JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Case Report DOI: https://doi.org/10.23950/jcmk/12725

COVID-19 associated rhino-orbital-cerebral mucormycosis with underlying diabetes mellitus

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Received: 2022-07-11.
Accepted: 2022-12-08

J Clin Med Kaz 2022; 19(6):108-113

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Abstract

Introduction: Since the beginning of the COVID-19 pandemic, there has been an increase in opportunistic infections such as mucormycosis, which is of some concern given the fairly rapid spread. The development of immunosuppression associated with COVID-19, coupled with the presence of comorbidities that exacerbate the progression of the disease and in some cases lead to a fatal outcome, plays an important role in this.

Case presentation: We have examined a real case of rhino-orbital-cerebral mucormycosis in comparison with earlier published contemporary studies on epidemiology, clinical manifestations, and risk factors. Autopsy materials of nasal mucosa, eye socket, brain of a patient with COVID-19 associated with diabetes mellitus have been subjected to a histological study.

Conclusion: The presented case demonstrates a unique pathomorphological pattern of rhino-orbital-cerebral mucormycosis, first registered in Kazakhstan and of great interest in the world practice.

Key words: mucormycosis, diabetes mellitus, COVID-19, corticosteroids

Introduction

The global COVID-19 pandemic, which is widespread throughout the world, is a threat to public health, socio-economic livelihoods and humanity as a whole. Clinical manifestations of the disease can vary from asymptomatic to severe forms. Regardless of the age of the patients, the mortality rate can be affected by the presence of comorbidities of the cardiovascular system, liver and kidneys, as well as diabetes mellitus [1-2].

Severe forms of COVID-19 are accompanied by bacterial and fungal infections. One of these opportunistic infections is mucormycosis, an upsurge of which has been reported worldwide [3]. Thus, the disease incidence in India rose to 26.7%. A significant role in the development of invasive forms is played by a weakening of the immune system due to a severe course of diabetes mellitus, immunodeficiency, cancer and transplantation. In clinical practice, quite often there are lesions of the sinuses, brain, lungs and other regions in patients with COVID-19. In the rhinocerebral form of mucormycosis, the most typical location is in the nose, but the disease may spread to the paranasal sinuses, orbit, facial bones, and skull cavity. The administration of glucocorticosteroids in the treatment of COVID-19 reduces resistance to opportunistic infections. The prevalence of clinical and radiological symptoms of coronavirus pneumonia makes it difficult to diagnose mucormycosis. This leads to late diagnosis and unfavorable prognosis [4-6].

According to a systematic review of 101 cases of mucormycosis of different localizations in patients with confirmed COVID-19 by Indian scientists Singh A.K. et al., 82 cases were reported in India, while there were 19 cases in other countries [7]. Nasal and sinus lesions were the most common (88.9%), followed by rhino-orbital (56.7%) and rhino-orbital-cerebral forms (22.7%). The leading risk factors in these cases were the presence of diabetes mellitus and COVID-19 therapy with glucocorticosteroids. Intracranial or orbital lesions associated with the immunosuppression drive a high mortality rate of 50-80%. Tissue necrosis is a distinctive feature of mucormycosis, but it appears late [7-8].

Our study shows what pathomorphological changes have been found in rhino-orbit-cerebral mucormycosis lesions in a single fatal case in Kazakhstan. The case report will be an instructive, scientific and educational tool for the work of pathologists, forensic experts of the world for the reason that in most cases of cerebral mucormycosis lesions in COVID-19 autopsies have not been conducted to avoid spread of infection, while we in Kazakhstan have performed autopsies followed by macro and microscopic examination of tissues.

Case presentation

Medical experts from Kazakhstan found a single fatal case of mucormycosis in COVID-19 with rhino-orbital-cerebral lesions in a 16 year old patient. After autopsy, a histological examination was performed. From the brief fact of the case, we know that the patient had a history of diabetes mellitus in her life. During the pandemic, she contracted COVID-19 infection identified by PCR assay (polymerase chain reaction). On admission to the hospital, her health status was assessed as extremely severe. The patient was in the intensive care unit for several days. While in the intensive care unit, doctors noticed that the girl gradually developed black spots on her face, mostly in the area of her nose.

