Necrotising sinusitis with orbital complication in patient with macrophage activation syndrome (MAS)

Markov S[1]. Chochkova L[2]. Shismanova A.[2] Stefanova-Kelly K.[2] Kraeva M.[1]

1. Department of Otorhinolaryngology Medical Faculty Medical University Plovdiv; Clinic of ENT Diseases, UMHAT St George, Plovdiv, Bulgaria
2. Department of Pediatrics and Medical Genetics Medical Faculty Medical University Plovdiv; Department of Pediatrics UMHAT St George, Plovdiv, Bulgaria

Abstract
Background: Macrophage activation syndrome (MAC) is a potentially fatal clinical-laboratory syndrome of uncontrolled hyperinflammation arising as a result of hereditary or acquired immune-mediated processes of cellular overactivation and non-malignant proliferation of tissue macrophages/histiocytes, which can cause multiorgan failure.
Case report: We present a clinical case of 15-years old child, who was diagnosed with juvenile idiopathic arthritis in 2019. The disease started with macrophage activation syndrome. In the next years the child had multiple hospitalizations in the Pediatrics clinic, but in the course of the disease it developed the picture of severe necrotic pansinuitis with an orbital complication, which required an immediate surgical intervention. Ever since the child had an ongoing necrotizing process in the area of the nasal passages, sinuses, upper jaw and hard palate. Other complications were breakthrough of the hard palate, loss of healthy teeth from the upper dentition and creation of direct communication between the oral cavity and the left maxillary sinus.
Conclusions: The diagnosis of MAS is difficult to make, but increased awareness of this disease is an essential for its recognition. The struggle with autoimmune diseases often lasts for years with periods of exacerbation and remission of symptoms. Complications related to them can affect different organs and systems and require interdisciplinary approach.
Keywords: orbital complication, macrophage activation syndrome, pansinusitis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a representative hyperinflammatory disease characterized by uncontrolled cytokine storm. HLH is classified as either primary (pHLH) or secondary HLH (sHLH) based on their etiology and pathogenesis. Both of them refer to the term cytokine storm syndrome (CSS). sHLH occurs in the context of an underlying immunological condition, including malignancy, infection, or autoimmune or autoinflammatory disease. sHLH associated with autoimmune or autoinflammatory disease is called macrophage activation syndrome (MAS) (1).

MAS is a life-treathening condition that could debut with symptoms from various organs and systems. Its quick recognition and timely treatment are essential for a good outcome. The first described case was in 1976 by Boone.

The most common autoimmune diseases associated with MAS are systemic juvenile idiopathic arthritis (SJIA). The first use of the term "activated macrophages" in patients with what we now refer to as sJIA was in 1985 by Hadchouel et al. The incidence of the syndrome is unknown. Various retrospective studies over a 20-year period assume that MAS develops in 6.7% of cases with systemic juvenile arthritis. Most of the theories about the pathogenesis stated that hemophagocytosis can develop due to dysregulation of immunologic phenomenons resulting in the exaggeration of inflammatory responses which is characterized by excessive activation of macrophages and T-lymphocytes that ultimately leads to cytokine storm (2).

The classical signs and symptoms of patients with MAS are a persistent high-grade fever, hepatosplenomegaly, lymphadenopathy, and

hemorrhagic manifestations. Abnormal results of investigation include cytopenia, coagulopathy, and hyperferritinemia (3). In active rheumatological disease, the symptoms of MAS are difficult to distinguish from those of the underlying disease. Therefore, strict monitoring of the lab tests and patient‘s vital signs is necessary - systolic blood pressure, heart rate, respiratory rate. If an immunosuppressive therapy was started, the clinical picture may be veiled - absent fever, normal CRP, low ferritin levels. In order to diagnose it many physicians use the HLH-2004 criteria for MAS diagnosis. Ravelli criteria, **MA**S 2005 and the EULAR/ACR Classification criteria for MAS 2016 can also be used. The features of MAS are similar to a disease flare-up and a systemic infection and sepsis making an early diagnosis and differential diagnosis challenging.

