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Review

Ear-nose-throat manifestations in Inflammatory Bowel Diseases

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SUMMARY

Inflammatory bowel diseases (IBD) refer to a group of chronic inflammatory disorders involving the gastrointestinal tract and are typically divided into two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by noncontiguous chronic inflammation, often transmural with noncaseating granuloma formation. It can involve any portion of the alimentary tract and CD inflammation has often been described in the nose, mouth, larynx and esophagus in addition to the more common small bowel and colon sites. UC differs from CD in that it is characterized by contiguous chronic inflammation without transmural involvement, but extraintestinal manifestations of UC have also been described. During the last few years many authors have reported serious complications of IBD manifesting in the ear-nose-throat (ENT) and influencing disease morbidity. The present article reviews the most important ENT manifestations in IBD patients.

Key Words: Inflammatory bowel disease, ear-nose-throat, comorbidity, extraintestinal manifestations.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic relapsing diseases of the gastrointestinal tract, widely known as inflammatory bowel diseases (IBD). They are thought to result from an inappropriate and ongoing activation of the innate immune system driven by the presence of luminal flora. Both UC and CD have a worldwide distribution and are common causes of morbidity in Western Europe and Northern America.

The extraintestinal manifestasions of IBD, however, are not of less importance. In some cases they are the first clinical manifestation of the disease and may precede the onset of gastrointestinal symptoms by many years, playing also a very important role in disease morbidity. As multisystemic diseases, IBD, have been correlated with many other organs, including the skin, eyes, joints, bone, blood, kidney, liver and biliary tract. In addition, the inner ear, nose and throat should also be considered as extraintestinal involvement sites of IBD.

The present paper reviews the most important ear-nose-throat (ENT) manifestations of IBD and describes how they may impact on clinical practice.

All ENT manifestations related to IBD are listed in tables 1-5.

INVOLVEMENT OF THE EAR

There is considerable evidence to suggest that hearing and vestibular function can be influenced by autoimmune processes. Immune mediated inner ear disease includes clinical conditions associated with rapidly progressive unilateral or bilateral forms of sensorineural hearing loss (SNHL), or even acute total deafness.[1,2,3] A systemic autoimmune disorder including IBD may present in one-third of the cases.[4,5] The clinical manifestation of the disease

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Abbreviations:

IBD= inflammatory bowel diseases
CD=Crohn's disease
UC=ulcerative colitis
ENT=ear-nose-throat

EAR-NOSE-THROAT MANIFESTATIONS IN IBD

Table 1. Ear manifestations in IBD

Type of manifestation	CD (Number of patients and authors)	UC (Number of patients and authors)
Sensorineural hearing loss (SNHL)	21 (Akbayir N et al.)	18 (Akbayir N et al.) 1(Kumar BN N et al.)
Autoimmune SNHL	1 (Staecker H et al.)	-
Acute total deafness and SNHL	1 (Kuczkowski J et al.)	-
Autoimmune inner ear disease	-	1(Herdman RC et al.)
CD and Melkersson-Rosenthal syndrome	1 (Ilnyckyj A et al.)	-
CD and Cogan's syndrome	1 (Buge A et al.)	-
Metastatic CD of the ear	1 (McCallum DI et al.)	-
Pyoderma gangrenosum	-	1 (Lysy J et al.) 1(Shelley ED et al.)
Relapsing polychondritis of the ear	1 (Touma DJ et al.)	1 (Asuncion AM et al.)

