



LETTER TO THE EDITOR

Intolerance of folic acid in a patient receiving methotrexate for Crohn's disease

Dear Sir,

Folic and folinic acid supplementation have been shown to reduce methotrexate oral and gastrointestinal side effects in rheumatoid arthritis patients¹ and this seems to be also the case in patients with inflammatory bowel disease. Still, it is not clear whether folic is different from folinic acid in reducing methotrexate gastrointestinal side effects.²

We present herein a patient with a "difficult-to-treat" long-standing Crohn's disease who was diagnosed with gastrointestinal intolerance due to accidental intake of high-dose folic acid.

A 21-year old female patient with Crohn's disease under combined adalimumab–methotrexate maintenance therapy came to the outpatient clinic because of abdominal discomfort and nausea for the last 2 weeks.

Patient was diagnosed with ileocolonic Crohn's disease 7 years ago and for the last 5 years with severe bilateral uveitis and peripheral arthritis rheumatoid factor negative. Initial therapy included corticosteroids and azathioprine but due to loss of response the patient was switched to infliximab. Despite good initial response to infliximab patient experienced severe allergic reaction with dyspnea and skin rash and was switched to adalimumab. After 4 months on adalimumab the patient lost response and followed an intensification scheme with 80 mg/week. Despite intensified scheme patient relapsed again with disabling bowel and arthritis symptoms. Oral methotrexate 25 mg/week was added with folic acid supplementation. After 2 months of combined adalimumab–methotrexate therapy the patient complained of continuous unspecified gastrointestinal discomfort with bloating and nausea for the last 2 weeks. After excluding other clinically and laboratory obvious causes we initially thought that methotrexate was responsible for this adverse reaction. However, by revising therapy and to our surprise we realized that the patient misunderstood the folic acid dosage and was taking 5 mg of folic acid daily. Discontinuation of folic acid resulted in complete resolution

of gastrointestinal symptoms within 1 week. Patient was advised to take 5 mg/week of folic acid just the day after methotrexate.

The mechanism by which folic acid may have caused this unspecified gastrointestinal intolerance to this patient is unknown. Folate achieves modest reductions of plasma homocysteine³ and the presence of folic acid in the intestinal lumen significantly inhibits the transport of zinc, probably by competitive inhibition.⁴ We may hypothesize that the excess folic acid combined with possible micronutritional element deficiencies related to Crohn's disease might have resulted in zinc deficiency. Because zinc is known to be an essential element of over 70 human enzymes, its deficiency is associated with a wide variety of medical conditions, which are too many to monitor.

References

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