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LITERATURE REVIEW

Invasive fungal rhinosinusitis

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ABSTRACT

Invasive fungal rhinosinusitides are a group of disorders with three subtypes (acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis and granulomatous invasive fungal rhinosinusitis), requiring urgent diagnosis and early treatment due to the reserved vital and functional prognosis. This disorder occurs in immunocompromised patients, but it can also occur in immunocompetent people. Aspergillus and Mucormicosis species are the most common microorganisms found in invasive fungal rhinosinusites. The otorhinolaryngologic clinical examination and imaging techniques provide important diagnostic information in patients with risk factors for invasive fungal rhinosinusitis, including intracranial or orbital extension identification. The treatment of invasive fungal rhinosinusites (acute or chronic) consists of reversing immunosuppression, appropriate systemic antifungal therapy and aggressive and prompt surgical debridement of the affected tissues.

KEYWORDS: rhinosinusitides, Aspergillus, invasive, acute, chronic.

INTRODUCTION

Invasive fungal rhinosinusitides (IFRS) are a group of disorders with three subtypes (acute IFRS, chronic IFRS and granulomatous IFRS), requiring urgent diagnosis and early treatment due to the reserved vital and functional prognosis. This disorder occurs in immunocompromised patients, in patients with neutropenia, immunosuppressive therapy, malignant haematological disorders, organ and bone marrow transplantation, advanced HIV infection, diabetes, protein malnutrition and cortico-dependent patients. More rarely, IFRS may occur in immunocompetent individuals. Thus, most patients with IFRS already have a low immune system due on the one hand to the associated diseases, and on the other hand to the treatment for the underlying disease, which is why, in these cases, the prognosis is reserved and mortality is high. In addition, these factors may cause difficulties in the diagnosis and treatment of IFRS. Therefore, the IFRS diagnosis should be established as soon as possible for the initiation of aggressive surgical and systemic antifungal therapy[1-4].

Aspergillus and *Mucormicosis* species are the most common microorganisms found in IFRS. Most invasive fungal infections (approximately 80%) are caused by *Aspergillus fumigatus*. The second most common pathogenic species (approximately 15-20%) is *Aspergillus flavus* and, to a lesser extent, *Aspergillus niger* and *Aspergillus terreus*[1,3].

In the literature, the following diagnostic criteria are proposed for the IFRS diagnosis: (1) rhinosinusitis (RS) confirmed on the imaging exam; (2) histopathological evidence of fungal invasion of the mucosa, submucosa, blood vessels or paranasal sinus bones; (3) necrotic tissue with minimal infiltration of inflammatory cells[1-3,5].

It is difficult to formulate the clinical suspicion of IFRS relying solely on the clinical picture, although the fungal etiology should be considered in the cases of rebellious chronic purulent rhinosinusitis

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after two or more prolonged antibiotic treatments[1,2].

The otorhinolaryngological clinical examination can provide important diagnostic information in patients with risk factors for IFRS. The most common sign is a nasal mucosa with pale and edematous areas, which bleeds very little and is painful to the touch. Black eschars appear in the last phases of the disease and are due to vascular thrombosis and tissue necrosis and are considered almost pathognomonic for IFRS. In the case of orbit involvement, we detect limitations of eyeball movements, palpebral ptosis or decreased visual acuity. Being a potentially invasive condition, in IFRS there may be lesions on the skin, the palate and the soft palate, or the intracranial extension may be associated[1].

Imaging (CT, MRI) can provide significant help in the diagnosis of invasive fungal rhinosinusitis. Although many aspects found on CT images are suggestive of IFRS, none of them can be considered pathognomonic. For example, there are authors who consider that the earliest evidence of the fungal disease is the infiltration of adjacent soft tissues[1,6]. However, other authors argue that, in patients at risk, sinus mucosal thickening associated with unilateral nasal inflammation may be predictive signs of IFRS[1,7]. In the case of a suspicion of intracranial extension, magnetic resonance imaging is indicated, which is more sensitive to the identification of intracranial or orbital lesions[1].