Table 2. Nose manifestations in IBD

Type of manifestation	CD (Number of patients and authors)	UC (Number of patients and authors)
Saddle nose deformity	1 (Akikusa JD et al.) 1 (Merkonidis C et al.)	-
Nasal septal perforation	1 (Kriskovich MD et al.) 1 (Kryssia RC et al.) 1 (Sari S et al.)	1(Bachmeyer C et al.)
CD manifesting in the head and neck	(Bradley PJ et al.)	-
Oral CD	1 (Ghandour K et al.)	-
Extraintstinal CD	1 (Ulnick KM et al.)	-
Nasal manifestations	1 (Pochon N et al.)	-
Nasal involvement	1 (Venail F et al.) 1 (Cilursu AM)	1(Cilursu AM)
Nasal mucosa	1 (Kinnear WJ et al.)	1 (Easton LA)
Nasal localization	1 (Ferjaoui M et al.)	-
Nasal polyposis	-	(Sclano G)
Chronic sinonasal disease	116 (Book DT et al.)	125 (Book DT et al.)
Polypoid pansinusitis	1 (Ernst A et al.)	-
Rhinosinusitis	-	32 (Yang PC et al.)
Sinonasal malignant lymphoma	-	1 (Suzumiya J et al.)
Eosinophilic angiocentric fibrosis of the sinonasal tracts	-	1 (Slovik Y et al.)
The trichorhinophalangeal syndrome	-	14 (Tuzovic S et al.)
Trisomy 9 syndrome	1 (Wooldridge J et al.)	-
Atrophic polychondritis	-	1 (Demerjian N et al.)
Relapsing polychondritis	-	1 (Ueno Y et al.)

Table 3. Throat manifestations in IBD

Type of manifestation	CD (Number of patients and authors)	UC (Number of patients and authors)
Ulceration of the mouth, pharynx and the larynx	20 (Croft CB et al.)	-
Cricopharyngeal CD	1 (Rowe PH et al.)	-
CD of buccal mucosa and posterior pharynx	1 (Estrin HM et al.)	-
Bucco-pharyngeal CD	1 (Peix JL et al.)	-
CD of the oral and pharyngeal cavities	1 (Borner H et al.)	-
Primary CD of the oropharynx	1 (Johnson DA et al.)	-
Granulomatous tonsillitis	1 (Bozkurt T et al.)	-
Tonsillar granulomas	1 (Turchi RM et al.)	-
Tonsillectomy higher prevalence in CD	100 (Mate-Jimenez J et al)	120 (Mate-Jimenez J et al)
Pharyngeal perforation during intubation	1 (Kras JF et al.)	-
CD resembling SLE	1 (Shimizu T et al.)	-
Sideropenic dysphagia	-	1 (Wright R)
Sore throat due to IFX	11 (Han PD et al.) 25 (Farell RJ et al.)	-
Chronic cough	(Auliac JB et al.)	-
Esophageal ulcer	-	1 (Asakawa A et al.)

Table 4. Laryngeal manifestations in IBD

Type of manifestation	CD (Number of patients and authors)	UC (Number of patients and authors)
Ulceration of the mouth, pharynx and the larynx	20 (Croft CB et al.)	-
Cricopharyngeal CD	1 (Rowe PH et al.)	-
Epiglottis, aryepiglottic folds	1 (Wilder WM et al.)	-
Upper airway obstruction	1 (Ulrich R et al.)	-

Table 5. Oral manifestations in IBD

Type of manifestation	CD (Number of patients and authors)	UC (Number of patients and authors)
Ulceration of the mouth, pharynx and the larynx	20 (Croft CB et al.)	-
CD of oral and pharyngeal cavities	20 (Croft CB et al.) 1 (Borner H et al.)	-
CD of buccal mucosa and posterior pharynx	1 (Estrin HM et al.)	-
Bucco-pharyngeal CD	1 (Peix JL et al.)	-

is most often bilateral and progressive. The hearing level often fluctuates, with periods of deterioration alternating with partial or even complete remission. The tendency is for the gradual evolution of permanent hearing loss, which usually stabilizes with some remaining auditory function but occasionally proceeds to complete deafness. Vestibular dysfunction, particularly disequilibrium and postural instability, may accompany the auditory symptoms. A syndrome resembling Meniere's disease may also occur with intermittent attacks of severe vertigo.[6]

Many diagnostic tests have been proposed to identify inner ear autoantibodies that may be the cause of such hearing loss. The only test that is currently available for clinical use is the Otoblot test, specific only for antibodies against bovine heat shock protein 70, which is only one of the many cross reacting proteins against the inner ear in suspected immune-mediated hearing loss.[7] Humoral mechanisms may also be involved in the deposition of circulating immune complexes from bacterial antibodies or viral antibody complexes. Another mechanism that has been proposed is a cell mediated immune response involving cytotoxic T cells against specific inner ear targets.[8] Vascular changes, i.e. the deposition of circulating immune complexes and T-cell mediated cytotoxicity,[9] have been described during the genesis of the bowel involvement in CD disease.