Despite the ongoing therapy (which included glucocorticosteroids), the patient developed coma and died. Provisional forensic diagnosis: Cerebral infarction (in question), COVID-19 associated pneumonia (in question), Nasal septal mucosa necrosis of unknown genesis.

Due to the disfigurement of the face with blackened skin color, the parents complained to the investigators about the actions of doctors and suspected oxygen burns of the face in the intensive care unit, so a forensic medical examination was appointed.

On autopsy, macroscopic examination showed: the internal organs were anatomically correctly positioned. Changes were found in the brain with predominant brown softening in the frontal lobe in the area of the olfactory nerve and basal part in the region of the oculomotor nerve on the left. In the lungs, in the pleural cavity, hemorrhagic fluid with overlapping fibrin strands, lung parenchyma of dense consistency, red in color on section. The pancreas was small and lobular in shape, of dense consistency.

Topically: necrotic changes of the soft tissue of the nasal mucosa, facial skin in the orbital region with bruising and black tint, mainly in the nasal region with necrotic destruction of the nasal septum, extending to the eye socket with scab and facial disfigurement. Figure 1 (A, B, C) shows the fungal lesion region with facial disfigurement.

Figure 1 - Fungal lesion region with facial disfigurement: A, Necrosis of the skin and subcutaneous tissue in the form of a black scab from the nasal cavity area. B, Necrosis of the skin of the bridge of the nose, zygomatic region and eyelids of the eye socket. C, Necrosis of skin and mucous membrane of eyelid and sclera in the form of black scab.

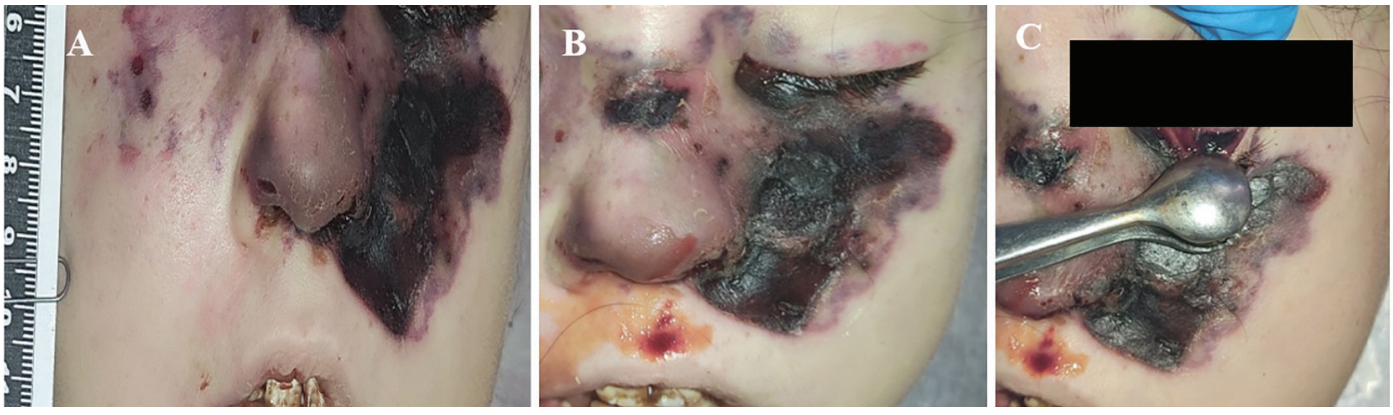


Figure 2 - Photomicrograph of a histological examination of necrotic nasal cavity tissue with a cluster of mucormycosis bacilli, fungal hyphae of mucormycosis. Hematoxylin and eosin, x 200.

