Implications of Endodontic-related Sinus Aspergillosis in a Patient Treated by Infliximab: A Case Report

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Abstract

Introduction: Sinus aspergillosis is a potential complication after root canal therapy of antral teeth. Indeed, zinc oxide–eugenol cement overfilling in the sinus may promote fungal infection. Moreover, if sinus aspergillosis triggers chronic sinusitis with aspergilloma, it may also lead to invasive phenomena, especially for immunocompromised patients. Methods: We reported a sinus aspergillosis case of a patient treated with infliximab (Remicade; Janssen Biologics BV, Leiden, Netherlands). The purpose of this article was to explore the mechanisms of this pathosis, especially the impact of the root canal sealer overextension, which is a contributing factor for fungal infection. The surgical management and the follow-up are also described. Results: Six months after surgery, the patient showed no clinical signs and presented with a healthy and airy right maxillary sinus on the computed tomography scan. Conclusions: In conclusion, prevention and screening of aspergillosis of maxillary sinus may be considered before starting an anti–tumor necrosis factor alpha therapy. (J Endod 2015;41:125–129)

Key Words

Aspergillosis, endodontics, maxillary sinusitis, root canal filling, therapeutic use, tumor necrosis factor alpha thera py.

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Case Report

Clinical Observation

A 64-year-old patient was referred for an oral health evaluation before starting prosthetic treatment. Anamnesis showed many health problems such as psoriatic rheumatism history, stabilized non–insulin-dependent diabetes, dyslipidemia, chronic cough, and sinusitis associated with facial pains. Consequently, the patient provided her prescriptions, which included an anti–TNF-α (Remicade), biguanide (metformin), and statin (pravastatin).

Overall, the clinical examination revealed poor oral health without associated symptoms. The panoramic view highlighted the anatomic continuity between the maxillary sinus and the apex of the upper molars and also an important sealer overextension in the right sinus close to tooth 16 (Fig. 1). Rhinoscopy was implemented but did not reveal any nasal sign. A CT scan was prescribed to thoroughly check the sinus obstruction and the overfilling extent and its aspect. The sealer overfilling in the right sinus appeared as a hyperdense structure and was surrounded by peripheral and nonhomogeneous opacification associated with a severe hypertrophic mucous membrane (Fig. 2). A slight bone densification of the sinus lining was also observed, and the patency of the maxillary ostium sinus was correct. No invasion of the surrounding structures was noticed.

Symptoms could either correspond to chronic sinusitis of bacterial origin or sinus aspergillosis. Taking into account the clinical and paraclinical data and the specificity of the radiologic image, noninvasive sinus aspergillosis was suspected.
The patient was referred to a pneumologist to check breathing function and detect potential chronic obstructive bronchopathologies. A thoracic CT scan was normal, and, except the chronic cough, no bronchopathologies or lung issues were noticed including lung aspergillosis. With the suspicion of aspergillosis and the potential risk of complications, it was decided to implement a surgical procedure.

Treatment

The surgical therapy was based on tooth extraction associated with Cadwell-Luc surgery. A periapical lesion with inter-radicular bone resorption of tooth 16 was visible on the CT scan. Although this issue could have probably been solved by endodontic retreatment, a collegial decision of extraction was made by the rheumatologist and the odontologic team because of 2 main elements: (1) the rheumatologist wanted a radical and quick attitude toward infection sources considering that anti–TNF-α treatment would not be resumed after the surgery until the patient was free of dental infectious sources and (2) the tooth showed no strategic importance for the future prosthetic rehabilitation considering the poor bone level and its isolated position.

The surgical procedure indicated for clearing the infected maxillary sinus was Cadwell-Luc surgery. The indications for which surgical technique should be used (ie, Cadwell-Luc surgery, endoscopic surgery for meatotomy, or a combination of these 2 techniques) have remained controversial for more than 20 years. According to Costa et al (11), endoscopic surgery is the treatment of choice for sinus aspergillosis, and Cadwell-Luc surgery must be considered as a complementary technique (11). However, Ferreiro et al (12) showed no recurrence with Cadwell-Luc therapy, and a recurrence rate of 6.8% after endoscopy. Because the accessibility of the sinus is more difficult during a meatotomy, the risk of residual remnants, an important factor of recurrence, would be more important. According to Dufour et al (13), Cadwell-Luc surgery is always insufficient when the maxillary ostium is blocked, and endoscopic treatment is more often indicated to restore drainage.

In the present case, Cadwell-Luc surgery alone was preferred for the following reasons: (1) there was good ostium patency, (2) it allowed good accessibility to the fungal balls localized in the lower part of the sinus, and (3) the extraction of tooth 16 and closing the oroantral fistula with a buccal flap were scheduled at the same time and the same flap would allow access to the anterior wall of the sinus for curettage.