The diagnosis of certainty is established following the histopathological examination, which gives the possibility to detect necrosis, inflammation but also mycelial filaments[1].

The treatment of acute or chronic IFRS consists of reversing immunosuppression, appropriate systemic antifungal therapy and aggressive and prompt surgical debridement of the affected tissues[3].

ACUTE INVASIVE FUNGAL RHINOSINUSITIS

Acute invasive fungal rhinosinusitis is, generally, a rare condition, but the most dangerous form of fungal rhinosinusitis and the most common form of IFRS. It presents a progressive, rapid evolution of up to 4 weeks, endangering the patient's life and requiring immediate medical attention. In the past, patients with this condition had a survival rate of 20-75%, correlated with the control of the underlying disease. Recent studies have highlighted, concurrently with improving the diagnosis, treatment and prophylaxis (active surveillance of risk population, reversal of neutropenia and other causes of immunosuppression, reversal of diabetic ketoacidosis, aggressive and prompt surgical debridement and systemic antifungal chemotherapy), the improvement in survival rates, with a reduction in mortality from 50-80% to about 18%[3,8-10].

The disorder appears quite rarely – up to 4% of patients with bone marrow transplantation – particularly affecting severely immunocompromised patients. People diagnosed with leukemia, acquired immunodeficiency syndrome, aplastic anemia, uncontrolled diabetes or hemochromatosis are the most vulnerable. Patients with organ or bone marrow transplantation, those receiving long-term chemotherapy or corticosteroid treatment are also vulnerable[9,11,12].

Often, infection is attributed to fungal invasion, which previously colonized the sinuses, or to spores of inhaled fungi. *Aspergillus* or fungi of the *Zygomycetes* class are the most common causative agents, the disorder they provoke having a sudden and extremely aggressive evolution. Fungi develop and progress rapidly by invading arterial blood vessels. Tissue necrosis, secondary to the obstruction of blood flow, leads to a pale, gray or black tissue infarction. Fungi extend through the bone tissue of the sinuses and invade the adjacent areas (the hard palate, the orbit, the cavernous sinus, the cranial nerves, the skull base, the carotid artery and the brain). The disorder can spread rapidly (hours or days) and can endanger the patient's life if it is undiagnosed or untreated[2,9-11].

The first symptoms may mimic a chronic bacterial RS and include fever, nasal congestion, facial pain, epistaxis, headache. Subsequently, patients may present a "latent" phase in which pain may be transient, phase that is rapidly followed by severe signs and symptoms. Late symptoms include facial or palate numbness, palpebral ptosis, visual disturbances, facial edema, dental pain, central neurological symptoms and even death. The disorder, especially in the case of intracranial extension, can be rapidly fatal, with a short-term mortality rate of 30-83%, and a mortality rate of 97-100% in the untreated condition[8-10].

The most common factor that predisposes to acute IFRS is neutropenia, especially less than 1000 neutrophils/μL of blood, which significantly reduces the inflammatory response and the body's ability to fight the infection[9,13].

Acute IFRS is best seen in nasal endoscopy and usually affects the nasal septum, the nasal turbinates and the paranasal sinuses. Initially, necrotic ulcers are present in the nasal septum (eschars); afterwards, the other structures may be affected (Figure 1)[9,10,12].