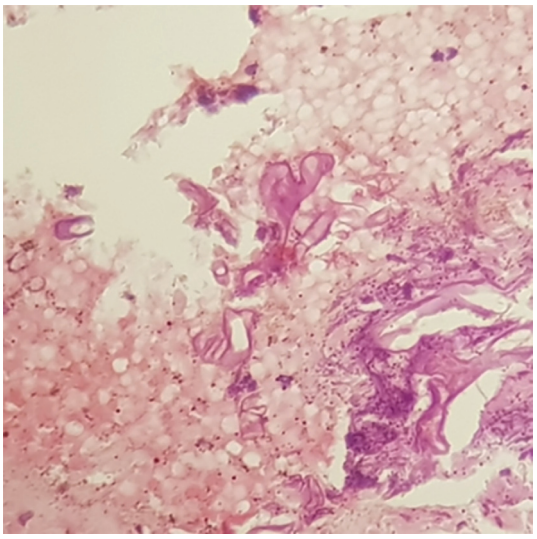


Figure 3a - White matter of the brain with glial reaction to introduction of mucormycosis hyphae, spherulas. A, branches of mucormycosis hyphae and spherules in the white matter of the brain. Hematoxylin and eosin staining, x150.

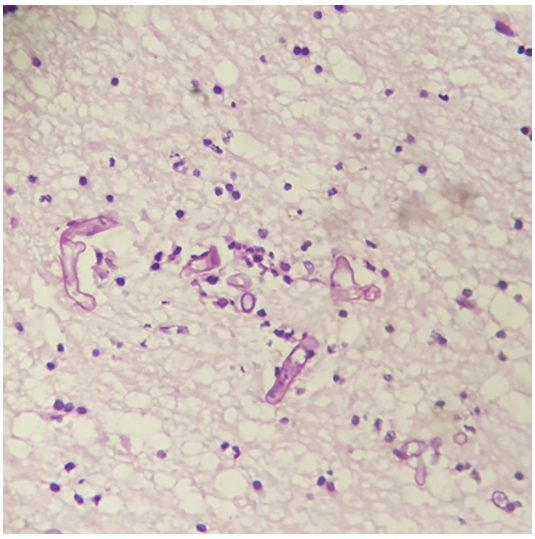


Figure 3b - B, Same area of white matter at low magnification with glial reaction to accumulation of mucormycosis hyphae and spherulas. Hematoxylin and eosin, x40.

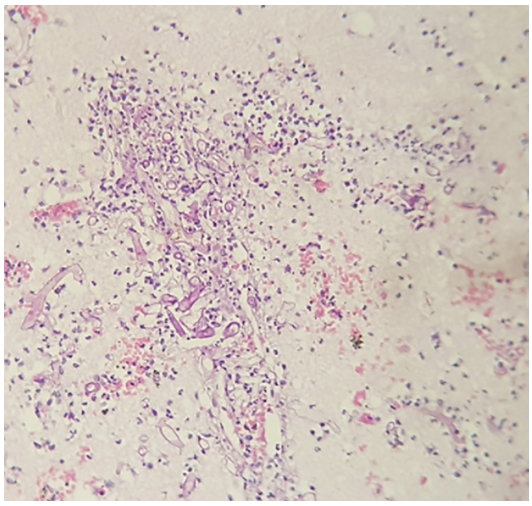


Figure 4b - B, Ring-shaped accumulation of mucormycosis hyphae and spherulas with perifocal cellular reaction and small foci of hemorrhage. Hematoxylin and eosin, x40.

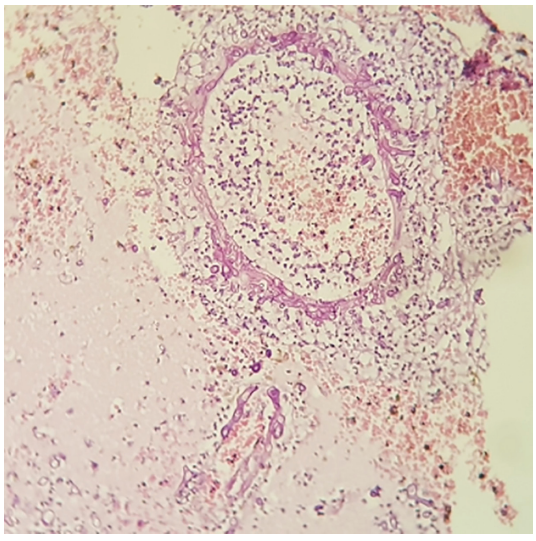


Figure 5b - B, Ring-shaped brain lesion with accumulation of mucormycosis bacilli (hyphae). Hematoxylin and eosin, x 400.

