Potential predisposition for nasal septal perforation with methotrexate use: Report of 2 cases and literature review

Scott L. Lee, MD; David Neskey, MD; Jason Mouzakes, MD

Abstract

Methotrexate is a dihydrofolate reductase inhibitor with application both as a chemotherapeutic agent and as a disease-modifying antirheumatic drug. Although its ability to inhibit cellular proliferation is a desired effect in its role as an antineoplastic agent, this property may also hinder normal physiologic regeneration of the nasal epithelium. This effect may predispose patients to septal cartilage ischemia, necrosis and, eventually, perforation. We report 2 cases of septal perforations in the setting of prolonged methotrexate use and present a literature review. Patient 1 is an 8-year-old boy with juvenile rheumatoid arthritis managed with weekly methotrexate who developed a 4-mm septal perforation with an unremarkable biopsy. This was closed with a mucosal advancement flap without incident. Patient 2 is an 11-year-old boy with non-Hodgkin lymphoma treated with methotrexate. His examination was significant for a large perforation of the dorsocaudal septum. A biopsy was negative for malignancy in this patient. Repair has been deferred—initially for chemotherapy and currently for treatment relapse. We hypothesize that prolonged use of methotrexate alters the balance between physiologic desquamation and epithelial regeneration. This imbalance may promote septal ischemia and predispose patients to the development of septal perforations.

Introduction

Juvenile rheumatoid arthritis (JRA) affects as many as 4 per 1,000 children, and treatment typically involves nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).[1] Methotrexate, a dihydrofolate reductase inhibitor with immunosuppressive properties, is the most commonly used DMARD for JRA.[2] Although its role as a chemotherapeutic agent is well established, its mechanism of action as an anti-inflammatory agent remains elusive.

Non-Hodgkin lymphoma (NHL) accounts for 60% of all childhood lymphomas.[3] Of the four subtypes of childhood NHL—small noncleaved-cell lymphoma (Burkitt and non-Burkitt), lymphoblastic lymphoma, large-cell lymphoma, and anaplastic large-cell lymphoma—lymphoblastic lymphoma accounts for about 30%.[4] Treatment typically consists of multiagent chemotherapy, with little role for surgical debulking or radiotherapy.[3]

Although the ability of methotrexate to inhibit cellular proliferation is a desired effect in its role as an antineoplastic agent, this same property may also hinder physiologic regeneration of nasal epithelium. We hypothesize that prolonged use of methotrexate alters the balance between physiologic desquamation and epithelial regeneration. This imbalance may promote septal ischemia and predispose patients to the development of septal perforations.

Case reports

Two patients followed by the Division of Pediatric Otolaryngology at University Ear, Nose & Throat (Albany, N.Y.) are presented. Both patients developed a septal perforation after treatment with methotrexate; neither had a history of trauma or drug abuse.

Patient 1. An 8-year-old boy with JRA was being treated by the rheumatology service with methotrex-

From the Ear, Nose & Throat Center, Altru Health System, Grand Forks, N. Dak. (Dr. Lee), Albany Medical College, Albany, N.Y. (Dr. Neskey), and University Ear, Nose & Throat, Albany, N.Y. (Dr. Mouzakes).
Corresponding author: Scott L. Lee, MD, Ear, Nose & Throat Center, Altru Health System, 1000 S. Columbia Rd., Grand Forks, ND 58201. Phone: (701) 780-6301; fax: (701) 780-1889; e-mail:slee@altru.org

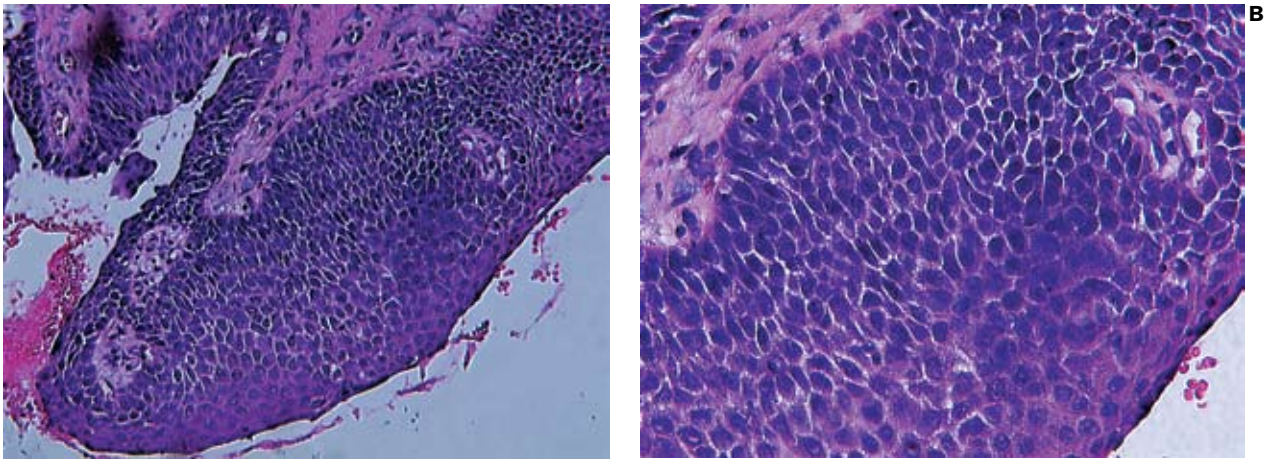

*Figure 1. Nasal biopsies from patient 1 (original magnification ×200 [**A**] and ×400 [**B**]; both stained with hematoxylin and eosin) demonstrate squamous epithelium with moderate atypia. This is different from the ciliated columnar epithelium typical of the nasal mucosa.*

ate, 30 mg weekly. He developed a 4-mm nasal septal perforation but was otherwise healthy. The perforation was closed with a mucoperichondrial advancement flap after biopsy specimens revealed no malignancy (figures 1 and 2). However, instead of the typical ciliated columnar nasal epithelium, squamous epithelium with moderate atypia was observed (figure 1). Figure 2 shows this patient's otherwise unremarkable nasal septal cartilage.