In the case of acute IFRS the CT examination can reveal the thickening of the mucosa at the level of

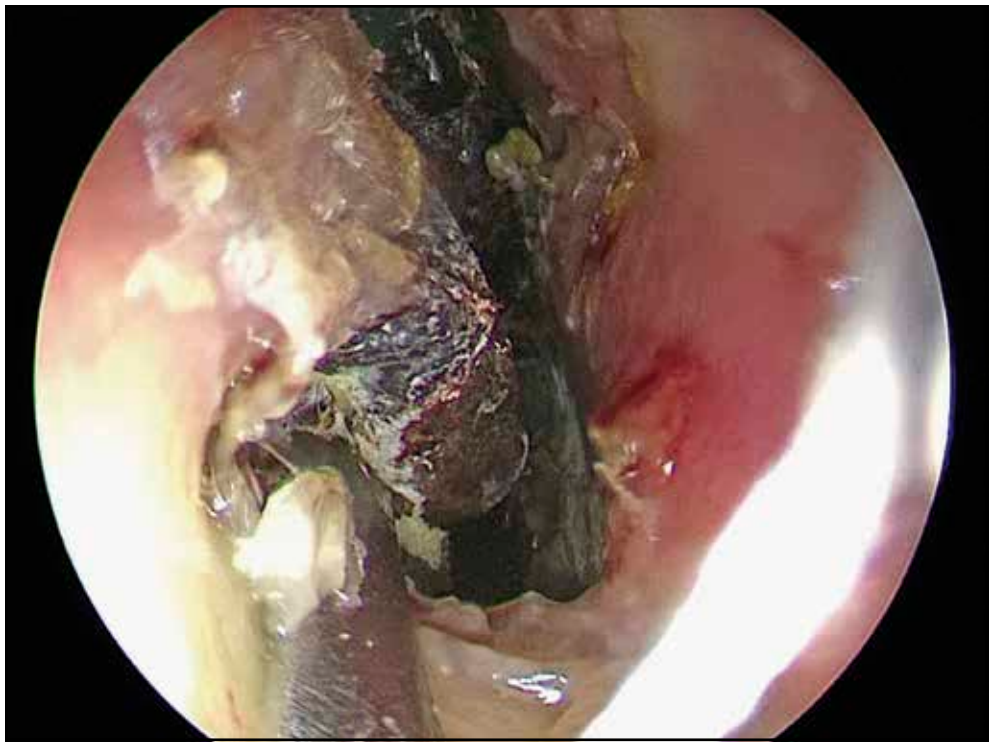

Figure 1 Endoscopic nasal exam – necrotic area in the nasal septum and the right inferior nasal turbinate mucosa. (archive of the ENT Clinic, "Sfanta Maria" Hospital, Bucharest, Romania)

the nasal cavity and the mucoperiosteal thickening in the paranasal sinuses (especially unilateral damage), bone erosion, orbital invasion, edema of soft facial tissues and infiltration of periantral or retroantral soft tissues. Bone destructions can easily be seen on CT images – the intracranial and intraorbital extension of the inflammation is an extremely suggestive picture for acute IFRS, but often found late (Figure 2A). A predilection for unilateral involvement of the ethmoid and sphenoid