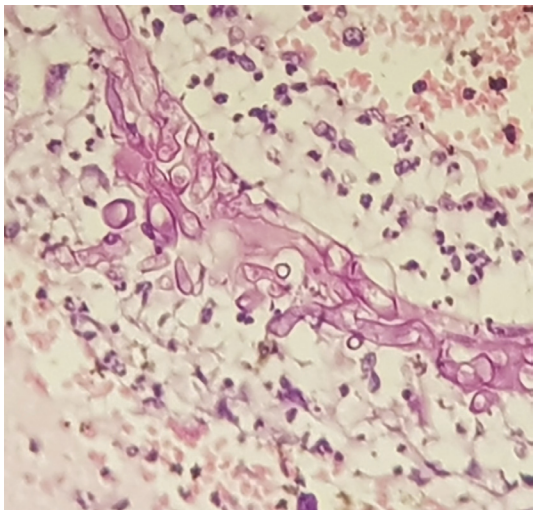


Figure 4a - Grey matter lesion of the cerebral cortex with mucormycosis. A, Massive accumulation of mucormycosis bacilli with glial-cellular reaction. Hematoxylin and eosin, x 400.

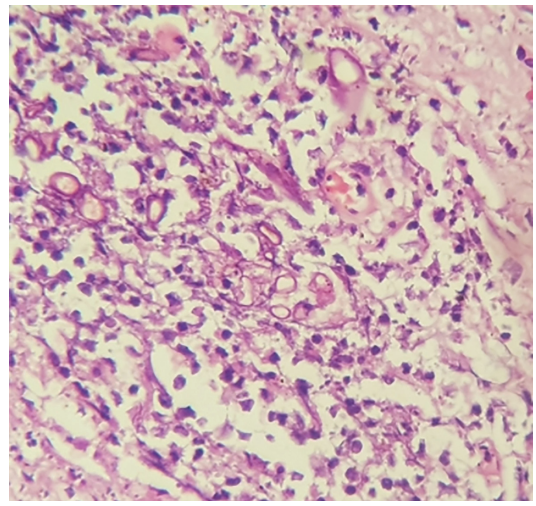


Figure 5a - Photomicrograph of the brain with mucormycosis lesions: bacilliform tube-shaped hyphae with septa and spherulas. A, Grey matter of the cerebral cortex with infiltration of mucormycosis hyphae and softening of the substrate around the vessel.

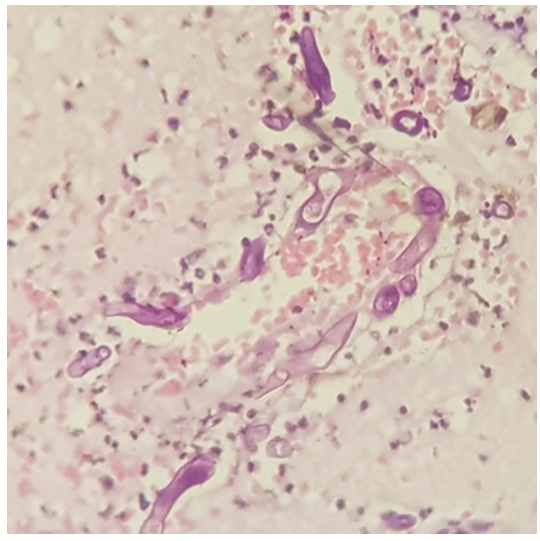


Figure 6a - Photomicrograph of nasal cavity mucosa and eyelid mucosa with mucormycosis lesions. A, Mucormycosis accumulation in the submucosal layer with perivascular localization.

