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Methotrexate-induced gingival ulceration in a young patient suffering from juvenile idiopathic arthritis: A review of the literature and clinical report

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This literature review and clinical report presents a case of a 14-year-old boy with gingival ulceration and associated recession. The patient had been diagnosed with juvenile idiopathic arthritis and was medicated with methotrexate and non-steroidal anti-inflammatory drugs. The patient reported that his oral ulceration became significantly worse after beginning medical treatment for the condition. Once the dose of his medication was adjusted, the patient did not suffer from further gingival ulceration and remained orally and periodontally stable. This report summarises the mechanisms of action of methotrexate, its side effects and describes the potential for the occurrence of methotrexate-induced gingival ulceration and recession.

■ Introduction

Juvenile idiopathic arthritis (JIA) is a chronic childhood disorder. It has a UK incidence of 1 in 10,000, a prevalence of 1 in 1000 and is reportedly more frequent in females[1,2].

JIA refers to episodes of arthritis lasting for at least 6 weeks, with an onset before 16 years of age. Usually 6 months after the start of the disease, one of seven subtypes can be diagnosed, depending upon the number of affected joints and non-joint symptoms, as discussed below[3].

This disease is characterised by synovitis, cartilaginous and osseous joint destruction with increased levels of acute-phase proteins in the serum for example, C-reactive protein[4]. Pro-inflammatory cytokine levels including interleukin-1 (IL-1), interleukin-2-receptor (IL-2R), tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) are also increased in both the serum and synovial fluid[5].

There have been several theories propounded for the aetiopathogenesis of JIA, including abnormal immunoregulation, genetic predisposition or latent viral infection, though a definitive answer still remains elusive[6].

JIA is classified according to the International League of Associations for Rheumatology (ILAR) into seven subtypes, based upon the number of joints involved and extra-articular features present (Table 1). This is useful in determining prognosis[3,7].

There are special problems associated with arthritis in the child[7].

Table 1 JIA classification into seven subtypes according to the International League for Associations of Rheumatology.

JIA subtype	Features
1. Systemic-onset (5%)	Arthritis with daily fever for at least 2 weeks with an evanescent (non-fixed) erythematous rash, lymphadenopathy, hepatosplenomegaly or serositis. This form is usually refractory to standard treatment.
2. Oligoarthritis (Fig 1)	Arthritis affecting 1 to 4 joints during the first 6 months. This is the most common subtype and is: i. persistent; affecting less than 4 joints throughout the course of the disease ii. extended; affecting more than 4 joints after the first 6 months, which has implications for treatment.
3. and 4. Polyarticular onset (25%, Fig 2)	Affects five or more joints during the first 6 months, can be: i. rheumatoid factor negative ii. rheumatoid factor positive; similar to adult rheumatoid arthritis.
5. Psoriatic arthritis	Arthritis and psoriasis and at least two of the following: dactylitis (swelling of a digit), nail changes (pitting/onycholysis) or psoriasis in a first-degree relative.
6. Enthesitis-related arthritis	Arthritis and enthesitis (tenderness at the insertion of a tendon to bone) or enthesitis with at least two of the following: i. sacroiliac tenderness or inflammatory back pain ii. HLA B27 positive iii. onset of arthritis in a boy over 6 years of age iv. acute anterior uveitis v. history of spondyloarthritis in a first-degree relative.
7. Undifferentiated arthritis	Unable to fit into any or fit more than one category. Exclusions are described for all categories.

JIA is associated with systemic disturbance in affected patients. These include the following.

- Growth disturbance due to JIA may be localised or generalised. Overgrowth in the knees may lead to leg length discrepancy and temporomandibular joint (TMJ) involvement may lead to retrognathia and/or malocclusions. Active JIA may also result in short stature and delayed puberty due to inflammation, poor nutrition and the effects of medications such as corticosteroids.
- Uveitis. This is inflammation of the anterior part of the eyes, which may be asymptomatic in young children and can lead to blindness. It is common in the oligoarticular subtype with positive serology for anti-nuclear antibodies (ANA) and thus baseline and periodic eye checks are essential.
- Psychosocial impact. Loss of independence due to pain, limited mobility and poor self-image due to deformity or side effects of treatments such as steroids is common. Loss of school days has an impact on education and increased stress for both patients and their families is well recognised and documented.

Not withstanding its implications for systemic health, JIA is also believed to impact oral health in several ways. Research to date has primarily focused in the areas of associations with periodontal disease, dental caries, salivary abnormalities, TMJ pathology and effects on facial growth[6].

Miranda et al[4] demonstrated that despite similar plaque and marginal bleeding levels, adolescents with JIA had greater periodontal attachment loss compared with healthy controls. It is believed that despite their different aetiology, an association between JIA and periodontal disease may exist through a common dysregulation of the immune-inflammatory response in these patients. Such dysregulated inflammation is also believed to underpin the association between periodontitis and other chronic tissue-destructive diseases, such as inflammatory bowel disease and glomerulonephritis[4].