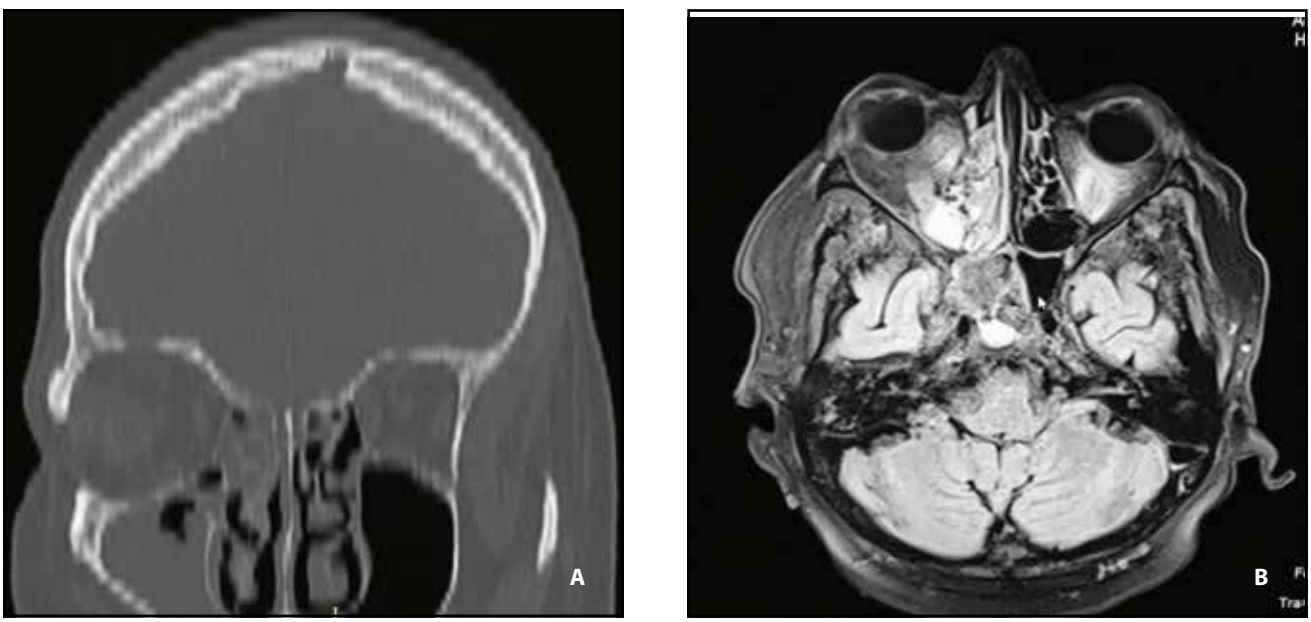

Figure 2 Acute IFRS in a 54-year-old man. **A** – The cranio-facial CT, coronary section, reveals a right maxillo-ethmoid sinusitis. **B** – The cranial MRI reveals the invasion of the orbit and the cavernous sinus. (archive of the ENT Clinic, "Sfanta Maria" Hospital, Bucharest, Romania)

sinuses has been noticed [5,9,10].

MRI is another imaging technique useful in the detection of acute IFRS. The method is more sensitive in early screening and the diagnosis of acute IFRS, compared to CT, being superior to the latter in assessing the intracranial and intraorbital extension of the disorder[5,9,10] (Figure 2B).

Nevertheless, "the gold standard" for the diagnosis of acute IFRS is the histopathological examination, but it is time-consuming and can delay diagnosis and administration of the treatment. The histopathological examination reveals fungal hyphae within the sinus mucosa, submucosa, blood vessels or bones, as well as invasion of the soft tissues[5].

The proposed diagnostic criteria for acute IFRS include: (1) thickening of the mucosa or fluid–air levels corresponding to sinusitis on imaging; (2) histopathological evidence of fungal hyphae in the mucosa, submucosa, blood vessels or sinus bones[9].

Clinical examination and nasal endoscopy are essential for determining the signs of significant edema, pallor, ischemia or necrosis of the nasal mucosa and paranasal sinuses. Imaging, clinical examination and biopsy endoscopy are crucial in the positive diagnosis of the disorder[5,14].

Given the high mortality rate and early nonspecific symptoms, acute IFRS should be suspected in any patient who has symptoms of chronic rhinosinusitis and a history of immune system dysfunctions or poorly controlled diabetes[8].

The treatment of an acute IFRS should include: (1) aggressive and prompt surgical debridement of the affected tissues, which represents "the gold standard"; (2) reversing immunosuppression; (3) appropriate systemic antifungal therapy (Amphotericin B – intravenous doses of 0,25-1,0 mg/kg/day up to a total dose of 2-4g, for 6-8 weeks)[5,9,10,12,15]. After exclusion of the species of *Mucormicosis*, Voriconazole is administered intravenously (6 mg/kg in 2 doses and then 4 mg/kg every 12 hours) – effective remedy for the treatment of *Aspergillus* and *Dematiaceous* species[4].