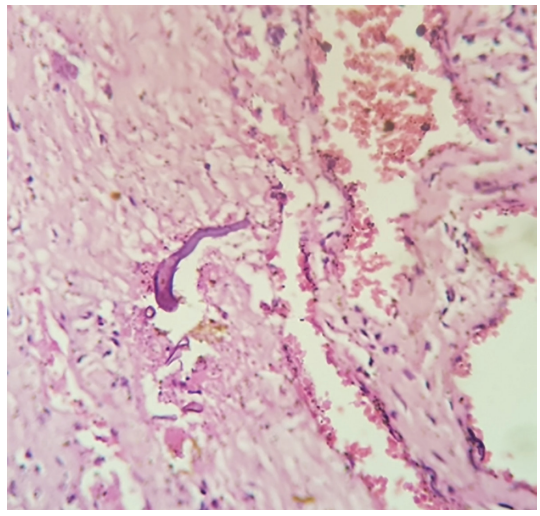


Figure 6b - B, Complete necrosis associated with mucormycosis of the lower eyelid mucosa with accumulation of mucormycosis hyphae.

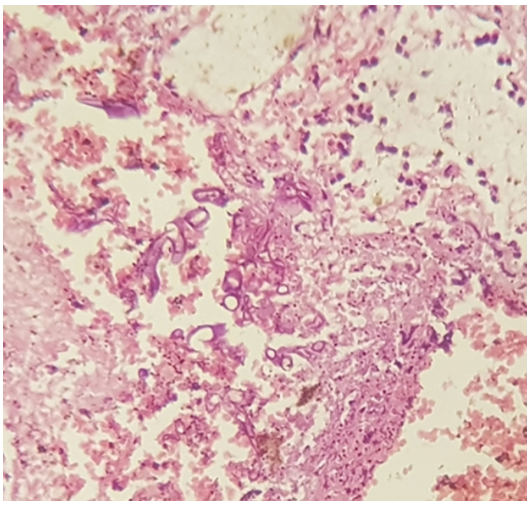


Figure 6c - C, The same region of the lower eyelid in the deeper tissue with accumulation of mucormycosis bacilli.

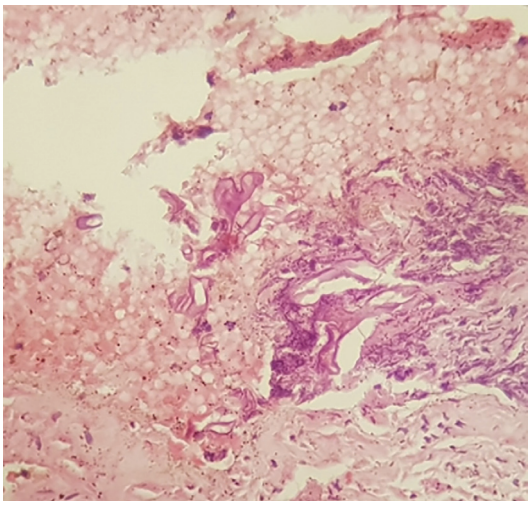


Figure 6d - D, Photomicrograph of a histological examination of necrotic nasal cavity tissue with accumulation of mucormycosis bacilli, mucormycosis fungal hyphae. Hematoxylin and eosin, x200.

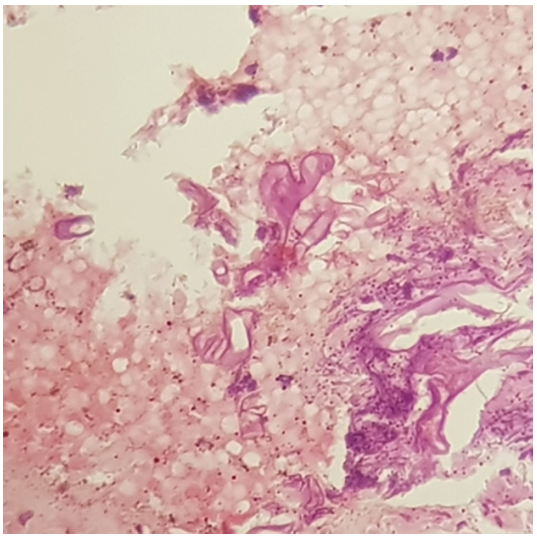


Figure 7a - Lung tissue with ARDS/DAD (diffuse alveolar damage): Masson's bodies and autophages. A, Exudate from mononuclear cells with erythrocytes admixture in lumen of respiratory alveoli with polypoid connective tissue nodule - Masson's bodies with foci of organizing pneumonia. Hematoxylin and eosin, x100.