The clinical response to steroid therapy is thus the mainstay in the diagnosis of immune mediated hearing loss and therefore constitutes first-line therapy. Kuczkowski J. et al. report the case of a 31 year old woman with Lesniowski-CD who presented with acute autoimmune sensorineural hearing loss of one ear and acute total deafness on the other ear after she got pregnant. Hearing level improved after treatment with steroids was initiated.[1] However, Kumar BN et al. reported sensorineural hearing loss and UC in a 12-year old boy which initially responded to steroid therapy, but four years later resulted in bilateral profound sensorineural hearing loss in spite of good control of his bowel disease.[3] Immediate treatment with steroids with or without immunosupressive agents is essential, as delay may lead to irreversible hearing loss. TNF-α blockade by specific antibodies, such as infliximab, may offer an additional treatment option for these patients,[10] indicating that TNF-α may play a critical role in the pathophysiology of the disease.

Many authors report auricular pyoderma gangrenosum in IBD patients, especially with UC. In one case it was simulating fungal infection and preceding IBD diagnosis by 11 years.[11] Treatment with cyclosporine 10mgr/kgr/d has been successfully administered in a lot of cases such as a 58-year old woman with sclerosing cholangitis and UC who was diagnosed with right ear pyoderma gangrenosum spreading over the entire right side of the face. The dosage of cyclosporine was progressively tapered and then discontinued after 7 months, when healing was complete.[12] It seems that cyclosporine merits serious attention for treatment of both pyoderma gangrenosum and sclerosing cholangitis.

Relapsing polychondritis causing swelling of the ear has been reported, which coincided with an exacerbation of coexisting UC and eventually led to colectomy despite oral prednisone therapy.[13,14] The disease is multisystemic and its etiology is not well understood. It is believed to be an autoimmune disease since circulating antibodies to type II collagen have been demonstrated in the patients' sera. IgG, IgA and C_3 have been found in affected cartilage by direct immunofluorescence examination. Damaged cartilage may release collagen fragments and lead to the formation of circulating immune complexes, resulting in immune complex-mediated disease. In approximately one third of patients, polychondritis has been associated with other diseases including rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, ankylosing spondylitis, Behcet's syndrome, thyroid disease, primary biliary cirrhosis, malignancies and IBD. Cranial neuropathies as well as typical cochlear or vestibular nerve complications can occur and are presumed to be vasculitic in etiology. Progressive dilatation of the aortic ring, with destruction of the valve cusps, may lead to aortic insufficiency. Myocarditis, pericarditis and aneurysms of the ascending thoracic aorta, abdominal aorta and subclavian artery may also occur. Renal involvement with segmental necrotizing glomerulonephritis has been described. In addition to inflammation and swelling of the auricles, the mucocutaneous manifestations include apthous ulcers, palpable purpura, livedo reticularis, urticaria and erythema nodosum. Serious otitis media can occur, as well as hearing loss. Respiratory tract involvement, on rare occasions, may be fatal. These manifestations include hoarseness, aphonia, cough, tenderness over the thyroid cartilage or anterior trachea and in severe cases dyspnea or stridor.

Cogan's syndrome is a rare disease found in young patients, characterized by deafness, vertigo, ocular conjunctivitis, keratitis and aortitis. Buge A. et al. reported a case of this syndrome, co-existing with CD.[15]

In addition, Ilnyckyj A et al. report the case of a 30 year old woman diagnosed with CD disease and a subsequent diagnosis of Melkersson-Rosenthal syndrome (recurrent facial paralysis, recurrent and eventually permanent facial edema, placation of the tongue), with severe ear pain.[16]

Metastatic CD disease with involvement of the retro-auricular areas has also been described by McCallum DI et al. [17]

Another interesting area of investigation is the presence of subclinical sensorineural hearing loss, especially in IBD patients. Akbayir N et al. investigated 39 IBD patients using otoscopy, tympanometry, and pure tone audiometry.[2] It was demonstrated that a subclinical sensorineural hear-

ing loss might be associated with UC and somewhat with CD affecting mainly the high frequencies. In the light of this finding the authors suggest that all IBD patients should be investigated with labyrinth functions. Periodical follow-up is advisable in patients with positive findings.