If acute IFRS is refractory to treatment or the patient is intolerant to Amphotericin B, the alternative treatment is with Isavuconazole (Cresemba), a newly approved, safe and clinically effective antifungal. This preparation offers distinct advantages over Amphotericin B and Posaconazole, because it is not associated with nephrotoxicity, has excellent absorption and bioavailability and is well tolerated[8].

Antifungal medication can be administered orally and intravenously, depending on the severity of the infection, the pathogen, the ongoing immunosuppressive treatment or the underlying disease[9].

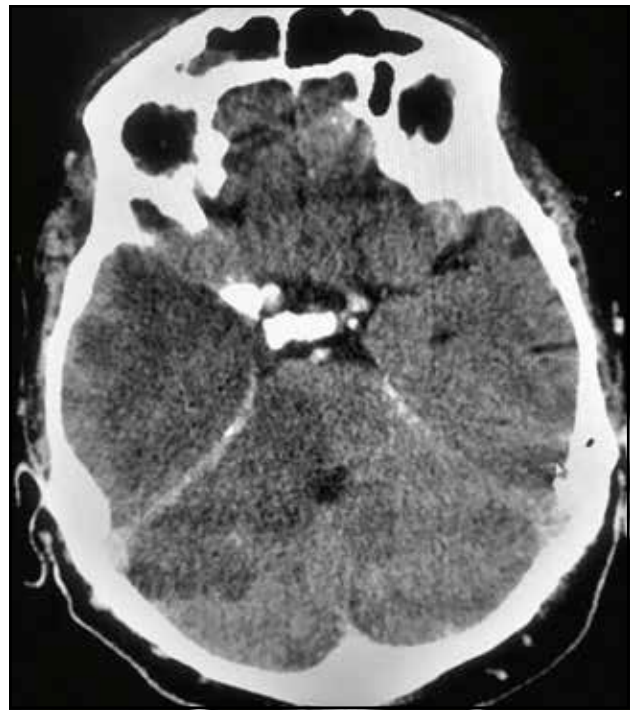

Figure 3 Stroke in a patient with IFRS. (archive of the ENT Clinic, "Sfanta Maria" Hospital, Bucharest, Romania)

Taking into consideration the rapidity with which acute IFRS evolves, treatment should be as prompt as possible. It consists of a combination of surgical therapies and aggressive antifungal medication in order to restore patient immunity. Repeated surgical procedures are often required, precisely in order to completely clean the area and stop the disease. The combination of surgical and antifungal treatment has a healing rate of 30-80% and a mortality rate of 10-40%. The lowest healing rate is associated with the intracranial extension of the lesion[4,5,9,12,15].

Increasing the absolute number of neutrophils in patients with quantitative neutropenia is an important step in the treatment of acute IFRS [9].

The prognosis is extremely poor if the host's immune response does not improve.

CHRONIC INVASIVE FUNGAL RHINOSINUSITIS

Unlike acute IFRS, chronic invasive fungal rhinosinusitis is much rarer and has a much slower destructive process. The insidious evolution takes place over several months to years, during which fungal microorganisms invade the mucosa, submucosa, blood vessels and bone walls of the paranasal sinuses. Expansion to the vascular

network or adjacent structures and inflammatory reactions are very rare. The most affected are the ethmoid bone or the sphenoid sinuses, but other sinuses can be affected equally easily[3,9,10].

The disease develops over an interval of up to three months, being frequently triggered by fungal species *Mucor, Rhizopus, Aspergillus, Bipolaris* and *Candida*[4,9,10].

Patients diagnosed with this condition are usually immunocompetent, but is also common in patients with diabetes or immunocompromised patients. Symptoms may be represented by pain in the paranasal sinuses, sero-haemorrhagic nasal discharge, epistaxis, fever. In case of lesion extension, patients may experience periorbital edema, ptosis, visual disturbances to blindness, paralysis of the cranial nerves and involvement of soft tissues.

Erosion of the cribriform plate may lead to the appearance of headache, convulsions, focal neurological deficits. Invasion into the pterygopalatine fossa, infratemporal fossa and skull base can be manifested by cranial neuropathy[9,10,12].