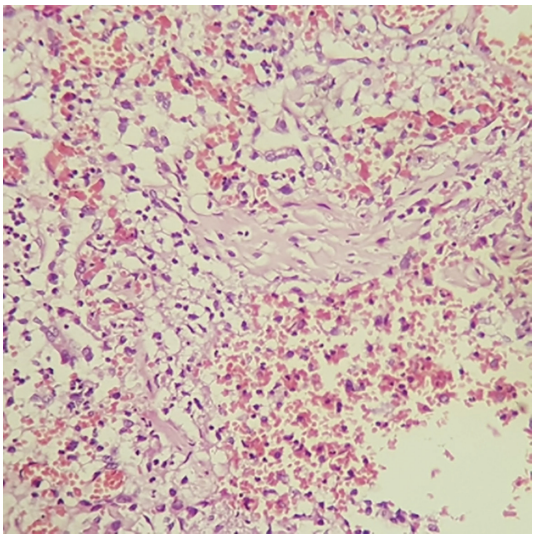
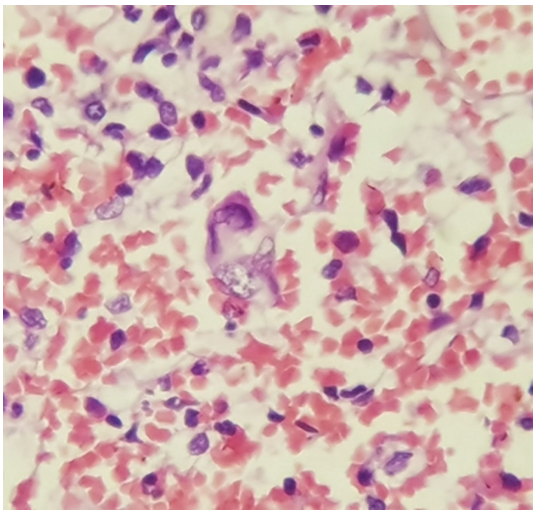
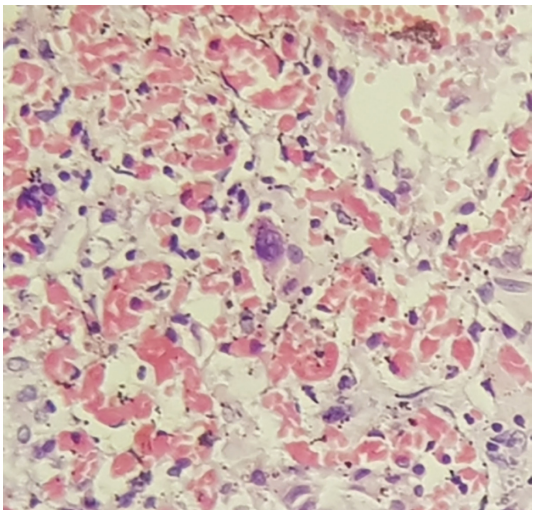


Figure 7b - B, Same region with autophages with viral inclusions in the cytoplasm of alveolar macrophages with hemorrhage. Hematoxylin and eosin, x400.

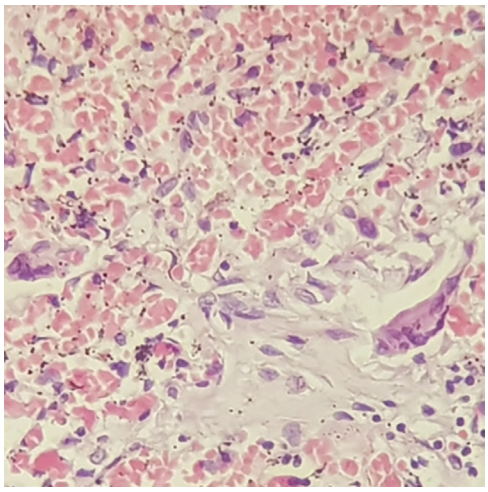
Figure 8a - Monster macrophages are multinucleated like giant cells. A, Multinucleated inclusions in the cytoplasm of autophages are clearly seen as monster macrophages.





