INDEX COPERNICUS INTERNATIONAL

ORIGINAL ARTICLE

An algorithmic approach to sinonasal evaluation preceding bone marrow transplantation

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Article history: Received: 23.12.2022 Accepted: 17.04.2023 Published: 21.07.2023

ABSTRACT:

Introduction: The authors conducted this study to review the available resources and prepare an algorithmic approach to pre-transplantation sinonasal evaluation.

Materials and methods: The sources of data were PubMed, Cochrane databases, and Google Scholar. We searched the available database for English-language studies using the keywords rhinosinusitis, transplantation, post-transplant sinusitis. Studies of all designs were included.

Results: Thirty-five relevant studies were retrieved from a total of 182 articles. The review of references guided us to 5more publications.

Discussion: We have proposed an algorithmic approach to sinonasal evaluation before transplantation which can provide a brief but comprehensive assessment of the patients. The evaluation begins with a thorough history and physical examination, including nasal endoscopy with careful attention to objective evidence of inflammation. CT scan should not be considered in all of the cases.

Conclusion: We have suggested an algorithm to provide a comprehensive and cost-effective way for the evaluation of sinonasal diseases before planned immunosuppression in order to assist in reducing post-transplantation morbidity and mortality.

KEYWORDS: algorithms, bone marrow transplantation, rhinosinusitis, transplant

ABBREVIATIONS

AAO – The American Academy of Otolaryngology
ABRS – acute bacterial rhinosinusitis
ANC – absolute neutrophil count
ARS – acute rhinosinusitis
BMT – bone marrow transplantation
BSACI – the British Society for Allergy and Clinical Immunology
CPG:AS – Clinical Practice Guideline: Adult Sinusitis
CRS – chronic rhinosinusitis
CT – computed tomography
EPOS – the European Position Paper on Rhinosinusitis and Nasal Polyps 2007
HCT – hematopoietic cell transplantation
IDSA – the Infectious Diseases Society of America
IFS – invasive fungal rhinosinusitis
JTFPP – the Joint Task Force on Practice Parameters
LMS – The Lund–Mackay scores
PNS – paranasal sinuses
RI – Rhinosinusitis Initiative
RSTF 1997 – The Task Force on Rhinosinusitis

INTRODUCTION

Bone marrow transplantation has been increasingly used as a curative method for a wide spectrum of diseases over the past decade. The prevalence of hematopoietic cell transplantation (HCT) is about 50,000 per year. Although post-transplantation care has improved, infection is estimated to be the main cause of death in 8% of autologous and 17% to 20% of allogeneic HCT recipients [1, 2]. Patients are susceptible to various infections for a long time after transplantation [3].

Sinusitis is a common complication after bone marrow transplantation (BMT). The prevalence of sinusitis after transplant is approximately 31%. HCT recipients also are at high risk of invasive fungal disease. Past history of noninvasive sinusitis can be an important risk factor in transplantation candidates. It has turned into a serious threat in the post-transplantation period [4, 5].

Sinonasal evaluation is routinely implemented before transplantation in many institutions; however, there is no standard, unanimous protocol, and due to the lack of specific guidelines, the extent of the workup varies substantially among centers. The goal of this study is to review the available resources in order to prepare an algorithmic approach for pre-transplantation measures to reduce the mortality and morbidity rates of rhinosinusitis post-transplantation.

MATERIALS & METHODS

We searched the available databases for English-language studies. A PUBMED advanced search using the keywords "transplant AND sinusitis" in the titles/abstracts was conducted; it revealed a total of

