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COVID-19-ASSOCIATED FRONTAL BONE OSTEOMYELITIS. CLINICAL CASE AND LITERATURE REVIEW

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COVID-19-associated osteomyelitis is a purulo-necrotic complication of past coronaviral infection. The majority of described cases of this complication are caused by *Mucorales* fungi. Mucormycosis is a severe complication of COVID-19 associated with high mortality rate. Most commonly it affects maxillary sinuses, facial bones, and orbits. Due to quick progression of the disease, it is important to remember the association between COVID-19 infection and purulo-necrotic lesions of the skull that can be complicated by brain involvement.
The article presents a very rare observation of COVID-19-associated osteomyelitis affecting the squamous part of the frontal bone complicated by formation of bilateral symmetrical subgaleal abscesses in the projection of the frontal eminences.

Keywords: COVID-19-associated osteomyelitis, complication of coronaviral infection, mucormycosis, purulo-necrotic complication, skull lesions, abscess

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BACKGROUND

COVID-19-associated osteomyelitis is a purulo-necrotic complication of acute viral respiratory infection caused by the SARS-CoV-2 virus. Since the beginning of the COVID-19 pandemic, many reports on development of purulo-necrotic complications during or after coronaviral infection were published. Cases affecting both the bones of the body and limbs and the face were described. The majority of cases of COVID-19-associated osteomyelitis in international literature were caused by *Mucorales* fungi [1]. Consequetively, the disease is traditionally called COVID-19-associated mucormycosis (CAM). The importance and interdisciplinarity of the problem are confirmed by the fact that this COVID-19 complication is encountered by doctors of various specialties – otorhinolaryngologists, maxillofacial surgeons, dentists, neurosurgeons – in all countries of the world. According to the Leading International Fungal Infection (LIFE) database, prior to the pandemic yearly worldwide mucormycosis morbidity was approximately 5,000 cases. Among patients with COVID-19, CAM incidence is 7 per 1,000 patients, and incidence of all fungal infections is 12 cases per 1,000 people. Additionally, there is a statistically significant difference between European and Asian countries: 7 cases in Europe versus 15 cases in Asian countries per 1,000 patients [2]. The most detailed information on the CAM problem comes from India where almost 30,000 cases of the disease were reported [3–10]. In this article, we present a very rare observation of COVID-19-associated osteomyelitis affecting the squamous part of the frontal bone with formation of bilateral symmetrical subgaleal abscesses in the projection of the frontal eminences.

CLINICAL CASE

Patient Ya., *62 years, was admitted to the Neurosurgical Division of the Clinic for Nervous Diseases named after A.Ya. Kozhevnikov at the I.M. Sechenov First Moscow State Medical University in May of 2022. During admission, the patient complained of headaches and presence of painful soft-tissue subcutaneous lumps on the forehead in the projection of the frontal eminences on both sides.*

According to the patient and his medical records: on 25.11.2021 he had acute ischemic cerebrovascular accident in the area of the pons Varolii on the left with development of right-sided hemiparesis and dysarthria. He was hospitalized to a neurological hospital where he subsequently was infected with COVID-19. During COVID-19 treatment, he was administered corticosteroids and humidified oxygen insufflation.

During hospitalization he noticed soreness in the frontal area and rhinorrhea. On 20.01.2022, swelling and deformation of the soft tissues on the forehead on the right acutely appeared but 3 days later these changes dissipated. On 13.02.2022, swelling of the forehead soft tissues on the right developed again, and 5 days later it appeared on the left. Gradually, in the area of the swelling 2 subcutaneous lumps of irregular round shape with dense elastic consistency formed. Antibacterial therapy was prescribed (amoxiclav 2000 mg/day) during which the size of the lumps decreased a little.

On 11.04.2022, the patient underwent magnetic resonance imaging (MRI) of the brain and skull; on 13.04.2022, computed tomography (Fig. 1). Imaging showed multiple foci of frontal bone destruction (osteomyelitis?), bilateral abscesses in the soft tissues of the forehead in the projection of the frontal eminences. MRI showed signs of frontal sinusitis. Moreover, prior to COVID-19 infection, the patient did not note any signs of chronic inflammation of the paranasal sinuses. Due to the signs of osteomyelitis, the patient was hospitalized to the neurosurgical division for surgical treatment.