The surgical treatment required infliximab interruption 4 weeks before the surgical procedure to reduce risks of severe infection (14). The surgery was performed under general anesthesia. After incision, the soft tissues over the maxillary sinus were elevated thanks to a trapezoidal flap to visualize the frontal wall of the right sinus. Then, a round bur was used to fenestrate the maxillary sinus and to make a sufficient opening for the cleaning step (Fig. 3). The sealer debris were carefully removed as well as brown soft tissue mass (Figs. 4 and 5) and the hypertrophic mucous membrane. Then, a gentle rinse was performed with Betadine (Meda Manufacturing, Merignac, France). A periosteal incision allowed closure of the surgical site without tension.

Finally, mycologic and anatomopathologic examinations were implemented to confirm the diagnosis. Histology showed a heterogeneous material with large and strong eosinophilic areas, which corresponded to fibrin enclosing a few red blood cells. Hematoxylin-eosin-safran and periodic acid–Schiff colorations indicated many aggregations of tightly packed hyphae with 45° dichotomous branching, characteristic of Aspergillus. Some fragments containing neutrophils, lymphocytes, and plasma cells were also observed, but cultures were

Figure 1. Orthopantomography.

Figure 2. A CT scan showing sealer overfilling in the right sinus appeared as a hyperdense structure surrounded by a peripheral opacification.

Figure 3. A clinical view of Cadwell-Luc surgery.
negative for Aspergillus. However, mycologic examination is well-known for leading to a high false-negative rate (11, 15–18), and this is why the role of fungal culture in the diagnosis of aspergillosis remains controversial (15). Therefore, on the basis of these known clinical and histopathologic findings, Aspergillus mycetoma was diagnosed.

Postoperative treatment included antibiotics (amoxicillin 2 g/day and clavulanic acid 250 mg/day), corticoids (prednisolone by mouth 60 mg/day and triamcinolone nasal spray twice a day), and antalgics (paracetamol 3 g/day). No systemic antifungal treatment was associated with the surgical treatment because it is indicated only in invasive sinus aspergillosis (11) and not for noninvasive forms (13).

Follow-up

The success of the therapy was evaluated 6 months after the surgery; the patient showed no clinical signs and presented with a healthy and airy right maxillary sinus on the CT scan (Fig. 6). Healing should be monitored at 1 year.

Discussion

Description of Aspergillosis

Aspergillosis is a fungal infection caused by fungi of the genus Aspergillus such as A. fumigatus or Aspergillus flavus, which are most frequent in Europe (5). These microorganisms are present in the ground, in plants, and in the air of closed environments (16, 19). This is why this kind of infection may take place in natural cavities such as sinuses or lungs. Aspergillosis can be caused by the inhalation of airborne spores or, more frequently, by the iatrogenic way, which occurs when there is oroantral contamination at the time of a dental procedure (20).

Multiple clinical forms of fungal rhinosinusitis have been described, ranging from benign aspergilloma to invasive and fulminant infection. Aspergilloma of the maxillary sinus seems most frequent in male patients with an average age of 64 years (range, 14–90 years) (21).

The clinical setting is quite similar to unilateral chronic sinusitis, which is frequently unsuccessfully treated with conventional protocols. When symptoms are present, they combine a unilateral nasal obstruction with or without purulent nose blowing, cacosmia, and facial pain (20). For instance, pressure applied on the anterior side of the sinus can be painful. However, this pathosis is often asymptomatic and accidentally discovered during radiologic examination. Orthopantomography generally shows opacity of the maxillary sinus associated with calcifications (22, 23). These elements may also be revealed with occipitomental radiography. A CT scan is essential; it confirms these observations with more accuracy and helps the practitioner perform the surgical intervention. Clinical and/or radiologic diagnosis must be confronted with pathologic and mycologic examination even if the latter is often negative (18), as in the present case report.

Correlations between Aspergillosis and Endodontic Procedures

Frequently, aspergillomas are associated with overfilling during an endodontic procedure, and radiologic examination shows dental material in the maxillary sinus (1). A study including 85 cases of
aspergillomas concluded that endodontic treatment associated with overfilling was responsible for 85% of the cases (17).

Iatrogenic root canal preparation or filling, such as misevaluation of the working length, poor master cone adjustment, or use of an excessive quantity of sealer may lead to overfilling. If no contraindication exists (pacemaker), the working length should be determined by confronting X-ray data with electronic apex locator use (24). Indeed, this device, when properly used, is more relevant than radiographic estimation alone, which may be distorted by artifacts and operator subjectivity (25). Furthermore, it is well admitted that root canal filling should require a maximal quantity of gutta-percha for a minimal quantity of sealer even if the latter still remains essential (26). Consequently, the use of a lentulo spiral should be avoided because of the risk of leakage, instrument fracture, and especially overfilling in cases of open apices.