Involvement of the nose

Nasal manifestations in IBD are quite rare. They are typified by chronic mucosal inflammation, obstruction, intermittent epistaxis and occasionally septal perforation, signs and symptoms that are common to many disease states of the nose. Nasal findings, much like oral lesions can precede the more typical gastroenterologic manifestations of IBD, or parallel the activity of intestinal inflammation. The review of the literature, scarce, shows some cases of nasal involvement in IBD (especially CD) and few associations between these illnesses and other systemic diseases, such as vasculitides, collagen vascular diseases, sarcoidosis, Wegener's granulomatosis or relapsing polychondritis.[18] Among these diseases we can find atypical conditions mixing different features of the most classical systemic diseases, presenting as 'overlap syndromes'. Regular follow up can help us to identify systemic disease with the research of new extra-sinonasal symptoms.[19]

CD manifesting in the head and neck has many clinical presentations, both specific and non specific in the oral cavity, nose and larynx.[20-22] Kinnear WJ et al. reported the case of a 36-year-old woman with chronic nasal congestion, crusting and inflamed nasopharyngeal tissue.[23] Pochon et al.[24] and Ulnick et al.[21] described nasal obstruction in two adults and Ferjaoui M et al.[25] reported nasal localization of CD manifesting as chronic atrophic rhinitis. In addition, Akikusa JD et al.[26] and Merkonidis C et al.[27] described saddle nose deformity as a nasal characteristic of CD.

Easton LA et al. on the other hand, have described nasal mucosal involvement in a patient with UC, sclerosing cholangitis and mouth ulceration.[28]

Perforation of the nasal septum is a serious complication which has been described in both CD and UC.[29-32] Excluding all the other common causes such as trauma, drugs, chemicals, neoplastic diseases and infections, perforation was thought to be associated with IBD and concomitant intestinal involvement. In most cases histologic examination showed nonspecific inflammatory changes without granuloma. Treatment is medical and/or surgical. Although an asymptomatic perforation rarely requires any treatment, topical nasal steroids, moisturizers and antibacterial ointments are recommended for nasal IBD. If these lesions fail to respond to topical therapy, systemic steroids and/or anti-TNF-α become the mainstay of treatment. If they prove to be unsuccessful, a silicone button may be helpful to prevent a subsequent saddle deformity.[32] Otolaryngologists should be aware of such an association between perforation of the nasal septum and IBD and consider this diagnosis (especially CD) in atypical cases of nasal disease.

Nasal polyposis with asthma and UC seem to consider a new perspective, possibly due to their common pathogenetic hypotheses.[33] It has been suggested that the above diseases are caused by a lentivirus that infects the fibroblasts of the lamina propria of the bronchial, nasal or intestinal mucosa, respectively. The infected cells secrete a viral protein, the envelope glycoprotein, which acts as an allergen. Individuals who respond to the infection with a Th2 reaction are susceptible to the disease, while individuals who respond with a Th1 reaction are resistant. In addition, Ernst et al. report the case of a 17-year old female with CD, presenting with polypoid pansinusitis and peritonsillitis.[34]

Book DT et al. report an association between chronic sinonasal disease and IBD (35). In a cross-sectional study of 241 IBD patients from a tertiary IBD clinic it has been shown that the prevalence of chronic sinonasal disease is increased in IBD patients, occurring approximately in one-half of them who are followed at a tertiary IBD center. Patients with CD experiencing obstructive complications had significantly increased rates of sinonasal disease. The relationship between chronic sinonasal disease and obstructive CD is not well defined, but several hypotheses have been put forward. In addition, Yang PC et al. reported that rhinosinusitis derived Staphyloccocal enterotoxin B possibly associates with pathogenesis of ulcerative colitis.[36] The authors suggest that pathogenesis in UC in some patients may be associated with their pre-existing chronic rhinosinusitis by a mechanism of swallowing sinusitis-derived staphyloccocal enterotoxin B.