The treatment of macrophage activation syndrome is traditionally based on the parenteral administration of high doses of corticosteroids. Cyclosporin A (CyA) was found to be effective in severe or corticosteroid-resistant macrophage activation syndrome and some authors have proposed using this drug as the first-line treatment for macrophage activation syndrome occurring in childhood systemic inflammatory disorders. Increased production of tumor necrosis factor (TNF) in the acute phase of macrophage activation syndrome has suggested the use of TNF-α inhibitors as potential therapeutic agents (4). Neither standard approach confers a complete response for all patients. Appropriate treatment is also needed for the underlying disease that led to the onset of MAS. Unfortunately immunosuppressant use, predispose patients to infections. All types of infections, including bacterial, viral and opportunistic infections, have been reported.

Case report

A 15-year-old female patient with normal physical and intellectual development was acutely ill with high fever, sore throat, non-itchy maculopapular rash. There was also pain and swelling in both small and large joints. Pain was relieved with rest and worsened during movement. Subsequently, the complaints affected only the large joints. The diagnosis of juvenile arthritis complicated by MAS was accepted. Multiple hospitalizations because of the recurrence of the disease with adverse effects from the treatment administered. The therapy included corticosteroids in large doses, TNF-α inhibitors and symptomatic treatment, but multiple complications followed (hypercorticism, steroid diabetes, arterial hypertension).

In september 2019 during a severe recurrence the patient аеэевдзеа orbital complication - edema of upper and lower eyelids on the left. A CT scan was performed with evidence of left-sided pansinusitis with orbital complication eyelid edema (fig.1).

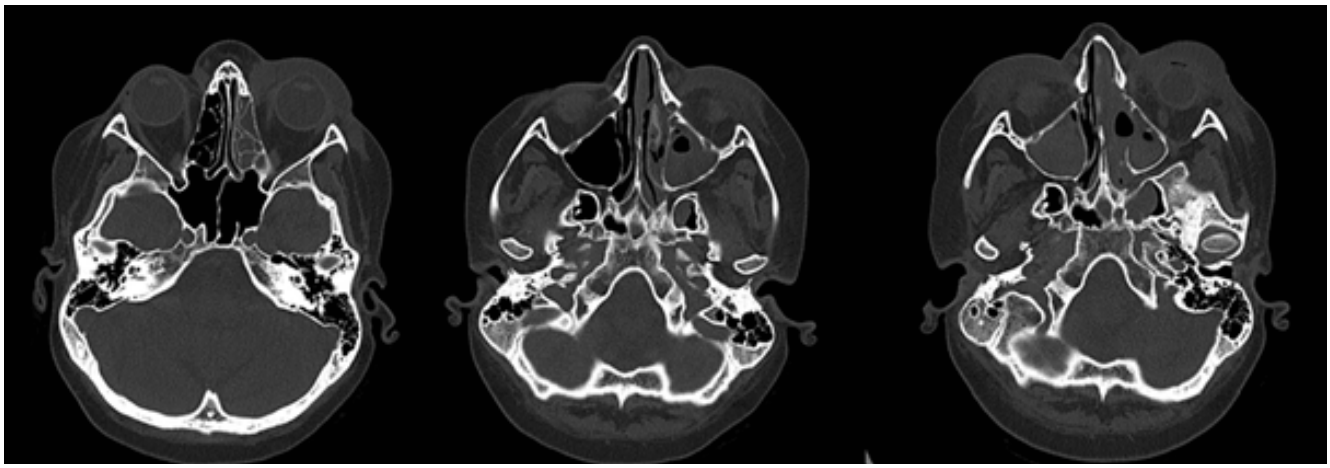


Fig.1. Pansinuitis on the left side with eyelid edema

ENT examination was performed and showed the presence of a necrotic area in the hard palate without communication between the oral and nasal cavities (fig.2). The orbital complication necessitated the rapid implementation of operative intervention – left pansinusotomy with right maxillary sinus punctrure. The result was good and there was rapid reversal of the eyelid edema.