At admission, neurological status of the patient showed bilateral spastic hemiparesis, 4 points. Tendon reflexes were activated on the right side with expansion of reflexogenic zones; additionally, on the right side, pathological Babinski, Oppenheim and lower Rossolimo»s reflexes were induced. These changes considering the patient»s medical history were interpreted as consequences of acute cerebrovascular disease.

Blood and spinal fluid tests did not show signs of inflammation. No signs of disseminated lesions in the rest of the skeleton were found.

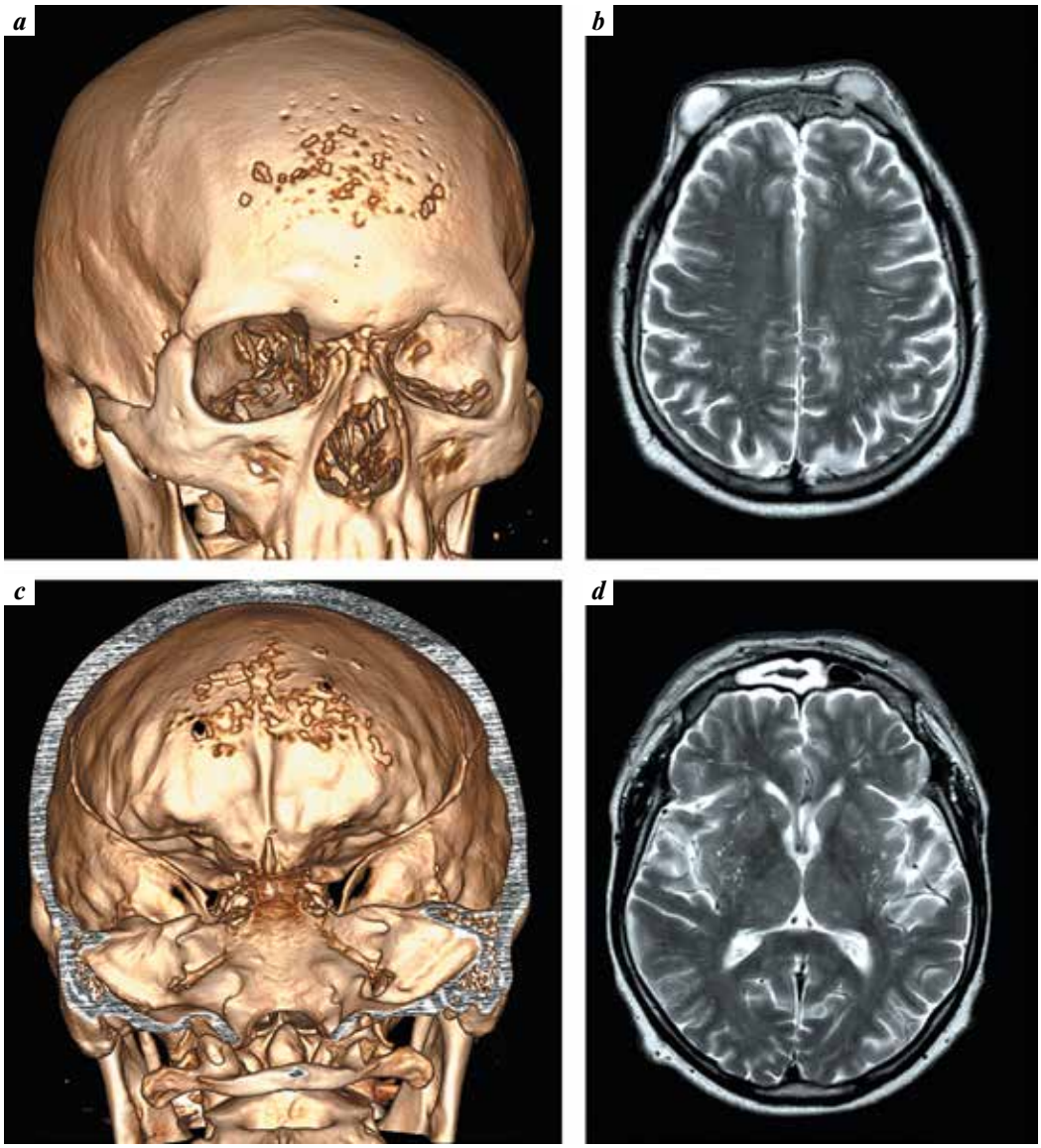

Fig. 1. *Computed tomography with 3D reconstruction of the skull (a, c) and magnetic resonance imaging (b, d) prior to surgery: a, c – computed tomography images with 3D reconstruction clearly show multiple destruction and perforation lesions in the frontal bone; b, d – T2-weighted images in the axial plane show multiple abscesses of the soft tissues (b) and signs of frontal sinusitis (d)*

