ignored.

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Authors

- Dana Crisan, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University

of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Internal Medicine. E-mail: crisan.dc@gmail.com

•Lucreția Avram, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Geriatrics and Gerontology. E-mail: avram.lucretia9@gmail.com

•Alina-Bianca Olar, Clinical Hospital of Infectious Diseases, 23 Iuliu Moldovan Street, postal code: 400348, Cluj-Napoca, Romania. E-mail: olar_bialina@yahoo.com

•Anda Gâța, CF Clinical Hospital, 16-20 Republicii Street, postal code: 400015, Cluj-Napoca, Romania. E-mail: andapstl@yahoo.com

•Sergiu Văcăraș, Clinical of Surgery Oral and Maxillofacial I, 33 Motilor Street, postal code: 400001, Cluj-Napoca, Romania

•Mihaela Coman, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. E-mail: mihaela_c87@yahoo.com

•Bogdan Micu, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș

Street, postal code: 400012, Cluj-Napoca, Romania Department of Surgery. E-mail: micubogdan@yahoo.com

•Mihaela Cocis, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Intensive Care Unit. E-mail: mihaela_cocis@yahoo.com

•Constantin Bodolea, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Intensive Care Unit. E-mail: cbodolea@gmail.com

•Sorin Crișan, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Internal Medicine. E-mail: crisan.sorin@gmail.com

•Călin Ionescu, Clinical Municipal Hospital, 11 Tăbăcarilor Street, postal cod: 400139, Cluj-Napoca, Romania. University of Medicine and Pharmacy, "Iuliu Hațieganu", 8 Victor Babeș Street, postal code: 400012, Cluj-Napoca, Romania Department of Surgery. E-mail: ionescu.calincj2002@gmail.com

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