Tumour necrosis factor inhibitor-associated sinusitis*

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Abstract

Aim: To describe the features of chronic sinusitis associated with the use of tumour necrosis factor (TNF) inhibitors.

Methodology: A retrospective review of the medical records between 2003 and 2011 revealed that five patients had developed chronic sinusitis after the start of TNF inhibitor administration and required rhinological evaluation and treatment.

Results: The incidence of refractory sinusitis associated with TNF inhibitors was approximately 2%. Of the five patients identified, four patients were medicated with etanercept and one with infliximab. The maxillary sinus was most commonly involved and cultures of the sinus discharge revealed *Pseudomonas aeruginosa* in three cases. Two patients showed improvement of sinusitis with antibiotic medication, despite the continuous use of TNF inhibitor, while in two other patients, sinusitis was resistant to antibiotic medication. Another patient who had developed recurrence of sinusitis after complete remission of previous chronic sinusitis by endoscopic sinus surgery showed remission only after cessation of TNF inhibitor.

Conclusion: Chronic sinusitis associated with TNF inhibitors is considered to be a new disease entity, and it will become more common due to the increasing use of TNF inhibitors.

Key words: TNF inhibitor, sinusitis, etanercept, infliximab

Introduction

Tumour necrosis factor (TNF) inhibitors are recently developed biological drug products for chronic inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease and psoriasis. Because TNF inhibitors have been proven to be clinically effective, they have been used in a rapidly increasing number of patients in recent years, and are recommended for the treatment of medication-resistant RA in the guidelines for RA management [1,2].

On the other hand, as TNF-α, the target of these drugs, plays an important role in the immune system [3,4], the use of TNF inhibitors potentially induces increased susceptibility to infection, particularly in the airway, where the TNF-α mediated immune response is important in mucosal host defense against constantly invading pathogens. TNF-α is required for induction of inflammatory cytokines and subsequent leukocyte recruitment, and to increase the potential for phagocytosis by macrophages to prevent the progress of bacterial infection. When TNF-α knockout mice are infected by aerosol challenge with *Mycobacterium tuberculosis*, bacterial growth is markedly elevated and mice show poorer survival compared to infected wild-type mice [5]. Previous clinical studies have revealed that TNF inhibitors sometimes cause serious infective adverse events, such as tuberculosis and pneumocystis pneumonia [4,6-8]. With regard to the upper respiratory tract, sinusitis is reported to be one such complication. Clinical trials have shown an increase in sinusitis in patients with RA treated with TNF inhibitors [9], and a longitudinal study of rheumatic disease outcome revealed that etanercept, a TNF inhibitor, significantly increases the risk of sinus problems [10]. However, there have been few reports [11] focusing on sinusitis associated with the use of TNF inhibitors.

In the present study, we report the clinical features of chronic

Table 1. Clinical features of patients.

Patient No.	Sex	Underlying disease (Age*)	TNF inhibitors (Age**)	Other medications before and at TNF inhibitor onset	Other adverse events
1	F	RA (53)	Etanercept 50 mg/week (56)	MTX (2~6 mg/week)	None
2	F	RA (30)	Etanercept 50 mg/week (50) and up to 100 mg/week (52)	PSL (5~30 mg/day) and MTX (4~10 mg/week)	Pneumonia and OME
3	F	RA (54)	Infliximab 3.7 mg/kg/2 months (57)	PSL (2.5~5 mg/day) and MTX (10~14 mg/week)	Pneumonia and cellulitis
4	F	RA (45)	Etanercept 50 mg/week (50) (short-term infliximab and adalimumab)	PSL (5~15 mg/day), MTX (8~13 mg/week) abatacept for short time	Septic shock due to pneumonia and OME
5	F	RA (50)	Etanercept 50 mg/week (73)	salazosulfapyridine (2000 mg/day)	None

Age* = age at diagnosis; Age** = age when TNF inhibitors were started; F = female; RA = rheumatoid arthritis; PSL = prednisolone; MTX = methotrexate; OME = otitis media with effusion

Table 2. Clinical features of sinusitis.