On 04.05.2022 surgery was performed: resection trephination of the skull in the frontal area, resection of subgaleal abscesses of the soft tissues in the projection of the frontal eminences, resection of the frontal bone changed by osteomyelitis and epidural abscess of the frontal area, sanitation of the frontal sinuses. The surgery was performed through biauricular access. The frontal bone was removed with wide resection of the upper walls of the frontal sinuses. Purulent depositions on the surface of the dura mater were removed. No signs of dura mater perforation and intradural advancement of the inflammatory process were observed. After resection of the frontal sinus mucosa, their tamponade was performed using autologous transplant of subcutaneous fatty tissue which was immobilized using biological glue (Fig. 2).

Until the results of bacteriologic examination, empirical antibacterial and antifungal therapy was prescribed. Due to negative result of bacteriologic examination for aerobic, anaerobic bacteria and fungi, the therapy was stopped on day 8 after surgery.

The postoperative period was uncomplicated. Fever, liquid and blood accumulation in the surgical area were not observed, the patient was mobilized on day 1 after surgery. The

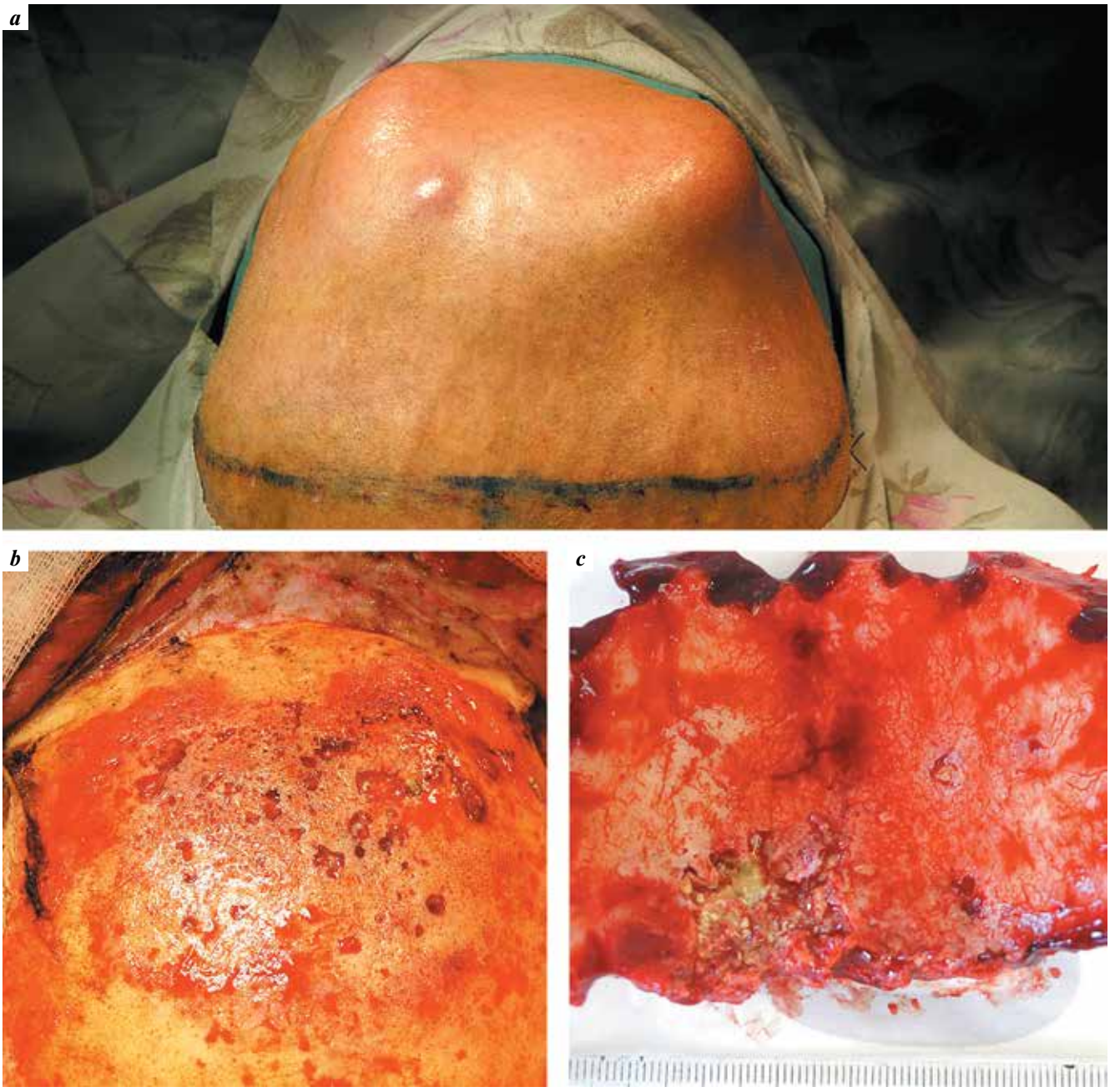

Fig. 2. *Intraoperative photos: a – abscesses of the soft tissues above the surface of the frontal eminences; b – damaged squamous part of the frontal bone; c – internal surface of the frontal bone after its resection*

sutures were removed on 14th postoperative day. Examination of the nasal cavity showed intact mucosa before and after surgery. The patient was discharged from the hospital for dynamic observation and future decision on reconstruction of the bone defect.

DISCUSSION

Currently, two main elements of pathogenesis of purulo-necrotic lesions of the maxillary sinuses during COVID-19 infection are being considered. The first one is abnormal microcirculation in the bone vessels and mucosa of the sinuses leading to formation of areas of osteomalacia and necrosis serving as a substrate for colonization by conditionally pathogenic flora. Abnormal microcirculation is caused by angiopathic effects of SARS-CoV-2 including abnormalities of the hemostasis system, development of intravascular clotting and macrothrombi in bone vessels and mucosa of the paranasal sinuses, oral and nasal cavities [1, 11, 12].