However, root canal sealer overextension alone does not necessarily lead to aspergillomas. Even if zinc oxide–eugenol–based cements, which are frequently used, are present and paraformaldehyde–based sealers have been indicated to be correlated with sinus aspergillosis (27, 28), additional factors seem necessary to initiate this pathosis.

Aspergillosis and Zinc Oxide–Eugenol–Based Sealers
Stammberger et al (29) and Kopp et al (25) described the implication of root canal filling materials in aspergillosis physiopathology; they confirmed the results of a previous study that showed that growth and metabolism of A. fumigatus depend on the presence of heavy metals such as zinc oxide (1, 4, 23, 29). However, Karapinar (30) showed the antifungal activity of eugenol on Aspergillus parasiticus. Menzi et al (2) suggested that zinc oxide might act as a substratum for aspergillomas. In the same way, the inhibition property of eugenol on A. fumigatus is gradually lost. Zinc influences not only the metabolism of Aspergillus but also could be responsible for reactionary mucosal hyperemia and mucociliary paralysis associated with potential epithelial dysfunction. The latter could result in the accumulation of calcium phosphate concretions, which constitute a refuge for inhaled spores (31, 32). Microcalcifications mixed with the sealer debris could be explained by the presence of calcium phosphate, which can be observed as typical radiologic images (2).

Other Etiologies
Paraformaldehyde may trigger irritation and necrosis of the sinus mucosa (33). Nowadays, this product is no longer used because it is known to be allergic and neurotoxic (34). Predisposition such as some systemic diseases and/or immunosuppressive treatment can lead to an invasive evolution of aspergillomas. These cases mimic a tumorigenic process by destroying surrounding anatomic structures and result in serious complications. A fatal case of orbital and ethmoidal tumor formation by destroying surrounding anatomic structures result in serious complications. A fatal case of orbital and ethmoidal tumor formation by destroying surrounding anatomic structures in a patient whose medical status was non–insulin-dependent diabetes and hepatic cirrhosis (35). Gungor et al (36) reported the case of a patient with chronic sinus aspergillosis after a kidney transplant involving an immunosuppressive treatment who later developed invasive disseminated aspergillosis.

Patients under Anti–TNF-α
Several cases of aspergillosis have also been described in patients treated with anti–TNF-α for rheumatoid arthritis or chronic inflammatory bowel disease (37). Rheumatoid arthritis, because of its dysimmune nature (38) and the associated treatments (anti–TNF-α in particular) (10, 39), notably increases the risk of infection (40).

TNF-α is a proinflammatory cytokine involved in the recruitment of neutrophils and the potentiation of the antifungal activity of neutrophils and macrophages (19). Anti–TNF-α modulates TNF-α, thus preventing inflammation and limiting its long-term consequences. Opportunistic infections and reactivation of latent infections such as tuberculosis, legionellosis, listeriosis, pneumocystosis, histoplasmosis, and aspergillosis have been described in biotechnology (8, 41).

Sixty-four cases of invasive pulmonary aspergillosis in patients treated with anti–TNF-α (with 48 under infliximab) have been reported by Tsiodras et al (37) with a high mortality rate (82%). However, no case of sinus aspergillosis was reported, but the authors did not specify if sinusal location was sought.

A polycentric study from Leboime et al (39) including 550 patients treated with anti–TNF-α reported 6 cases of sinus aspergillosis (1.1%). No evolution to an invasive form of the disease can be found in this study.

One case of invasive pulmonary aspergillosis has been described for a patient who began treatment with infliximab for chronic inflammatory bowel disease. The presence of latent chronic sinus aspergillosis was shown thanks to an ear, nose, and throat examination (7).

However, none of these works gave any indication regarding the occurrence of endodontic treatments presenting overfilling as in the present case. To our knowledge, if recommendations concerning the detection of tuberculosis before setting anti–TNF-α treatment can be found, there is currently no consensus about aspergillosis, which is of lower occurrence (42).

Guidelines for Medically Compromised Patients
Considering the growing indications of anti–TNF-α therapy and the increased risk of infection associated with it, it seems necessary to detect patients at risk before initiating this type of treatment. A dental examination and panoramic radiography are considered necessary in this context. Leboime et al (39) suggested implementing a systematic search of sinus aspergillomas by performing a scanner before establishing biotherapy.

If anti–TNF-α therapy is planned and if root canal sealer overextension is discovered on a panoramic view, preventive surgery should be performed to avoid aspergillosis occurrence and potential severe extensions in the future.

Overall, for immunocompromised patients and when root canal therapy has to be performed for antral teeth, particular attention should be paid on shaping protocols and working length assessment. The latter should be preferentially determined using an electronic apex locator.

Finally, if the patient is already being treated with anti–TNF-α, it could be argued that cements containing zinc oxide or formaldehyde should be proscribed and replaced by other types of endodontic sealers. In conclusion, further studies regarding the correlation between anti–TNF-α and sinus aspergillosis should be performed.

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References