CASE REPORT

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Chemotherapy in severe nasal polyposis - a possible beneficial effect? A report of three cases*

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SUMMARY

Background: *Nasal polyposis is an inflammatory process of the nasal mucosa. Treatment has changed from surgery to an anti-inflammatory approach, but neither of these treatments addresses the underlying cause. Topical steroids and occasional use of systemic steroids in patients with nasal polyposis can frequently control the polypoid disease. In a few cases, when the disease is more aggressive, the repeated application of systemic steroids together with sinus surgery is required.*

Material and Methods: *We present our experience with one case of rheumatoid arthritis and two cases with malignant diseases, all of which were treated with chemotherapy and were also accompanied by severe nasal polyposis. All of our patients had eosinophilic polypoid disease. Various chemotherapeutic treatment schemes were utilized.*

Results: *During chemotherapy all three patients were markedly improved symptomatically including olfaction along with a significant reduction in their nasal polyposis. Duration of remission lasted for a few months in two cases and for three years, in a third case.*

Conclusion: *This is the first report describing the successful treatment of severe nasal polyposis with chemotherapy. Based on this experience, we suggest a phase II trial with chemotherapy, preferably "low dose" methotrexate, in patients with severe nasal polyposis.*

Key words: nasal polyposis, chronic rhinosinusitis, chemotherapy, methotrexate, cyclosporin A

INTRODUCTION

Nasal polyposis, sometimes called "asthma of the nose", is frequently associated with asthma and aspirin intolerance. The symptoms can be extremely troublesome to the patient and very challenging for the physician. Like asthma, nasal polyposis is characterized by a Th2-type inflammation, which can be inhibited by cortisone therapy. Nasal polyposis is clearly an inflammatory disease [(1)]. The etiology is controversial and still unknown. In most cases, polyps are dominated primarily by activated eosinophils, but in some cases neutrophils are increased compared to healthy mucosa. Other features are epithelial damage, thickened basement membrane, oedema and invasion of fibroblasts. There are an increased number of T-lymphocytes (CD3 and CD25), and of the cytokines, IL-5 seems to have a key roll [(2)].

We present three patients with severe nasal polyposis who received chemotherapy treatment for rheumatoid arthritis (RA) or for malignant diseases, whose nasal polyposis symptoms were remarkably improved as a result. Chemotherapy may be considered as an alternative anti-inflammatory therapy in nasal polyposis.

CASE 1 *(SER)*

The first patient is a 63-year old retired white coal miner who recently stopped smoking. He had a balloon angioplasty for claudicatio intermittens and had been treated with simvastatin 20 mg daily for hypercholesterolemia and had a penicillin allergy. He was a patient at the ENT clinic with a 20-year history of severe nasal polyposis. He had been treated with surgery (3 times) and also with local and systemic steroids. After his fourth polyp operation, he was enrolled into a clinical study using topical Amphotericin B solution. One year after the study polyps were observed under the middle turbinate, and continued to grow with the passage of time.

A year after the last nasal surgery, the patient experienced a sudden onset of sero-positive rheumatoid arthritis. He was treated with peroral methotrexate 12.5 mg/week. After one year of methotrexate treatment, the patient noted improved olfactory and nasal breathing function. After three years, he was totally asymptomatic with normal olfaction and nasal breathing. On nasal endoscopic examination, no polyps were visible.

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For the first time in 10 years the patient has not needed any steroid medication, either topical or systemic.

CASE 2 *(POE)*

A 59-year old white male was seen with a 10-year history of bilateral nasal polyposis and asthma. He had been anosmic for approximately 15 years. After several snare polypectomies, he was referred to our department for endoscopic sinus surgery. After two operations, the polyps recurred, probably because the patient was reluctant to use topical nasal corticosteroids. He did agree to systemic oral steroids, which resulted in some improvement. Two weeks after completing this treatment, however, the nasal obstruction recurred and two months post-operatively several small polyps were noted bilaterally in both the nasal roof and middle meatus. Histology demonstrated classic polyps with eosinophils as the dominant inflammatory cell. Six months later, multiple myeloma was diagnosed and the patient had four courses of chemotherapy including vincristine, doxorubicine, cyclophosphamide and high dose oral steroids for 4 days repeated every third week, followed by high dose melphalan with stem cell support. During therapy, the patient reported a complete relief of nasal obstruction and experienced total recovery of olfaction (tested with butanol step 6). The patient was treated with maintenance alpha-interferon for 5 years. He was followed in our department for 5.5 years without any recurrence of nasal polyposis on endoscopic examination. The patient died of his multiple myeloma one month after he was last seen in our department.

CASE 3 *(ID)*

A 59-year old white female, without asthma, had a history of nasal polyposis for 10 years and 3 previous operations for nasal polyposis. Her persistent primary symptoms were nasal obstruction and anosmia. Treatment consisted of topical nasal steroids with occasional bursts of systemic oral steroids of 2-5 days duration. Because of massive polyposis (bilateral grade 3) and complete opacification of all sinuses on CT, surgery was planned. The surgery was cancelled because the patient was diagnosed with breast cancer. She then received 7 months treatment with 9 courses of chemotherapy given every four weeks including cyclophosphamide, methotrexate, 5-fluorouracil together with a low dose of betametasone (2 mg daily for 6 months). High-dose corticosteroids were administered for three days before each course of chemotherapy as emesis prophylaxis. Five months after chemotherapy, nasal endoscopic examination revealed one tiny polyp in each middle meatus, and she was completely free of nasal symptoms. Six months after completing chemotherapy, nasal polyps recurred massively (bilateral grade 2) requiring surgical intervention. Six months post endoscopic sinus surgery the polyps recurred (right maxillary sinus) in association with culture positive aspergillus growth. This was treated "mechanically" in addition to topical antifungal lavage with voriconazole (6 weeks). Unfortunately, the patient had recurrent breast cancer and was again treated with chemotherapy consisting of 5-fluorouracil, cyclophosphamide and doxorubicine. During chemotherapy, she was again free of nasal symptoms. Six months after finishing the chemotherapy, symptoms of nasal obstruction recurred and bilateral grade 2 nasal polyps were seen in endoscope. Symptoms were controlled with topical steroids and occasional systemic oral steroids.