More recently Reichert et al[8] demonstrated that patients with JIA had a significantly higher plaque index, which may have been attributable to more ineffective oral hygiene compared with controls, and a slightly higher mean percentage of sites with pathological attachment loss. However, there was no statistical difference between JIA and controls in the number of subjects who had periodontitis and thus it was concluded that (after adjustment for microbial plaque) JIA is not a risk factor for periodontitis.

Modern treatment protocols for JIA aim primarily to control disease, prevent joint damage, maximise physical function and to obtain a normal lifestyle for patients[1]. Initial treatment includes regular non-steroidal anti-inflammatory drugs (NSAIDS), intra-articular steroid injections and physiotherapy. If the disease is then not well controlled, treatment with a disease-modifying anti-rheumatic drug (DMARD) such as methotrexate (MTX) is required[9,10,11]. If JIA is refractory to MTX, anti-TNF therapy with etanercept (Enbrel®, Amgen, Cambridge, UK) is then considered.

Although MTX has previously been linked to oral ulceration, herpes simplex virus infection and candidosis, adverse effects related to gingival health have not been reported. Therefore, the purpose of this report is to summarise the mechanisms of action of MTX, its side effects and describe a case of possible MTX-induced gingival ulceration and associated recession.

■ Case description and results

An 11-year-old male patient was referred by his general dental practitioner in November 2003 to the Department of Paediatric Dentistry (Birmingham Dental Hospital). The patient complained that he had been suffering soreness and ulceration of his gingivae. On further questioning the patient also revealed that he suffered from recurrent oral ulceration monthly, which was not noted as having an impact on his life. He was a regular dental attendee with poor oral hygiene, swollen gingivae and had an area of gingival necrosis in the regions of teeth 12 and 13. The patient had been prescribed metronidazole, peroxyl (hydrogen peroxide-based) mouth rinse and had a full blood count, arranged by the general dental practitioner, and this was returned as unremarkable. The general dental practitioner had also planned for a hygienist to perform full mouth disclosure, oral hygiene optimisation and scaling, though the latter had not been performed as the gingivae were too painful.

The patient was seen as a new patient in December 2003 at the Periodontology Department (Birmingham Dental Hospital) complaining of soreness on brushing and chronic gum pain that had occurred for approximately the previous 6 months. The patient's medical history revealed that he was fit and well, receiving no medication and was unaware of any allergies. On examination he was in the early adult dentition stage which was unrestored. He presented with calculus associated with teeth 16, 25, 26 and ulceration of the labial mucosa adjacent to tooth 11. In addition he had false pocketing associated with teeth 12, 13, 15, 22, 23 and 33, no caries was present and no radiographic evidence of obvious pathology.

A diagnosis of chronic hyperplastic gingivitis was made, possibly complicated by mouth breathing. The following treatment plan was formulated:

- oral hygiene optimisation
- full mouth scaling (under local anaesthesia if required)
- referral to the Periodontology Department if no improvement occurred.

This treatment was performed by the general dental practitioner as well as a specialist in periodontology. The patient was re-referred to the Birmingham Dental Hospital in September 2006 at 14 years of age still presenting with gingival recession, soreness and ulceration. Chronologically the patient described that the margins of his gingival tissues had turned pallid and had subsequently receded and that he had suffered this episodically over the preceding 3-year period. These episodes were associated with pain, an unusual gingival symptom, though consistent with a history of ulcerative or erosive conditions. In addition, the patient reported that his oral ulceration had become significantly worse since beginning medical treatment.

The medical history revealed that the patient was diagnosed with JIA in April 2005. He had involvement of his knees, ankles, hips and right wrist (7 joints) within the first 6 months, suggestive of a polyarticular form; rheumatoid factor further indicated the rheumatoid factor negative subtype. However, he was diagnosed with undifferentiated arthritis because of a history of psoriasis in his mother, which is an exclusion criterion for polyarticular JIA. The patient was treated with the following: MTX, 20 mg/week (started at 7.5 mg/week and gradually increased to 20 mg/week by November 2005); folic acid, 5 mg/day after MTX; and piroxicam (a NSAID), 10 mg/day.

A social history revealed that the patient had never smoked and consumed no alcohol. However, his stress levels were noted as being fairly high for a 14-year-old and it was further recognised that his diet was relatively poor, most notably deficient in fresh fruits and vegetables.

On extra-oral examination there was bilateral submandibular lymphadenopathy which inferred a possible infective aetiology. Intraoral examination showed evidence of historical necrotising ulcerative gingivitis (NUG) and subtle evidence of active NUG in the regions of teeth 21 to 23.