Fig. 2. Necrotic area in the hard palate without communication between the oral and nasal cavities

The patient was referred to the pediatric clinic for continued treatment of the juvenile arthritis. Unfortunately, two months later, swelling appeared on the left cheek (fig.3). A new CT of the paranasal cavities was performed. The result showed the presence of inflammatory changes in the right maxillary sinus and a defect in the lateral and anterior walls of the left maxillary sinus, which led to an abscess in the soft tissues in front of the left zygomatic bone. A second emergency operation with revision of the operative cavity from the first operation was performed, enlarged with pansinusotomy of the right maxillary sinus which showed the presence of organized thick pus and fungal infection. External incision of the formed abscess on the left zygomatic bone was also made with a placement of a drainage for 3-4 days.



Fig. 3. Swelling appeared on the left cheek due to an abscess on the left zygomatic bone

For the period 2020–2021, the patient was hospitalized multiple times in a pediatric clinic in order to control the underlying disease. She developed numerous complications from various organs and systems as a result of the immunosuppressive therapy. Multiple ENT consultations were also performed in order to clean the operative cavity on the left, two of them under general anesthesia. New necrotic bone fragments were removed from the lateral wall of the left nasal passage. The size of the

necrotic area of the hard palate also increased (fig.4). During this period, the patient lost several teeth from the upper dentition on the left, which fell out without pain after a period of shaking. It has been suggested that the progression of the osteonecrotic process is due to the continued intake of a TNF-α inhibitors for the treatment of the juvenile arthritis.



Fig. 4. The necrotic area of the hard palate is 5/15 mm

In March 2022, the patient was hospitalized in the ENT clinic due to multiple retained secretions and new necrosis in the left nasal cavity. CT of the paranasal cavities shows fluid collections in the right maxillary sinus with hypertrophy of the left maxillary sinus with a large bone defect on the floor of the sinus /2.5 cm/ over the 5th and 6th teeth. During surgery was made a removal of secretions from the left nasal passage. An examination of the left maxillary sinus showed a mobile object in the cavity that was considered to be a part of the alveolar ridge and two upper teeth. The conglomerate was too large to be removed through the nasal cavity, so it was removed through the oral cavity using the maxillary floor defect (fig.5 fig.6 and fig.7).

Postoperatively, the patient was consulted by a maxillofacial surgeon, who placed a silicone obturator at the site of the hard palate defect. Currently, there is no evidence of further development of the necrotic process. The patient



Fig. 5. A part of the alveolar ridge and two upper teeth



Fig 6. maxillary floor defect

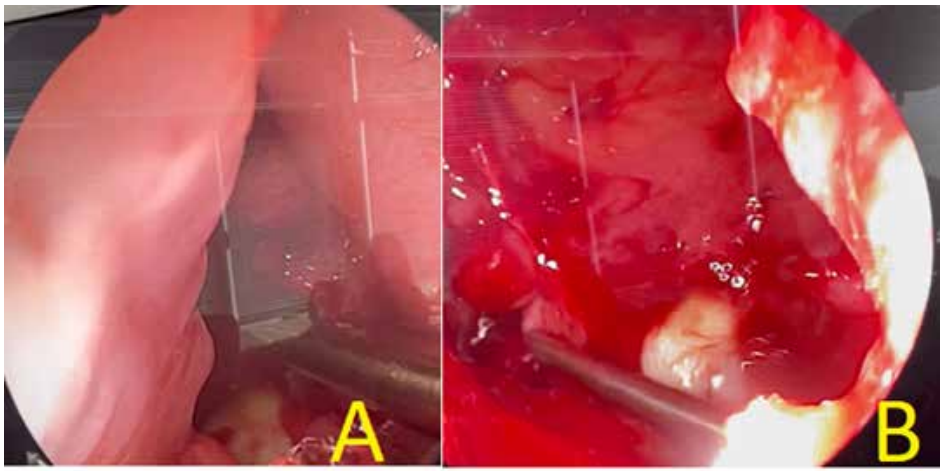


Fig. 7. The defect of the hard palate through the oral cavity (A) and the nasal cavity (B)

is monitored monthly for the condition of the paranasal cavities. Juvenile arthritis treatment continues.