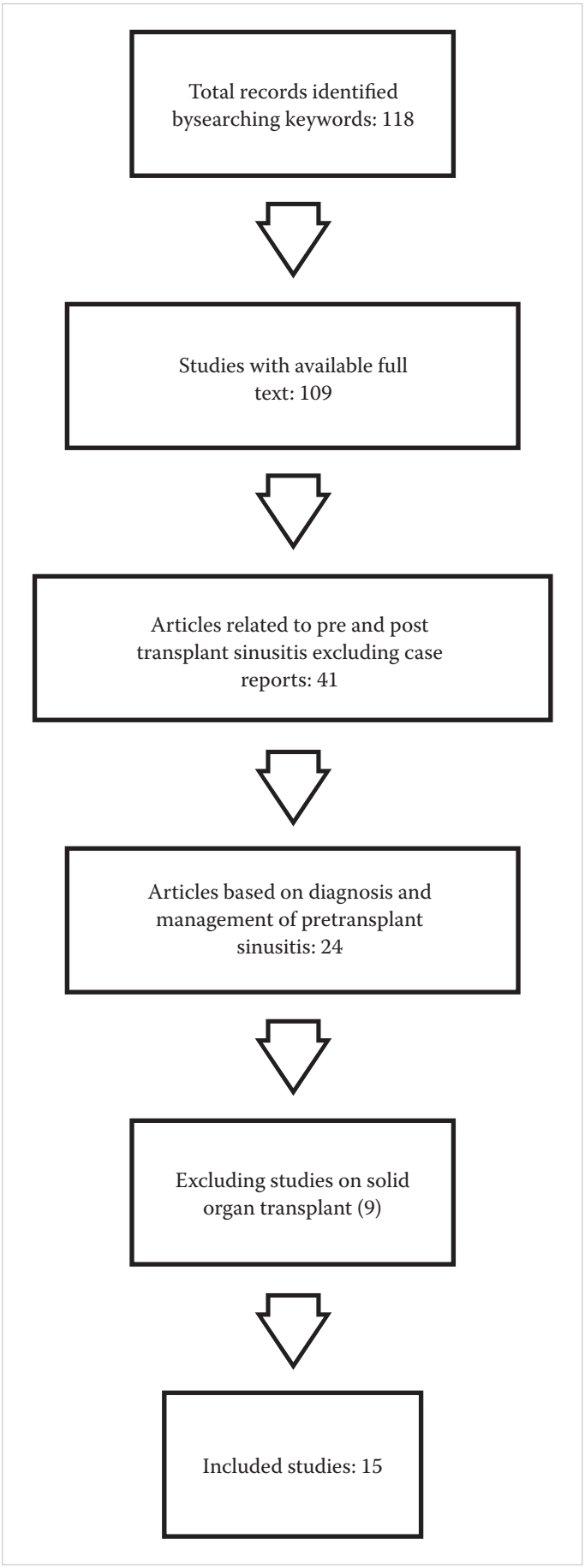

Fig 1. Flow plot of literature search.

111 articles, of which 35 were related to post-transplant sinusitis, although only 21 were associated with the diagnosis and management of pre-transplant sinusitis. A search in Google Scholar and a review of references guided us to 7 more publications (a total of 118 studies, in 109 of which full texts were available).

Excluding articles on solid organ transplant, we ultimately analyzed 15 studies on sinonasal assessment preceding stem cell transplantation. Studies of all designs were included except for exclusive case reports (Fig. 1.).

DISCUSSION

Sinonasal preparation before planned immunosuppression requires careful attention to the history and physical examination findings and judicious use of imaging modalities.

HISTORY

Taking a good history is of paramount importance and is considered the first step in diagnosing pre-transplant sinusitis. Transplantation is definitely not allowed in a patient with acute rhinosinusitis, but diagnosis is more challenging than for the general population. In immunocompromised patients, typical inflammatory responses may be diminished, so radiology of paranasal sinuses (PNS) is used to detect rhinosinusitis. According to a study, the PNS computed tomography (CT) scans of children after bone marrow transplantation were more involved than for normal children. There was a linear relationship between the severity of symptoms and the extent of CT abnormality in both groups [6]. In the immune-deficient patients, a thorough history of sinonasal disease plays a significant role in the diagnosis; however, patients with hematologic malignancies are in remission at the time of referral for transplant evaluation, so they are not considered immunocompromised.