Patient 2. An 11-year-old boy with NHL, lymphoblastic type, underwent positron emission tomography to rule out metastatic disease; the findings were normal. He was treated with weekly intrathecal methotrexate in a regimen of combination chemotherapy. Subsequently, he was referred to the pediatric otolaryngology service for a large perforation of the dorsocaudal septal cartilage. Nasal septum biopsies were negative for malignancy. This patient completed his initial chemotherapy but recently required further treatment for relapse. Septal repair has not been attempted.

Discussion

Methotrexate is a folic acid antagonist and inhibits dihydrofolate reductase, an enzyme essential to the biosynthesis of nucleic acids. This property makes it a common agent used in the treatment of neoplastic conditions. Methotrexate is also employed as a DMARD for JRA, although its mechanism of action as an anti-inflammatory agent is unclear. The antiproliferative properties of methotrexate that make it a widely used chemotherapeutic agent may also hinder normal cellular regeneration, including that of the nasal epithelium. Although the causes of septal perforation are numerous, prolonged methotrexate use may be a predisposing factor.

In the management of refractory rheumatoid arthritis, methotrexate is an effective second-line agent because patients can tolerate therapy for prolonged periods.[5-12] It is precisely this long-term tolerance that is concerning, since the side effects of methotrexate are believed to be related to the length of exposure to high plasma levels, rather than to actual peak levels.[13] The most commonly observed side effects of methotrexate therapy are gastrointestinal distress, headache, and oral and nasopharyngeal symptoms.[2] In a study by Kremer and Phelps, as many as 55% of patients receiving weekly methotrexate for 90 months experienced oropharyngeal symptoms in the form of oral ulceration or soreness.[14]

Epithelial ulceration results from acute damage to the proliferating cellular compartment, such that desquamation at the surface exceeds basal cellular regeneration. Chemotherapeutic agents have deleterious effects on both the surface epithelium and the underlying progenitor cell layer. The result is acute mucosal erythema, associated with an increase in vascular permeability, connective tissue edema, and inflammatory infiltrate. The associated loss of collagen may be the result of vascular changes leading to occlusion of capillaries, hypovascularization, and subsequent tissue ischemia.[15] Sensitivity of septal cartilage to this type of ischemia may predispose it to necrosis and subsequent perforation.

Histologically, these progressive changes may be evidenced by the observation that normal ciliated columnar nasal epithelium has been replaced by squamous epithe-

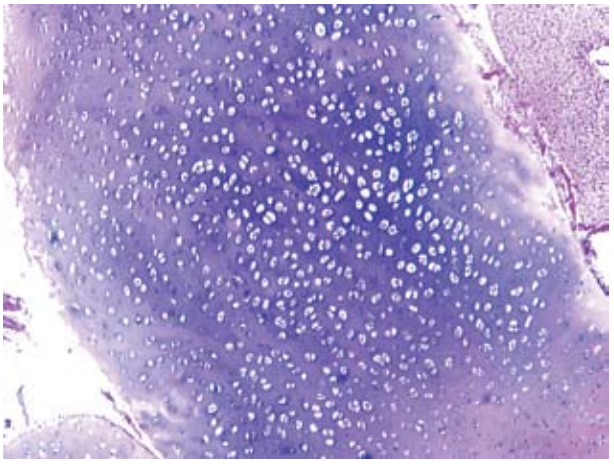

Figure 2. Nasal cartilage from patient 1 shows no evidence of malignancy (H&E, original magnification ×50).

lium with moderate atypia (figure 1). The surrounding septal cartilage is normal, which may reflect a localized effect at the central aspect of the nasal septum, where blood supply is most tenuous.

In addition to its role in the management of JRA, methotrexate is a prominent component of chemotherapeutic regimens for the treatment of NHL. Chemotherapy affects rapidly proliferating cells, both neoplastic and non-neoplastic. As described above, normal epithelial surfaces can become atrophic and ulcerate during chemotherapy. The extent of these degenerative states is proportional to the rate of epithelial proliferation.[16] The oral and nasopharyngeal mucosal epithelia behave similarly and are normally in a steady state of renewal, with approximately 10% of cells in the synthesis phase of mitosis.[17,18] Since the rates of cell proliferation in the nasal and oral epithelia are comparable, chemotherapeutic agents may similarly cause ulceration in both regions. Oral ulcers, such as those observed by Kremer and Phelps,[14] may hint at the potential for similar ulcers in the nasal epithelium. Denuded septal cartilage is then susceptible to chondrocyte ischemia, leading to eventual perforation.

In conclusion, otolaryngologists should recognize that the adverse effects of methotrexate—the most commonly used DMARD for JRA and a widely used chemotherapeutic agent—may manifest in the head and neck. A case-control study may help further elucidate whether the incidence of septal perforation could be influenced by age, sex, and/or choice of chemotherapeutic agents such as methotrexate. Such a study might also reveal whether there is a role for leucovorin "rescue" after methotrexate therapy to offset the adverse effects of prolonged treatment. Until this information becomes available, physicians prescribing methotrexate should be diligent about monitoring adverse effects such as nasal septal perforation.

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