The second most important element of CAM pathogenesis is immunodeficiency in patients with COVID-19 infection which presumably underlies primarily fungal nature of the infectious agent causing bone lesions. A connection between concomitant disorders promoting abnormal microcirculation and local immune response (in the first place, diabetes mellitus) and development of opportunistic infection, mucormycoses in particular, was observed [13, 14]. Apart from the above stated, analysis of literature data on CAM pathogenesis allows to identify several treatments of COVID-19 which increase the risk of this complication [8, 9, 15]:

- glucocorticoid therapy;
- high-flow oxygen therapy;
- massive antibacterial therapy.

It is supposed that active nasal oxygen insufflation with immunosuppression strengthened by glucocorticoids and microthrombi in mucosal vessels promote invasion of a pathologic agent into the mucosa and underlying bone tissue with subsequent development of osteomyelitis lesions.

Clinical picture of CAM is not particularly specific and usually depends on the location. Considering that the paranasal sinuses, facial bones and orbits are affected the most frequently, typical clinical manifestations are:

- difficulty breathing through the nose;
- pathological discharge (rhinorrhea) from the nasal cavity;
- dryness in the nasal cavity;
- pains in the areas of the mouth, nose, and face.

Computed tomography of the skull and paranasal sinuses allows to detect edema and hypertrophy of the maxillary sinus mucosa, bone destruction (osteomalacia) of the alveolar processes and maxillary sinus walls, frontal sinus, in severe cases – facial bones and frontal bone with formation of bony sequestrums [3, 16].

Computed tomography with bolus contrast allows to detect impaired blood flow in the areas of osteonecrosis.

Magnetic resonance imaging (MRI) has lower diagnostic value for detection of bone pathology, but it allows to evaluate the condition of maxillary sinus mucosa. Additionally, MRI allows to evaluate the condition of the orbits and brain matter in cases of their involvement in purulo-necrotic process [17].