There are no special criteria for chronic rhinosinusitis (CRS) diagnosis. The Task Force on Rhinosinusitis (RSTF 1997) described CRS clinically, defining some major and minor criteria. The major criteria were "pain or pressure in the face, obstruction of the nasal cavity, infected discharge in the nose, loss of smelling, or nasal infected discharge on examination." The minor criteria were "pain in the teeth or head, fever, halitosis, fatigue, cough, or sense of pain or pressure in the ear." CRS was defined as the existence of at least two major or one major and two minor criteria for at least 12 weeks. The sensitivity of the RSTF 1997 criteria was 89%, but the specificity was only 2%. The American Academy of Otolaryngology (AAO) introduced an improved version of the CRS guideline by considering radiologic and endoscopic findings as important diagnostic factors. There is still some controversy about the clinical diagnosis of CRS. Among CRS clinical symptoms, 'hyposmia' is considered a crucial symptom, involving about 67–78% of cases [7]. Again, special considerations should be taken in diagnosing chronic rhinosinusitis in immunocompromised patients, although according to a cohort study, immunodeficiency with CRS present with similar severity of disease as compared to controls with CRS in the ambulatory setting [8].

Another case series revealed that all patients who needed medical or surgical treatment before HCT had positive clinical, radiologic,

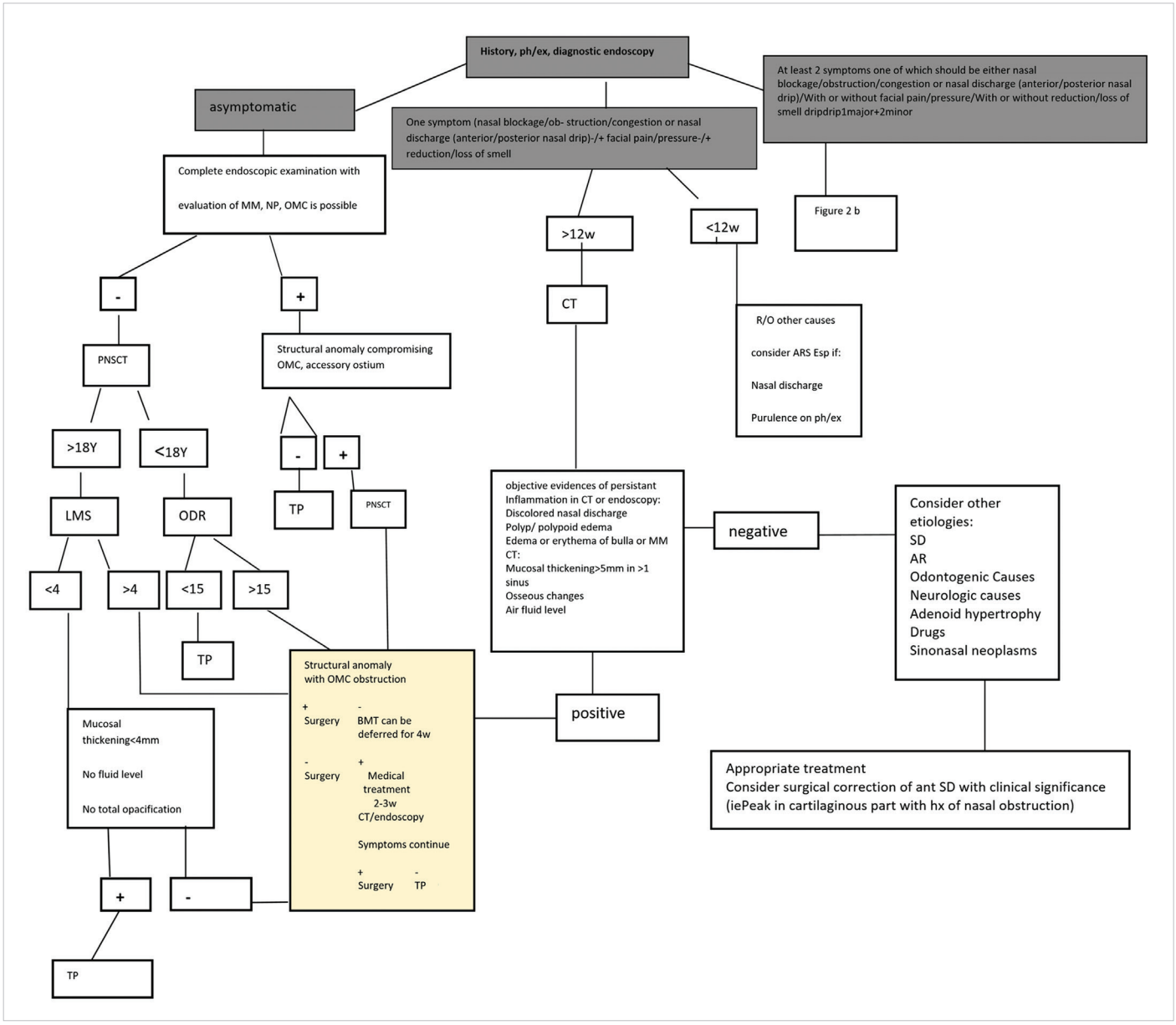

Fig 2. Algorithm for pre-transplant sinonasal evaluation; Ph/ex – physical examination; MM – middle meatus; NP – nasopharynx; OMc – osteomeatal complex; PNSCT – paranasal sinus CT scan; LMS – score: Lund Mackay score; ODR – opacification- development ratio; TP – transplantation permitted; SD – septal deviation; AR – allergic rhinitis; Ant – anterior; Hx –history; ARS – acute rhinosinusitis; BMT – bone marrow transplantation; URI – upper respiratory tract infection; Bx – biopsy; IV AB – intravenous antibiotic; F/U – follow-up.