A case of eosiniphilic angiocentric fibrosis of the sinonasal tract in a male patient with UC and rheumatoid arthritis has been described, suggesting that inflammatory or autoimmune factors may have a role in the development of this unusual pathological entity.[37]

Atrophic polychondritis associated with UC in a 46-year old patient who was admitted to the hospital for swelling of the nose has been reported.[38] Furthermore, Ueno Y et al. reported a case of relapsing polychondritis leading to collapse of the nasal cartilage in a patient with UC.[39]

Suzumiya J et al. reported the case of a 40-year-old patient with sinonasal malignant lymphoma of natural killer cell phenotype with pancreatic involvement and UC.[40] In addition, Tuzovic S et al. reported on 14 cases of a trichorhinophalangeal syndrome in five successive generations.[41] Besides the well-known characteristics of this dominant hereditary disorder, UC has also been described. Finally, Wooldridge J et al. reported a case of trisomy 9 syndrome and CD.[42]

Involvement of the oral cavity and throat (pharynx, larynx, upper esophagus)

The large majority of cases with oral and throat manifestations that have been so far reported include patients with CD. In CD any part of the gastrointestinal tract may be affected and up to 9% of cases have oral lesions which are usually painful and coincide with periods of active disease. In the oral cavity of CD patients there are both non-specific lesions (including aphthous ulcers and lesions related to poor nutrition and adverse effects of medication) and specific oral lesions, defined by macroscopic and microscopic changes similar to those observed in the gastrointestinal tract of persons with CD.[43,44] The distinction between the non-specific and specific lesions has not been well delineated and as a consequence the incidence of typical lesions has varied in many studies previously reported. The evolution of these lesions over time has also not been described. Therefore, in the absence of intestinal manifestations of CD, the correct diagnosis of isolated oral lesions with granulomatous changes may be difficult to ascribe to CD in some patients unless those patients are followed-up for many years.

It has been suggested that young patients who present with recurrent painful intraoral ulcerative lesions with no signs of systemic disease, apart from weight loss, should prompt inclusion of the possibility of CD amongst other possibilities in the differential diagnosis. As a general rule, the aphthae associated with CD tend to be more widespread and severe than those seen in other conditions; they may occur with, or precede, a symptomatic exacerbation of the intestinal disease. It has also been noted that colonic, rather than small intestinal, CD is more often associated with oral manifestations.

Patients may present with other forms of oral granulomatous disease, including Miescher chelitis (chelitis granulomatosa) and Melkersson-Rosenthal syndrome, which are the principal differential diagnoses to be considered when digestive symptoms are lacking. Both diseases are associated with mucosal edema and induration, angular chelitis, a chronic protracted course and granulomatous histologic features on biopsy. A predominance of lesions on the cheeks and associated facial palsy are additional characteristics of Melkersson-Rosenthal syndrome. The term orofacial granulomatosis has been proposed to encompass all these conditions. Histologically, non-caseating granulomas can be demonstrated in all of these entities. Clinically, similar or identical lesions can occur in the apparent absence of gut signs or symptoms and are therefore quite logically described as oral CD. Furthermore, Shimizu T et al. described a case of CD with the onset resembling systemic lupus erythematosus and presenting with fever, apthous oral ulcerations, sore throat and polyarthralgia.[45]

A rare but interesting phenomenon is the granulomatous inflammation of the tonsils.[46,47] Tonsillar granulomas are not associated with chronic tonsillitis or recurrent tonsillar infection and when present should raise the clinician's suspicion of systemic disease, such as IBD, sarcoidosis, infections (tuberculosis) or malignancies. However, in a study with 220 IBD patients (100 with CD) investigating the risk of tonsillectomy regarding inflammatory bowel disease location it has been shown that ileum is the most prevalent location of disease in CD patients with previous tonsillectomy.[48]

Laryngeal involvement is an uncommon extraintestinal manifestation of IBD. In a review of nine cases with CD,[49,50] all but two experienced gastrointestinal symptoms before laryngeal symptoms. Laryngeal lesions include gross edema of the epiglottis and arytenoid area, with multiple ulcerative lesions of the epiglottis and laryngeal vestibule.[51,52] Treatment involves stabilization and protection of the upper airway from obstruction, with the use of i.v. steroids; if there is no response to steroid therapy, antiTNF-α may be an alternative treatment option.[53]