No.	Interval	Sinuses involved	History of sinusitis	Bronchictasis as a comorbidity	Treatment for sinusitis	Culture of sinus discharge	Outcome
1	3 months	Bilateral maxillary sinuses	(-)	(-)	Roxithromycin for 4 months and nasal irrigation	Normal flora	Improvement
2	2 years (1 month after increase of etanercept)	Bilateral maxillary and frontal sinuses	(+)	(-)	Levofloxacin, garenoxacin, cefditoren-pivoxil and nasal irrigation	*Pseudomonas aeruginosa* (not MDR), Methicillin -resistant *Staphylococcus aureus*	Remission after cease of etanercept
3	1 month	Bilateral maxillary sinuses	(-)	(+)	Cefcapene -pivoxil, clarithromycin and nasal irrigation	*Pseudomonas aeruginosa* (not MDR)	Refractory
4	1 month	Bilateral maxillary sinuses	(-)	(+)	Ampicillin, clarithromycin and nasal irrigation	*Pseudomonas aeruginosa* (not MDR)	Refractory
5	3 months	Right maxillary sinus	(-)	(-)	Clarithromycin for 2 months, Intranasal steroid spray and nasal irrigation	Data not available	Improvement

Interval = Interval between the start of TNF inhibitors and onset of sinus symptoms; MDR = multidrug-resistant

sinusitis in five patients that occurred after the start of TNF inhibitor administration.

Materials and methods

After approval by the Research Ethics Committee of The University of Tokyo Hospital (protocol #2487), we retrospectively reviewed the medical records at the Department of Allergy and Rheumatology and at the Department of Otorhinolaryngology, between 2003 and 2011. This period was selected because TNF inhibitors have been used for RA in Japan since July 2003. During this period, a total of 188 patients, including 154 suffering from RA, underwent treatment with TNF inhibitors at

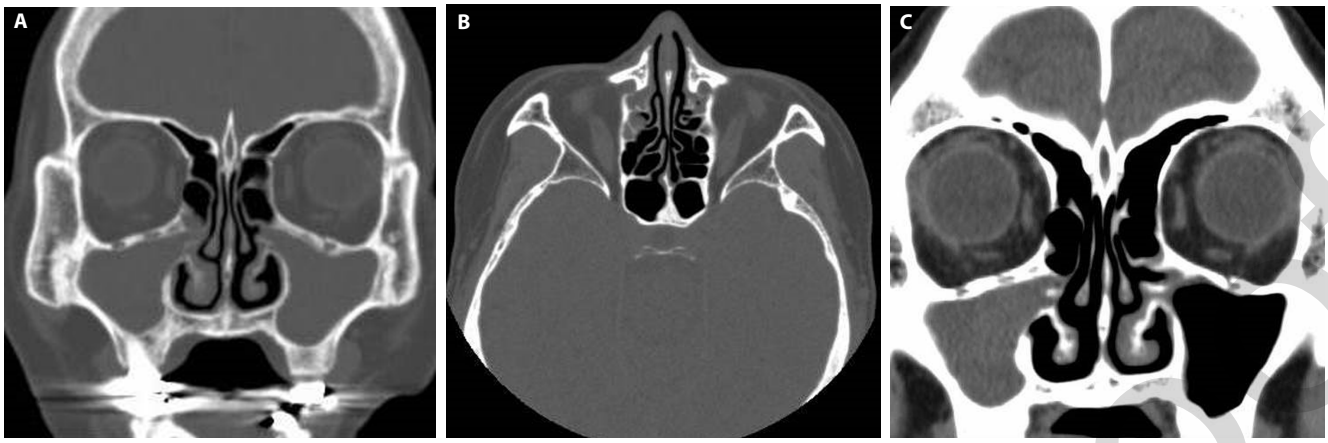

Figure 1. Computed tomography (CT) images of the paranasal sinuses in patient 1 before (A, B) and four months after (C) treatment of sinusitis. A. Coronal sinus CT before treatment showing total bilateral maxillary sinus opacification. B. Axial sinus CT before treatment showing no involvement of ethmoid and sphenoid sinuses. C. Coronal sinus CT four months after treatment with roxithromycin (150 mg/day) showing complete remission of left maxillary sinusitis and partial improvement of aeration in right maxillary sinus.

the Department of Allergy and Rheumatology. Four of these patients (2.1%) developed chronic sinusitis after the use of TNF inhibitor and were referred to the Department of Otorhinolaryngology for rhinological evaluation and treatment. The records at the Department of Otorhinolaryngology revealed one additional patient who developed chronic sinusitis after the use of a TNF inhibitor, and who was referred from another hospital for treatment at our clinic. These five patients were included in the present detailed analysis.

Of the five patients, four patients had been treated with etanercept, a soluble TNF-α receptor. The other had been treated with infliximab, which is a chimeric anti-TNF-α monoclonal antibody. All patients underwent head and neck examination, including nasal endoscopy and radiological evaluation by sinus computed tomography (CT). Diagnosis of chronic sinusitis was performed based on the definition reported in the European position paper for rhinosinusitis [12], i.e., two or more of the following symptoms for 12 weeks or longer: mucopurulent drainage, nasal obstruction, facial pain-pressure-fullness, or sense of smell; and findings of purulent mucus or oedema in the middle meatus or ethmoid region, polyps in the nasal cavity or the middle meatus, and/or radiographical imaging showing shadow of the paranasal sinuses. The following data were collected from the medical records: age; sex; diagnosis; type of TNF inhibitor used; other medications; interval between start of TNF inhibitor and onset of sinus symptoms; physical examination findings; endoscopic findings; sinus computed tomography (CT) findings; culture results; and co-morbidities, their treatment and outcome.