and CT scan findings. Thus, routine assessment of all asymptomatic transplant candidates was not recommended [9].

Physical examination

The next step in sinonasal evaluation is a complete physical examination; the most critical part is nasal endoscopy. Diagnostic endoscopy is considered a primary valid diagnostic stage in symptomatic patients. It not only guides the way to an accurate diagnosis, but it also helps reduce the usage of CT, which is not considered necessary in cases of positive nasal endoscopy [10].

Kolethekkat and co-workers showed that positive endoscopic findings (mucosal abnormality, purulent discharge, and polyps) are positively correlated with PNS CT. However, normal endoscopy does not rule out sinusitis in patients with sinusitis symptoms [11]. Endoscopic examination also can guide middle meatal culture; however, culturing is only used in unusual or complicated cases [12].

In a review, Meltzer and Hamilos compared various guidelines about sinusitis from the Rhinosinusitis Initiative (RI), the Joint Task Force on Practice Parameters, the Clinical Practice Guideline: Adult Sinusitis (CPG:AS), the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EPOS), and the British Society for Allergy and Clinical Immunology (BSACI). They found that nasal cavity examination is suggested by four of the guidelines for CRS diagnosis [European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EPOS), Rhinosinusitis Initiative (RI), Clinical Practice Guideline: Adult Sinusitis (CPG:AS), and British Society for