DISCUSSION

We have with our 3 cases shown that chemotherapy might be an efficient treatment for severe nasal polyposis. Although two of our patients received corticosteroids together with chemotherapy, the improvement was much better than their earlier experience with corticosteroids alone. The finding of treatment effect from chemotherapy was not unexpected due to the known anti-inflammatory and immunosuppressive effects of these drugs. Also, in a recent report of immunosuppressed transplant patients, the development of nasal polyps was lower than expected [3].

In our report, the chemotherapy varied due to the underlying systemic disease. If chemotherapy is to be used for patients with nasal polyposis, low-dose methotrexate is the most interesting strategy due to its low toxicity. Another consideration is the ability to treat for a prolonged period, which appears to be important. One of our patients (patient 1) was treated with low-dose methotrexate successfully for more than 3 years without toxicity, while another patient (patient 3) had a relapse six months after stopping treatment. Long-term low-dose methotrexate has been an established treatment for rheumatoid arthritis and Crohn's disease since many decades [4,5]. Other inflammatory disorders including Wegeners' granulomatosis, sarcoidosis, psoriasis, asthma and atopic dermatitis have also been reported to respond to such treatment [6-14].

The anti-inflammatory and immunosuppressive chemotherapy mechanisms of action are complex and vary depending on the agent. Concerning methotrexate, it is known that purine and pyrimidine synthesis are inhibited, but there may be other important factors, such as adenosine release [15].

Methotrexate has a crucial effect on the cascades of events induced by some cytokines (IL-1, IL-6, tumor necrosis factor), which we know play a major role in rheumatoid arthritis and other inflammatory disorders [16]. Other effects reported have included increased sensitivity of lymphocytes to the inhibitory effects of glucocorticoids [17]. A theoretically interesting approach is topical administration of chemotherapy. In a study by Ercan et al., methotrexate was sprayed topically to the nasal mucosa of rats in various doses for a month [18]. The drug was well tolerated both locally and systemically.

In conclusion, chemotherapy seems to be an effective treatment option for severe nasal polyposis though it needs to be further investigated in proper studies. Low-dose weekly peroral methotrexate is suggested, due to its low toxicity.

REFERENCES

1. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl 2007: 1-136.
2. Otto BA, Wenzel SE. The role of cytokines in chronic rhinosinusitis with nasal polyps. Curr Opin Otolaryngol Head Neck Surg 2008; 16: 270-274.
3. Botta RS, Ballas ZK, Hussain I. Development of nasal polyposis in immunosuppressed patients. J Allergy Clin Immunol 2008; 109: abstract 985.
4. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev 2005; 57: 163-172.
5. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev 2005: CD003459.
6. Ahmad I, Lee WC, Nagendran V, et al. Localised Wegener's granulomatosis in otolaryngology: a review of six cases. ORL J Otorhinolaryngol Relat Spec 2000; 62: 149-155.
7. Fenton DA, Shaw M, Black MM. Invasive nasal sarcoidosis treated with methotrexate. Clin Exp Dermatol 1985; 10: 279-283.
8. Harries MJ BA, Griffiths CEM, Chalmers RJG. Methotrexate for psoriasis. Cochrane Database of Systematic Reviews 2005.
9. Aaron SD, Dales RE, Pham B. Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials. Respir Med 1998; 92: 1059-1065.
10. Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults. Cochrane Database of Systematic Reviews 1998.
11. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. Chest 1997; 112: 29-33.
12. Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. Lancet 1992; 339: 324-328.
13. Goujon C, Berard F, Dahel K, et al. Methotrexate for the treatment of adult atopic dermatitis. Eur J Dermatol 2006; 16: 155-158.
14. Brion N, Paule B. Non-cancer uses of methotrexate. Presse Med 1996; 25: 1929-1934.
15. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implication for the treatment of rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2007; 65: 168-173.
16. Schmidt J FS, Heimann-Weitschat I, Lindstaedt R, Pomberg B, Werner U, Szelenyi I. Effect of corticosteroids, cyclosporin A, and methotrexate on cytokine release from monocytes and T-cell subsets. Immunopharmacology 1994; 27: 173-179.
17. Vrugt B, Wilson S, Bron A, et al. Low-dose methotrexate treatment in severe glucocorticoid-dependent asthma: effect on mucosal inflammation and in vitro sensitivity to glucocorticoids of mitogen-induced T-cell proliferation. Eur Respir J 2000; 15: 478-485.
18. Ercan I, Cakir BO, Basak T, et al. Effects of topical application of methotrexate on nasal mucosa in rats: a preclinical assessment study. Otolaryngol Head Neck Surg 2006; 134: 751-755.

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