Pharyngeal and esophageal ulceration with strictures and dysphagia in patients with CD has been well established.[51,54] In some cases of cricopharyngeal CD symptoms improved with corticosteroid treatment,[55] but when dysphagia was complete, treatment with balloon dilatation was necessary.[56] Kobayashi T et al described ulceration and stenosis of the hypopharynx in CD and its surgical management with reconstruction using a subcutaneous pedicle flap.[57] Ulceration of the buccal mucosa and pharyngeal cavities along with primary CD of the oropharynx have also been described.[58,59] The risk of perforation during intubation in these patients seems to be higher, either because of oral lesions changing the local soft tissue, or because chronic corticosteroid therapy has lessened tissue resistance to perforation.[60] In addition, Asakawa A et al[61] reported esophageal ulcers and

Wright R et al[62] sideropenic dysphagia in patients with UC, as well.

Finally, in cases of chronic cough, persisting for longer than one month, it is necessary to search for less common pathologies such as connective tissue disorders (Sjogren's syndrome, atrophic polychondritis), vasculitis (Wegener's granulomatosis), Horton's syndrome (cluster headaches), amyloidosis and IBD.[63]

However, it is important to bear in mind that this symptom is a common side effect of the treatment with the anti-TNF-α agent infliximab in IBD.[64,65]

Clinical and pathophysiological aspects

Common ENT manifestations, usually noticed in every day's clinical practice, such as sore throat and chronic cough, apthae, hearing loss and vertigo or nasal pain may not be as innocent as they have been thought to be in the past. Especially, recurrent symptoms not responding to topical or even to oral treatment should lead the otolaryngologist to search for an underlying multisystemic disease. IBD seem to be from the most common multisystemic diseases, responsible for the former manifestations.

Some ENT clinical manifestations such as epistaxis and edema of the epiglottis and arytenoid area need urgent attention and special treatment. Protection of the airway in such cases is mandatory.

The mechanisms involved in the pathogenesis of ENT manifestations of IBD are not clear, but increased bowel permeability during active disease may cause luminal antigens to be presented to the systemic immune system. As there is already activation of the immune system and pro-inflammatory cytokines such as interleukins (IL-1, IL-12) and TNF-α, this may lead to significant inflammatory responses elsewhere in the body.[66] The inner ear, nose and throat, like other extraintestinal involvement sites in IBD, can become targets of an autoimmune attack.

It has been known that some extraintestinal manifestations may correlate with several parameters of IBD, such as extent of disease, type of disease and duration of disease. In addition, they usually parallel the activity of intestinal inflammation. These findings may need to be elucidaded by further clinical and experimental studies performed with larger patient populations of IBD. An investigation of the natural course and autoimmune pathogenesis, including possible relations with autoantibodies for IBD such as pANCA (perinuclear antineutrophil cyto-