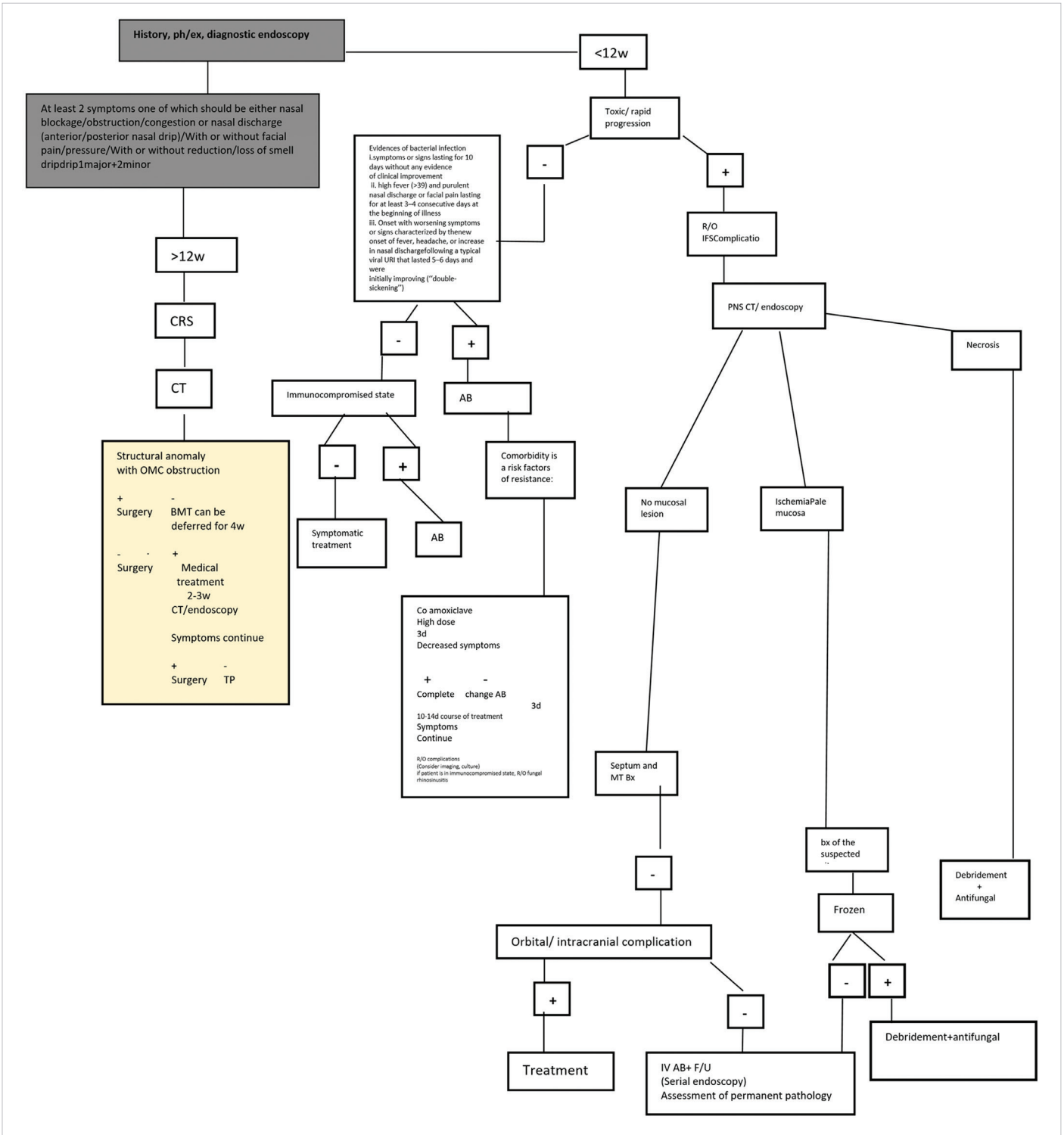

Fig 2. cd. Algorithm for pre-transplant sinonasal evaluation; Ph/ex – physical examination; MM – middle meatus; NP – nasopharynx; OMc – osteomeatal complex; PNSCT – paranasal sinus CT scan; LMS – score: Lund Mackay score; ODR – opacification- development ratio; TP – transplantation permitted; SD – septal deviation; AR – allergic rhinitis; Ant – anterior; Hx – history; ARS – acute rhinosinusitis; BMT – bone marrow transplantation; URI – upper respiratory tract infection; Bx – biopsy; IV AB – intravenous antibiotic; F/U – follow-up.

Allergy and Clinical Immunology (BSACI)]. Purulent secretion and middle meatus or ethmoid edema were among the supportive findings. Nasal culture was not suggested routinely for uncomplicated cases of acute rhinosinusitis (ARS), but the RI guidelines propose that nasal cultures by endoscope may be helpful in certain types of rhinosinusitis. According to the Joint Task Force on Practice Parameters (JTFPP), nasal culture is helpful in immunocompromised patients for fast and precise detection of the causative agents [13]. Also, rigid nasal endoscopy plays a significant role in the diagnosis of invasive fungal rhinosinusitis. Diagnostic endoscopy provides the possibility to thoroughly evaluate the nasal cavity, paranasal sinuses, and nasopharynx [14]. Also, tissue biopsy from suspicious lesions or areas (i.e., the middle conchae) followed by pathologic and cultural examinations are possible.

Imaging

Setzen et al. believe that PNS CT is not needed before starting or after completing successful medical management in normal patients with simple acute sinusitis. PNS CT without contrast is indicated in cases where medical treatment failed. In CRS patients with positive clinical findings, nasal endoscopy is sufficient for diagnosis and CT is not necessary. CT is useful in symptomatic patients with negative endoscopy results [15].