Histological examination identified fungal infiltration in the tissues from the nasal septum mucosa, soft tissue of the eye socket, and brain tissue in the form of bamboo sticks, hyphae, spherulas, and septa with inflammatory cellular infiltrates. Photomicrographs of these changes were captured with a Leika DM1000 microscope for scientific and practical purposes (Figures 2-8). Diffuse alveolar damage of lung tissue in the form of Masson's bodies - polypoidal fibrous nodules in the lumen of alveoli was found. Diffuse infiltration of the alveolar lumen by monster macrophages in the form of multinucleated cells due to penetration of viral particles into the cytoplasm of type 2 pneumocytes was observed, which corresponds to acute adult respiratory distress syndrome (ARDS) in the proliferative phase from 10 to 20 days' time from the onset of disease in COVID-19 (Figures 7, 8).

Figure 8b - B, Another region of the lung by giant cell macrophages with mononuclears in the lumen of the respiratory alveoli. Hematoxylin and eosin, x200.



Discussion

In this case, the patient developed coronavirus infection associated with diabetes mellitus. Due to the severe progression, she was prescribed glucocorticosteroids, which exacerbated the severe immunosuppression and led to the development of mucormycosis, even despite her young age. Comparison with data from the literature showed that with timely diagnosis, without manifestation with COVID-19, of this fungal infection in different countries is more effective and timely, as well as treatment, in many cases, patients recovered [7, 9, 10]. While doctors in Kazakhstan had not previously observed mucormycosis associated with COVID-19 in patients with coronavirus infection. Therefore, in described case the doctors, despite the presence of diabetes mellitus, due to the deterioration of the patient's health status, were forced to prescribe glucocorticosteroids for COVID-19 treatment as part of the complex therapy. As other studies also show, the combination of diabetes mellitus and immunosuppression with glucocorticosteroids dramatically increases the risk of mucormycosis [11-13]. Thus, our data have demonstrated that in patients with COVID-19 and comorbid diabetes mellitus, prescription of glucocorticosteroids must be avoided or combined with sensitive antifungal drugs. This opinion also coincides with that of other authors who have observed mostly in India [12]. In general, given the extremely rare confirmed case of mucormycosis in Kazakhstan (1 case), this case is an instructive example for clinicians in the future. Nevertheless, in further cases of severe coronavirus infection associated with comorbidities, every effort must be made to prevent and effectively treat mucormycosis.

An autopsy found specific evidences of macro and microscopic changes specific for mucormycosis, a detailed description of microscopic changes in the internal organs was made, confirmatory photographs were taken, which allowed to exclude oxygen burns of the face in the intensive care unit. Original microscopic photographs of the mucormycosis fungus itself, along with changes in the surrounding tissues and cells, were obtained.

In contrast to other countries, no other cases of this fungal infection, namely mucormycosis with a more favorable progression, were identified in Kazakhstan [14]. This can be explained by the low frequency of mucormycosis associated with COVID-19 coronavirus infection in Kazakhstan in general, relative to other countries, relatively low frequency of cases with a severe disease progression. Also interesting is the fact that this fungal infection developed in a young patient, whereas among older patients there were more fatal outcomes from COVID-19 during the pandemic, but no evidences of mucormycosis were found. It cannot be excluded that some elderly patients with fatal infection could have small foci of mucormycosis without destruction of soft tissue of the face, but not as in our case with facial disfigurement. Therefore, dissemination of the educational information about this extremely dangerous fungal infection, in the case of COVID-19 infection associated with diabetes mellitus, is very important for doctors of different disciplines.

Conclusion

This case allowed a detailed macroscopic, microscopic description and verification of specific evidences of rhino-orbital-cerebral mucormycosis in a young patient, clarification of predisposing factors, and conclusions about the need for timely prevention and treatment of this severe infection.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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