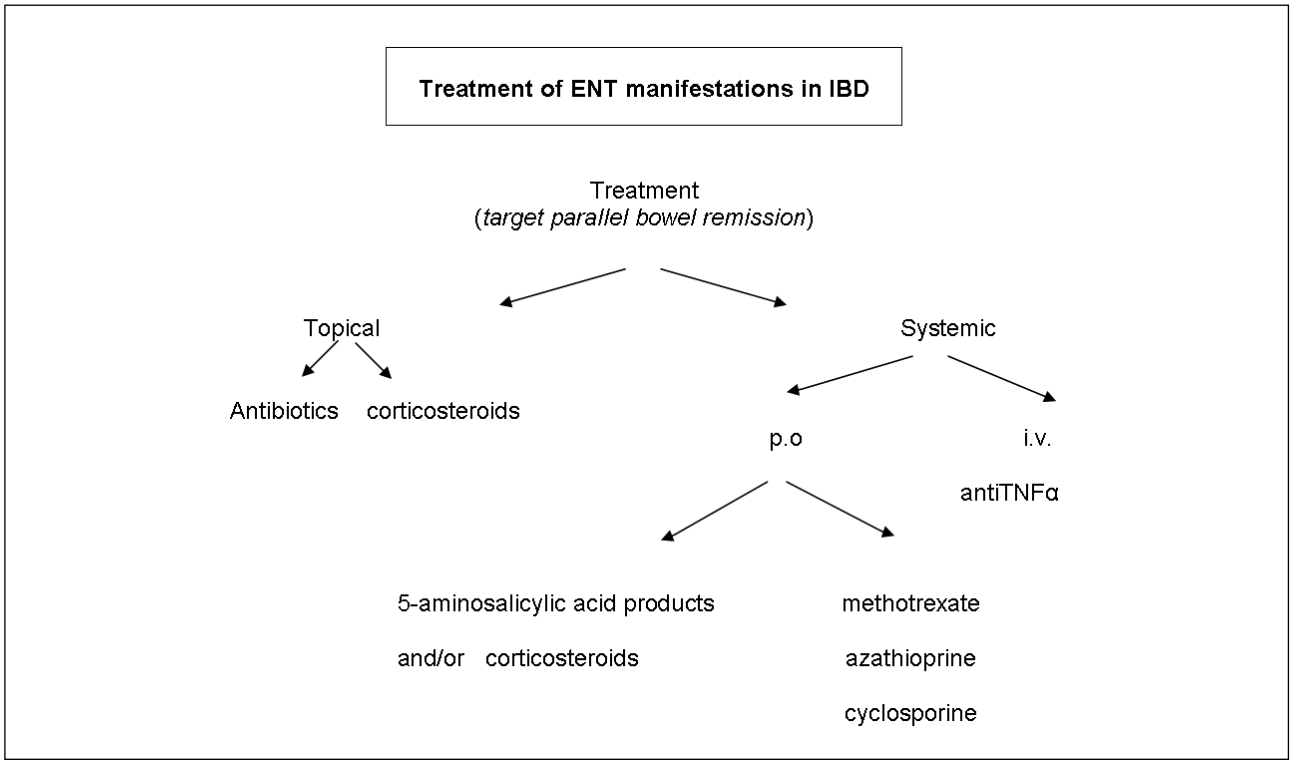

Fig. 1. Algorithm for treatment of ENT manifestations in IBD

plasmic antibodies) and ASCA (anti-Saccaromyces cerevisiae antibodies) may also be required.

The primary mode of treatment for moderate to severe IBD has been 5-aminosalicylic acid products, usually with steroids. In extraintestinal sites, the ulcers can be treated with topical and intralesional steroids. Topical steroids have been shown to be successful in > 50 % of oral ulcers. If topical treatment fails, the use of oral corticosteroids is indicated. However, because of the morbidity associated with long term steroid use, especially aseptic necrosis of the femoral head, osteoporotic fractures, diabetes mellitus, hypertension and formation of cataracts, immunosuppressive drugs such as azathioprine, methotrexate and cyclosporine have been used as well. The latter agents are well tolerated by the majority of IBD patients, with minor side effects from the ear, nose and throat. Antibodies against tumor necrosis α (anti-TNF-α) have shown statistically significant efficacy not only in the treatment of IBD, but also in distinguishing immune mediated oral ulcers from sporadic apthous ulcers. However, anti-TNF therapy can be complicated by a variety of adverse reactions, such as fever, nausea, dyspnea, headaches, rash (including a clinical lupus-like syndrome), urticaria, arthralgias and myalgias, possibly due to development of autoantibodies. Appropriate prophylaxis and therapy of these reactions will allow anti-TNF to be used safely in the vast majority of patients. In addition, patients should be screened and treated for tuberculosis before initiating anti-TNF therapy. An algorithm for the treatment of ENT manifestations in IBD is presented in Figure I.

Finally, the potential risk for maliganancies in patients with IBD has been well established previously and should also be kept in mind, especially in patients with CD. Furthermore, the high risk for cancer of the nose in patients on treatment with azathioprine has also been described.[67]

In conclusion, ENT manifestations should never be evaluated separately or underestimated in IBD patients. It is advisable to follow-up these patients for long periods of time, because some lesions may be manifestations of silent IBD or other multisystemic autoimmune diseases.

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