CAM treatment includes surgical sanitation of the focus and subsequent drug therapy which is corrected in accordance with the results of bacteriologic and mycologic assays. Currently, the standard treatment of invasive CAM is amphotericin B in cases of identified fungal causative agent. In other cases, standard postoperative antibiotic prevention in combination with antifungal therapy (isavuconazole, posaconazole, fluconazole) is acceptable. Additionally, correction of the concomitant pathology is necessary, especially glycemia control in patients with diabetes mellitus [8, 11, 13]. In all cases of osteomyelitis in patients with COVID-19, standard bacteriologic assay for aerobic and anaerobic agents with determination of antibiotic sensitivity and special mycologic examination with Sabouraud dextrose chloramphenicol agar seeding, as well as direct and fluorescence microscopy of biological material are necessary [1].

Mucormycosis is a severe complication of COVID-19. Overall mortality of sino-orbital mucormycosis without brain involvement is 24 %, with brain involvement – 59 %. Additionally, 46 % of survivors of these 2 groups experience vision loss [1, 18]. Due to fast progression of the disease, doctors of various specialties should keep in mind the connection between COVID-19 infection and purulo-necrotic infection of the skull which can be complicated by brain involvement.

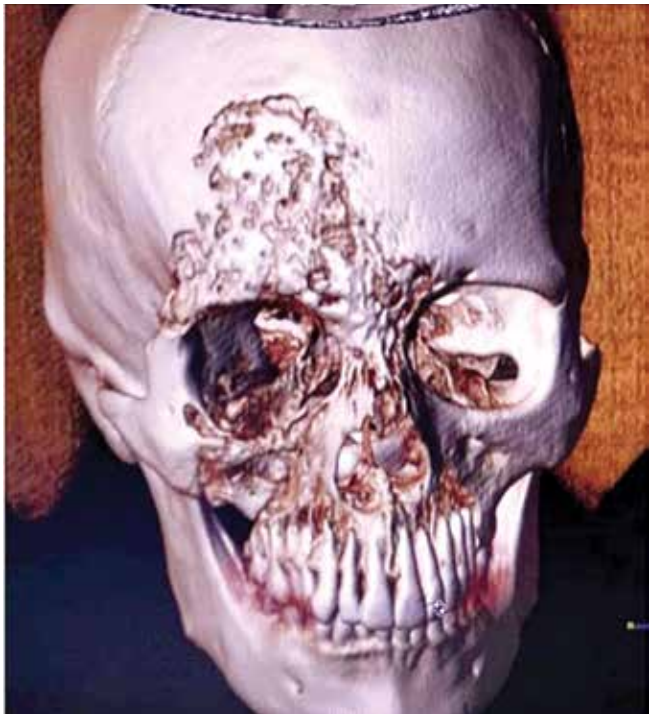

Fig. 3. *Computed tomography. 3D image. Multiple lesions in the facial bones, base of the skull and squamous part of the frontal bone. Illustration from the article by S. Eswaran et al. [19]*

Currently, the literature describes in detail lesions in the maxilla, nose, and orbit with secondary involvement of the squamous part of the frontal bone (Fig. 3) [19]. Cases of advanced lesions in the squamous part of the frontal bone without signs of involvement of the maxilla and orbit were not yet described in literature which was available to us for analysis. The presented observation is possibly the first such detailed description in clinical practice.

CONCLUSION

One of the dangerous purulo-necrotic complications of coronaviral infection is COVID-19-associated osteomyelitis (or CAM) which is usually caused by *Mucorales* fungi. This complication is encountered by doctors of various specialties: otorhinolaryngologists, maxillofacial surgeons, dentists, neurosurgeons. Due to high mortality and fast progression of the disease, the doctors should keep in mind that necrotizing suppurative lesions of the skull can be complicated by brain involvement. In all cases of osteomyelitis in patients with COVID-19, bacteriologic examination for aerobic and anaerobic agents with determination of antibiotic sensitivity is necessary. CAM treatment includes surgical sanitation of the lesion and subsequent drug therapy as well as correction of the concomitant pathology.

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Author's contribution
G.Yu. Evzikov: patient observation, performing a surgical operation;
D.Yu. Neretin: collecting data for analysis, analyzing the data obtained, monitoring the patient, reviewing the literature on the topic of the article, article writing.

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Compliance with patient rights and principles of bioethics.
The patient has signed an informed consent to the publication of his data.

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