Discussion

Macrophage activation syndrome (MAS) is a life-threatening complication of rheumatic diseases, requiring immediate and appropriate treatment. MAS is a disorder related to hemophagocytic lymphohistiocytosis (HLH), which is divided into primary and secondary HLH. Primary or familial HLH is an inherited disease, whereas secondary HLH is triggered by other diseases, including infections, malignancy, and autoimmune diseases. MAS is a secondary HLH, which is associated with autoimmune diseases. The most common autoimmune diseases associated with MAS are systemic juvenile idiopathic arthritis (SJIA) (3). Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis and one of the more common chronic childhood illnesses. As the term indicates, the cause is unknown. In fact, JIA is an umbrella term that refers to a group of disorders that have in common chronic arthritis. Diagnosis requires a combination of data from history, physical examination, and laboratory testing (5). Over the last fifteen years, the development of new therapeutics improved dramatically the outcome of children suffering from JIA. Unlike in the era of conventional treatment, patients treated with biological agents achieved complete remission for long periods, had lowered risk of decreased functional capacity. Conversely, blocking the inappropriate or excessive inflammatory response responsible of JIA may lead to undesired effects such as immunosuppression, with an increased risk of infections. Dumaine et al. made a study that included six hundred seventy-seven children with JIA on biological therapy. In the course of treatment, 75 of them (40.8%) developed infections that affected the ENT system and the upper respiratory tract (6). Complications can be caused by both viruses and bacteria as a result of weakened body defenses and unfortunately patient are at risk of developing life-threatening opportunistic infections, because the infection could also be caused by all types of unusual pathogens.

Acute rhinosinusitis is one of the most common complications related to the ENT organs. The invasive fungal pathogens are among the most frequently recovered agents (7). Acute invasive fungal rhinosinusitis (AIFR) has a rapidly progressive course and a dismal prognosis. Due to the immunosuppression, the symptoms may be non-specific at the beginning and the first manifestation of the disease may be with a complication, for example an orbital complication. According to Ritter et al. the most common symptoms related to the sinusitis are fever - in 31 and facial swelling – in 11 out of 34 immunosuppresed children that were included in their study (8). Rodrigues et al. concluded that the main etiological agent described for AIFRS in oncologic and hematological patients is Aspergillus - saprophytes that are found in decomposed substances, soil and fruits, as well as in the throat, nasal cavities and feces of healthy individuals, but can become pathogenic in immunocompromised patients (9) . Invasive fungal rhinosinusitis and all forms of rhinosinusitis that are suspected to be life-threatening are absolute indications for functional endoscopic sinus surgery in the paediaric population (10). FESS was carried out to obtain tissue and secretions for diagnosis, to clear the infection by debridement of necrotic tissue and to allow drainage of the infected sinuses to facilitate and enhance sinus mucosal healing (9). Díaz Molina et al. conducted a study in which they included 18 children with fungal rhinosinusitis. In 6 of these patients lesions in the mouth or nose (discoloration, crusty lesions or frank necrosis of the palate or nasal septum) were present (10).

In our case, after the first operation, progression of the inflammation in the sinuses was observed and gradually the right maxillary sinus was also involved. During the second operation, the presence of a fungal infection was registered, which occurred as a result of the active immunosuppressive therapy. Progression of the necrotic lesion of the hard palate was also recorded, leading to loss of teeth and part of the alveolar ridge. This necessitated placement of a

silicone obturator at the site of the defect by a maxillofacial surgeon.

Conclusions

The diagnosis of MAS is difficult to make, but increased awareness of this disease is an essential for its recognition. The struggle with autoimmune diseases often lasts for years with periods of exacerbation and remission of symptoms. Complications related to them can affect different organs and systems.

Rhinosinusitis in immunosuppressed children poses a diagnostic and therapeutic challenge. Fungal rhinosinuitis in particular, is a rapidly progressive life-threatening disease.

Endoscopic sinus surgery is considered to be a safe and efficient procedure for diagnosing and treating immunosuppressed pediatric patients with acute rhinosinusitis. The procedure enables good local control with low complication rate. Treatment success of MAS depends on a multidisciplinary approach to ensure early diagnosis, adequate treatment and control of the underlying disease, with special attention to disease relapse.

Reviewer of the article: Prof. M.K. Adala

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