The necessity of routinely performing sinonasal imaging before transplantation has been the subject of different studies with conflicting results. Some authors believe that endoscopic nasal examinations and PNS CT scans should be done before BMT. In this way, possible sinonasal diseases are diagnosed accurately in the early stages. Also, the structural anatomy of the PNS, the situation of the mucosa, and possible tumoral involvement can be evaluated in detail. Also, PNS CT is the preferred initial imaging in patients with suspected invasive fungal sinusitis [16].

Fulmer and co-workers retrospectively studied the charts of stem cell transplantation (SCT) patients. There was a positive correlation between pre and post-SCT PNS CT findings. The Lund–Mackay scores (LMS) were higher in patients with pre-SCT CT involvement [17].

According to a retrospective cohort study carried out by Sekine et al., there was a significant linear correlation between LMS and absolute neutrophil count (ANC) in the BMT patients. Despite a more severe disease in the BMT cases (with ANC <500 neutrophils/mm^3), the LMS was lower. Thus, LMS is not a reliable factor for evaluating sinonasal disease in BMT patients. Also, they did not find any association between LMS and the need for operation, response to medical treatment of sinusitis, or mortality rate [18].

Kasow et al. studied PNS CT scans of pre-SCT patients and found that it may be involved in many cases. They recommended that CT can be helpful in post-SCT care [19].

Tomazic et al. evaluated whether routine PNS CT is necessary in every transplant patient. There was a high rate (77.2%) of pathological CT scans unrelated to sinusitis symptoms, which were considered accidental. Considering the high false positive rate of CT, they concluded that it should not routinely be done in asymptomatic candidates for organ transplantation [20].

Gerull et al. assessed the reasons for delaying or cancelling transplants after admission for work-up in order to understand the significance of the different components of pre-transplant work-up. Major ENT findings consisted of sinusitis or rhinitis in most cases. They showed that while extensive testing seems justified before allogeneic transplantation, only a minority of the performed exams led to a significant number of major findings that necessitated further testing or therapy, or to postponement of the transplant. Furthermore, many of the major findings were not incidental but were either symptomatic or previously known [21]. Ortiz et al. carried out a prospective study to evaluate the effectiveness of pre-SCT PNS CT. They performed paranasal CT before and after SCT and concluded that CT is not useful for all patients before SCT. They also suggested that structural abnormality does not correlate with the clinical feature of sinusitis, but does affect its severity [22].

In general, it seems that if a careful history is taken and a complete physical examination that includes diagnostic endoscopy is done, PNS CT should not be considered in all cases. Routine PNS CT in pre-transplant patients thus can be avoided, and should only be performed in selected cases with relevant clinical symptoms and a history of sinusitis.

Another controversial issue is the importance of asymptomatic abnormalities and different anatomic variants found in PNS CT and the correlation between these findings and the occurrence of post-transplant rhinosinusitis. Abnormal sinus findings may be purely incidental. Mucosal thickening is commonly detected in routine sinus imaging of asymptomatic patients, with a prevalence of 30–80%, based on the sinuses which were evaluated, the age of the study group, and season of the study. The clinical importance of these findings has also been studied and some authors found mucosal thickening to be significant in the clinical course of rhinosinusitis. For example, Severino et al. evaluated the association between the opacity of PNS CT scans of asymptomatic patients aged 0–18 and the rate of early rhinosinusitis in a prospective cohort study. They concluded that more intense opacification increased the risk of developing upper respiratory signs and symptoms during the month following the first scan [23].

Other authors have suggested that radiological diagnostic criteria for RS should be limited to a mucosal thickness of 4 mm or more, complete sinus opacity, or air-fluid level [24]. Abnormal PNS CT scans in the absence of clinical symptoms may not increase the probability of post-SCT rhinosinusitis, but ideal treatment before SCT can decrease the rate of post-SCT rhinosinusitis [25].

There is a lack of consensus among investigators with respect to the prevalence and clinical significance of anatomical variations. One study showed a significant association between nasal blockade due to deviation in the caudal part of the nasal septum and invasive fungal rhinosinusitis (IFS); however, other nasal anatomic alterations (posterior septal deviation, posterior spur, inferior turbinate hypertrophy, concha bullosa, paradoxical curvature of the middle turbinate, hyperpneumatized agger cell, haller cell, and hyperpneumatized ethmoid bulla) and previous sinus disease did not reach statistical significance [26].