The intranasal examination reveals congestion of the nasal mucosa, which can be transformed into polyps[10].

The cranio-facial CT examination without contrast substance can reveal the thickening of the mucosa in one or more paranasal sinuses or lesions that can mimic malignant tumors associated with the destruction of sinus walls and extension beyond their limits. On MRI images, signal strength decreases on T1 images and signal strength on T2 images is significantly reduced. The sinus walls may present irregular bone destruction or sclerotic changes.

The invasion of adjacent structures – orbit, cavernous sinus, anterior cranial fossa – can lead to epidural abscess, abscess or parenchymal encephalitis, meningitis, cavernous sinus thrombosis, osteomyelitis, mycotic aneurysm, stroke and haematogenous dissemination[10] (Figure 3).

As with acute IFRS, restoration of the immune balance will be sought through the surgical exenteration of the affected tissues (Figure 4) and the formations developed and administration of systemic antifungal therapy[10,11]. Therapy should be as aggressive as for acute IFRS due to high rates of mortality and morbidity[10].

GRANULOMATOUS INVASIVE FUNGAL RHINOSINUSITIS

Granulomatous invasive fungal rhinosinusitis, also known as primary paranasal granuloma or indolent fungal rhinosinusitis, is found in patients with an easily identifiable immune deficiency. Moreover, the incidence of this disease is predominant in Sudan, India, Pakistan and Saudi Arabia. Usually, granulomatous IFRS is caused by *Aspergillus flavus*. The evolution is insidious and the symptoms include chronic migraines and gradual edema of the face, until vision can be affected[4,9,10,12].

Patients are generally immunocompetent. Symptoms include ptosis or the presence of a tumor mass extending into the nose, orbit or paranasal sinuses. The name of the disorder comes from a particularity used in diagnosis – the development of a non-caseous inflammatory granulomatous infiltration, with giant cells and hyphae (inflammatory nodular lesions). The evolution is indolent chronic, with a possible extension beyond the walls of the paranasal sinuses – into the orbit and/or intracranially[9,10,12].

The imaging findings are rare and similar to those of chronic IFRS. The condition is often detected only when the patient presents with an increased tumor in the cheek area, orbit, nose, or paranasal sinuses.

The microscopic analysis reveals specific granulomatous formations and the presence of *Aspergillus flavus* fungi.

The treatment includes a combination of surgery (debridement) and antifungal medicines[4,9,10,12]. The treatment with Itraconazole at a dose of 8-10 mg/kg/day decreases the high rate of postoperative relapse[12].

CONCLUSIONS

1. The histopathological examination is essential and it can diagnose the disorder with certainty, detecting necrosis, inflammation and mycelial filaments.
2. For the diagnosis of invasive fungal rhinosinusites the following diagnostic criteria are proposed: (1) confirmed on the imaging exam, (2) histopathological evidence of fungal invasion of the mucosa, submucosa, blood vessels or paranasal sinus bones and (3) necrotic tissue with minimal infiltration of inflammatory cells.
3. Most patients with invasive fungal rhinosinusitis already have a compromised immune system due to previous or concomitant pathologies, administered immunosuppressive treatments, so the prognosis is reserved and mortality is high.
4. The diagnosis of invasive fungal rhinosinusites should be established as quickly as possible in order to initiate the aggressive surgical and systemic antifungal therapy.