Results

Summaries of the clinical features of the five patients and their sinusitis are presented in Tables 1 and 2, respectively. All of the patients were Japanese females who had been treated with TNF inhibitors for their RA symptoms. The average age of patients when they started using TNF inhibitors was 57.2 years (50 – 73). All of the patients were also treated with other immunosuppressive drugs such as methotrexate (MTX), glucocorticoid and salazosulfapyridine. None of the five patients had neutropenia at the time of sinusitis diagnosis.

One patient (patient 2) was previously diagnosed as having sinusitis and had undergone endoscopic sinus surgery before the use of TNF inhibitor (see case report). A review of the medical records of the other four patients revealed no subjective or objective symptoms indicative of sinus problems before the use of TNF inhibitors, and none of them underwent radiological evaluation of the sinus condition before the use of TNF inhibitors. The interval from the start or increase in dose of TNF inhibitors until onset of sinus symptoms was one month (patients 2, 3 and 4), and three months (patients 1 and 5).

CT examination revealed that the maxillary sinus was most commonly involved. Four patients (patients 1, 2, 3 and 4) showed bilateral maxillary lesions and the other patient (patient 5) showed unilateral maxillary lesions. In one patient (patient 2), bilateral frontal sinus was also involved. Other local and systemic complications included otitis media with effusion in two patients (patients 2 and 4), bronchiectasis and pneumonia in three patients (patients 2, 3 and 4), and cellulitis in one patient (patient 3). Neither eosinophilia nor asthma was present in these five patients. Culture of nasal swabs yielded *Pseudomonas aeruginosa* in three patients (patients 2, 3 and 4), and methicillin-resistant *Staphylococcus aureus* (MRSA) was also identified in

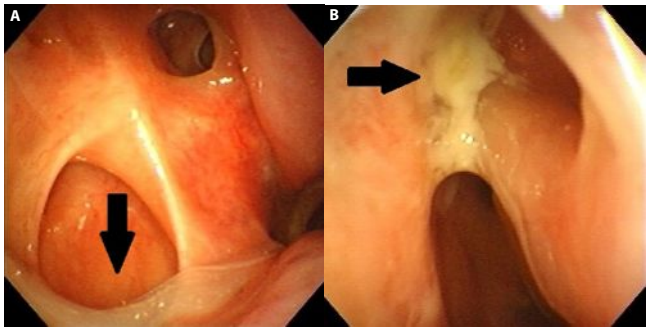

Figure 2. Endoscopic image of the patient 2 before cessation of etanercept. A. Purulent discharge from wide opening of the right maxillary sinus (arrow). B. Purulent discharge from frontal sinus (an arrow).

one of these (patient 2).

All of the patients were treated with antibiotics and nasal irrigation using saline. Two patients (patients 1 and 5) showed improvement with antibiotic medication despite the continuous use of TNF inhibitors. Sinusitis of two other patients (patients 3 and 4) were resistant to antibiotic medication, but these patients had been followed with the continuous use of TNF inhibitors without surgical treatment because they refused surgery. Sinusitis in patient 2 who had previously undergone endoscopic sinus surgery was also resistant to antibiotic medication and showed remission only after cessation of etanercept.

Case Reports

Patient 1

A 53-year-old female was diagnosed as having RA in 2005 and had received MTX (2~6 mg/week) for three years. With disease progression, she started taking 50 mg of etanercept every week, with MTX (2 mg/week) from August 2008. RA symptoms became well controlled thereafter, but postnasal purulent discharge developed in November 2008. When she was referred to our department in September 2011, we observed purulent rhinorrhea draining from bilateral hiatus semilunaris. CT revealed total bilateral maxillary sinus opacification (Figure 1A) and other paranasal sinuses were clear (Figure 1B). Culture of the sinus discharge revealed normal flora. The patient was treated with roxithromycin administration (150 mg/day) for four months and nasal irrigation. She noticed improvement of postnasal discharge thereafter, and follow-up CT four months later showed that her left maxillary sinus had become clear, and the right side was partially aerated (Figure 1C).

Patient 2

A 30-year-old female was diagnosed as having RA in 1987 and was treated with prednisolone (5~30 mg/day) and MTX (4~10 mg/week). She suffered from chronic sinusitis from 1998 and underwent ESS in 2006. Her sinusitis had been in complete remission after ESS.