Viral *vs.* bacterial ARS

The detection of a high density of bacteria (≥10^4 colony-forming units per ml) in the paranasal sinuses is the gold standard for confirming the presence of acute bacterial rhinosinusitis (ABRS). Nevertheless, aspiration of sinus secretion is not recommended routinely because it is painful, invasive, and time-consuming. Rhinoviral infections usually last 7–10 days. Thus, if the disease takes longer than 10 days, it is considered ABRS. Involvement with more signs or symptoms means a higher predictive value. The presence of any of the following situations confirms the diagnosis of acute bacterial over viral sinusitis: at least a 10-day duration of clinical features without improvement, early presence of severe signs or symptoms (i.e., high fever (>39 °C), infected nasal secretions, or

facial pain for 3–4 days), "double-sickening," or a viral infection that improves during 5 or 6 days before the clinical feature worsens again because of a bacterial super- infection [12, 27, 28].

Treatment:

Acute viral rhinosinusitis

The diagnosis of acute viral rhinosinusitis is made when the disease is present for fewer than 10 days without worsening. Antibiotics are not needed for treatment.

Acute bacterial rhinosinusitis

According to the Infectious Diseases Society of America (IDSA), management of ABRS is as follows:

Empiric treatment is amoxicillin-clavulanate rather than amoxicillin alone. A high dose of amoxicillin-clavulanate (2 g or 90 mg/kg/day, orally twice daily) should be used in regions with more than a 10% prevalence of penicillin-resistant *S. pneumoniae*, severe disease (i.e., fever >39 °C), or complicated cases. Other indications for high-dose treatment include daycare attendance, patients younger than 2 or older than 65 years, recent history of antibiotic usage (in the previous month) or hospitalization, and immune deficiency. If the patient's condition worsens after 3 days or does not improve after 3–5 days of appropriate treatment, the possibility of antibiotic resistance, structural abnormality, or a wrong diagnosis should be considered [29].

Chronic rhinosinusitis

According to the American Academy of Otolaryngology – Head and Neck Surgery, maximal medical treatment should be done for CRS. The goal of therapy is to reduce symptoms and complications by minimizing inflammation and controlling the infectious components of CRS. The common initial treatments include identifying and addressing contributing factors, intranasal corticosteroids, antibiotics, oral steroids, saline irrigation, and leukotriene antagonists. A complete discussion of each strategy is beyond the scope of this article. Endoscopic sinus surgery is indicated in resistant cases which do not respond to the maximal medical treatment [30, 31].

Of particular importance is the fact that in patients referred for pre-transplant sinonasal evaluation, there is often a time limit for preparing the patients. In this regard, we did not find any recent relevant article, but Mirza et al. (in 1998) suggested that pre-existing noninvasive sinusitis may be a significant risk factor for post-transplantation fungal rhinosinusitis, so all chemotherapy or bone marrow transplant candidates should be approached according to their proposed guideline. In their algorithm, if transplantation could be delayed 2–4 weeks, medical treatment was recommended [32].

CONCLUSION

The structural sinonasal variations can predispose patients to sinusitis [26, 33]. We propose an algorithmic approach to sinonasal evaluation before bone marrow transplantation (Fig. 2.). We hope that this algorithm can provide a comprehensive and cost-effective way of evaluating sinonasal diseases before planned immunosuppression for otolaryngologists and may assist in reducing post-transplantation morbidity and mortality.

Another area for future research is the post-operative assessment of BMT candidate patients undergoing endoscopic sinus surgery and the time required for adequate follow-up without unnecessarily delaying transplantation.

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Competing interests: The authors declare that they have no competing interests.

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Cite this article as: Ghazizadeh M., Mehrparvar G., Ghazizadeh M.: An algorithmic approach to sinonasal evaluation preceding bone marrow transplantation; Otolaryngol Pol 2023; 77 (4): 7–13; DOI: 10.5604/01.3001.0053.4752