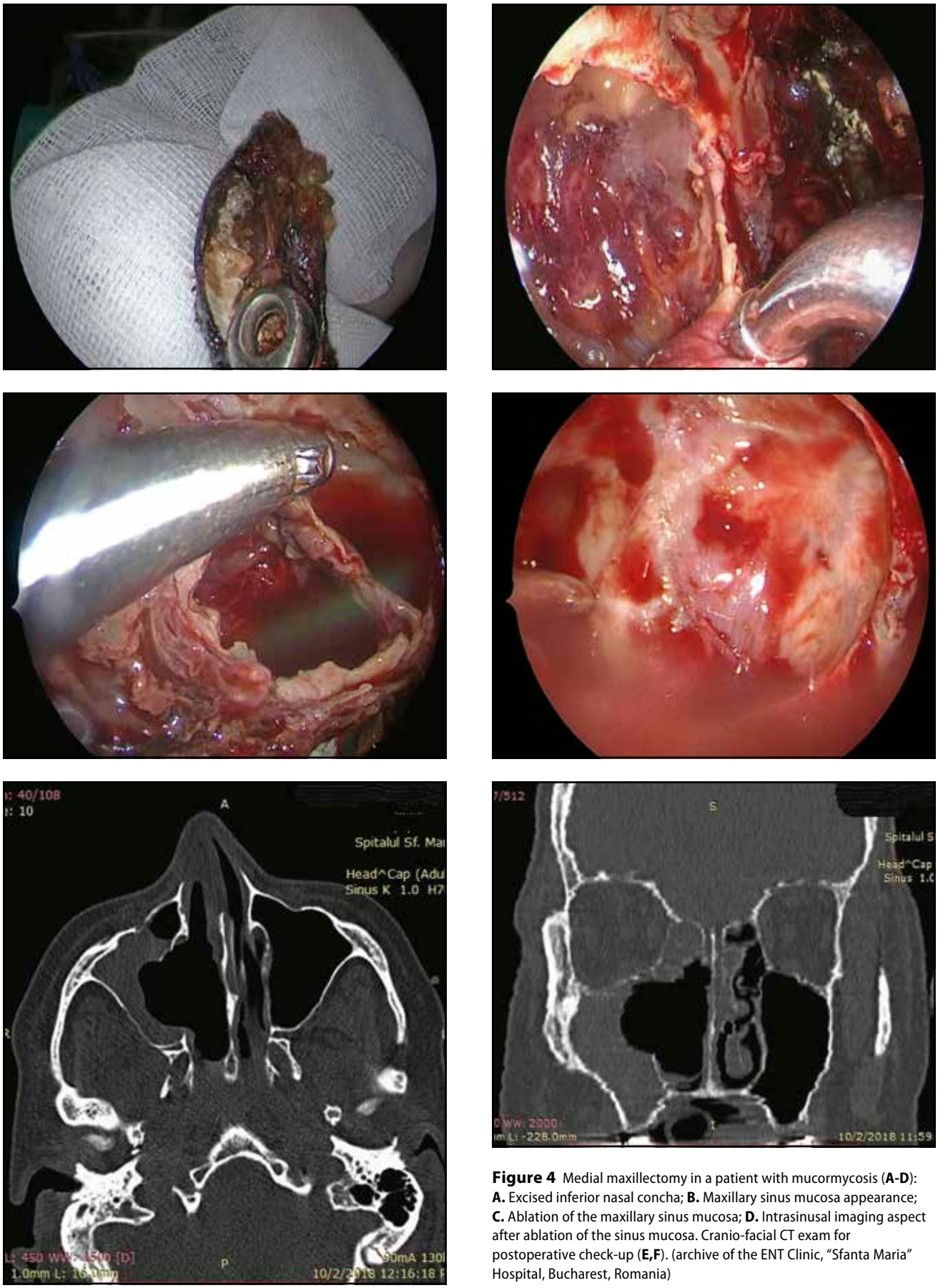

Figure 4 Medial maxillectomy in a patient with mucormycosis (**A-D**): **A.** Excised inferior nasal concha; **B.** Maxillary sinus mucosa appearance; **C.** Ablation of the maxillary sinus mucosa; **D.** Intrasinusal imaging aspect after ablation of the sinus mucosa. Cranio-facial CT exam for postoperative check-up (**E,F**). (archive of the ENT Clinic, "Sfanta Maria" Hospital, Bucharest, Romania)

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