To control RA symptoms, she started using 50 mg of etanercept a week with MTX (6 mg/week) from April 2007 at the age of 50 years. The dose was raised to 100 mg/week in April 2009. A month later, purulent rhinorrhea increased and nasal endoscopy revealed purulent discharge draining from the widely opened bilateral maxillary sinus and also from the bilateral frontal sinus (Figure 2A, B). Culture of the nasal swab revealed *Pseudomonas aeruginosa* and MRSA. Her sinusitis was resistant to antibiotic treatment using cefditoren pivoxil, levofloxacin and garenoxacin, and she also developed pneumonia. She stopped using etanercept, and her sinusitis has since been well controlled with daily nasal irrigation.

Discussion

We herein described five cases with chronic sinusitis that developed after the use of TNF inhibitors. The incidence of sinusitis with the use of TNF inhibitors is reported to be 7-15% [13,14], which is higher than that in general adult populations (5.7% in women and 3.4% in men) [15]. Our study further suggests that the incidence of refractory sinusitis which requires rhinological evaluation and treatment was approximately 2%.

Although there is no direct evidence that repeated administration of TNF inhibitors caused chronic sinusitis in our patients, the time lapse between the two events suggests a strong relationship. As all of the patients also used immunosuppressive medication in addition to TNF inhibitors, however, we cannot exclude the possibility that sinusitis was induced by synergistic immunosuppressive effects of TNF inhibitors and such concomitant drugs rather than TNF inhibitor alone. In our case series, two patients developed symptoms associated with sinusitis after the start of etanercept at 50 mg/week, while other patients developed sinusitis only after increasing the dose of TNF inhibitors to 100 mg/week. The dose that induces sinus pathology may thus vary with each patient.

Our data also demonstrated that there was a time lag between TNF inhibitor administration and the onset of sinus symptoms. All of our patients developed sinus symptoms within a few months of starting or after an increase in the dose of TNF inhibitors. Similar time lags were documented by Haroon et al. [11], sinusitis occurred within a few weeks of starting adalimumab, which is a fully human anti-TNF-α monoclonal antibody. The reasons underlying this time lag are unclear, but it may reflect the differences in short-term and long-term effects of TNF inhibitors on the airway mucosa. As TNF-α is a proinflammatory cytokine, the use of TNF inhibitors should lead to inhibition of inflammation in the short-term. In fact, experimentally acute sinusitis induced by lipopolysaccharide in rats was improved by admi-

nistration of TNF inhibitor [16]. On the other hand, as described in the Introduction, the inflammation mediated through TNF-α is an essential element of mucosal immunity against pathogens [3], and thus long-term suppression of TNF signaling may lead to chronic infection.

In the present cases, the maxillary sinus was the most commonly involved site. Cultures of sinus discharge showed *Pseudomonas aeruginosa* in three of the five patients. These characteristics have been found in patients with infective sinusitis of other systemic etiology, such as those with cystic fibrosis [17,18] and immunocompromised patients with haematological diseases, HIV infection or organ transplantation [19,20]. This is in contrast to the sinusitis associated with eosinophil infiltration, which usually shows ethmoid sinus-dominant involvement [21]. The reason why the maxillary sinus was most commonly involved in our patients remains unknown, but it may reflect yet unspecified differences in immune response of the mucosa between maxillary and ethmoid sinuses. Interestingly, two patients also had bronchiectasis as a comorbidity. It remains unclear whether the sinusitis and bronchiectasis were coincident in our patients or whether they are closely associated [22].

One limitation of this retrospective study is that histological examination of the sinus mucosa in TNF inhibitor-associated sinusitis was not performed in any of the five patients, because of the lack of specimen availability. It is necessary to address this issue in a future study.

Clinical management of chronic sinusitis associated with TNF inhibitors has not been fully discussed due to the paucity of reports. In patient 2, purulent discharge continued to drain from the ostium of the maxillary sinus after opening by endoscopic sinus surgery. This phenomenon suggests that sinusitis is induced by the pathological alteration of the mucosa itself and not by the obstruction of the ostium, thus, cessation of TNF inhibitors is considered necessary in such cases.

It is interesting that sinusitis in patient 1 responded well to long-term macrolide therapy [23]. The effectiveness of macrolide therapy should therefore be further examined.

Although not common, chronic sinusitis associated with TNF inhibitors is considered to be a new disease entity. Because TNF inhibitors are now becoming more commonly used, this entity should be kept in mind.

Authorship contribution

All authors were involved in the design and conduct of this study. Data collection and analysis was performed by S, KKo, KKa, KS, SB, MT-H, SK, YI, KF. SY and KKo wrote the manuscript. SY, KKo and TY take overall responsibility for the integrity of the study.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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