Haematological investigations were performed, including a full and differential blood count, liver and

Fig 1 JIA, oligoarticular subtype. Right knee swelling.

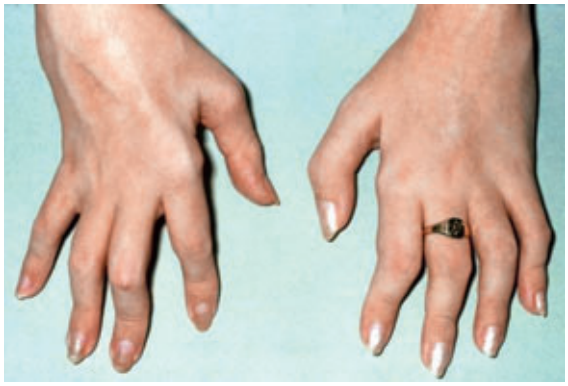


Fig 2 Polyarticular JIA, small joints of hands.

renal function tests, random glucose and serology. The results showed evidence of reduced haemoglobin (Hb) and packed cell volume (PCV), but normal mean corpuscular volume (MCV) indicating a normocytic anaemia that may be related to chronic inflammatory arthritis[12]. A reduced PCV can also result from myelosuppression, which is a side effect of MTX. The serology showed negative rheumatoid factor and a positive (although low titre) antinuclear antibody (ANA). A dental diagnosis of chronic gingivitis was made with evidence of localised NUG. Initial treatment involved the following:

- metronidazole 200 mg 3 times a day for 3 days to treat any active NUG, due to its spectrum of bactericidal activity against the anaerobic organisms associated with NUG
- oral hygiene optimisation over several visits with the hygienist, fine scaling and prophylaxis.

At a subsequent appointment, an area of ulceration (1 cm^2) in the region of 25, 26 free and attached gingivae was documented (Fig 3c). There was no inflammation at the gingival margins, no probing pocket depths above 2 mm and recession was recorded on the mesio-buccal aspect of 26 of approximately 5 mm (Figs 3a to c).

The unusual site and appearance of the lesion in addition to the localised extent and subsequent recession led to the hypothesis that the ulceration may have been MTX-induced.

Thus, in correspondence with the patient's attending physician, the following plan was formulated:

- advice on oral hygiene instruction and on the use of an antiseptic mouthwash (chlorhexidine gluconate)
- regular review in the Periodontology Department
- dosage of all three medications to be adjusted, by the Consultant Rheumatologist, to: MTX, 15 mg/week (July 2007), 10 mg/week (March 2008), 7.5 mg/week (June 2008 as JIA had improved); folic acid, 5 mg/day (March 2006); piroxicam, 10 mg/alternate days (stopped July 2007).

At a review appointment, 5 mm of recession was noted on the mesio-buccal aspect of tooth 26 (Fig 4). The patient had not suffered from further gingival ulceration since his medication dose was adjusted (a period of 22 months) and remained orally and periodontally stable.

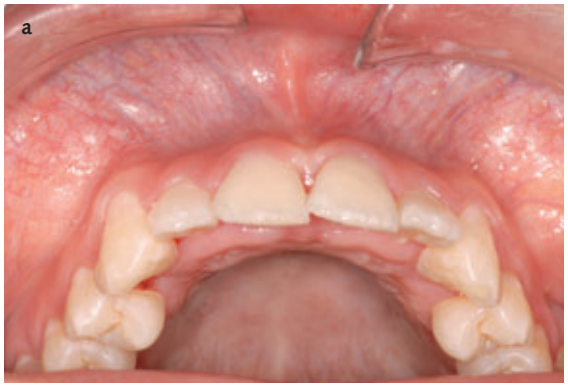
■ Discussion

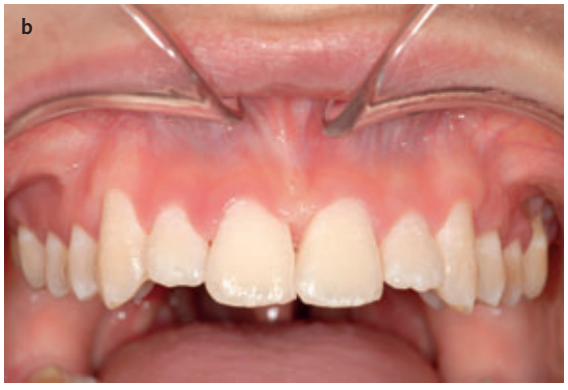
MTX was first used as a chemotherapeutic drug in the treatment of acute lymphocytic leukaemia in 1948. It has been used since in the treatment of various malignancies including osteosarcoma, lymphomas, head and neck cancer, lung cancer and breast cancer[13].

When prescribed for malignancies MTX is given in high doses, though at lower doses MTX is effective in the control of chronic inflammatory conditions such as arthritides and psoriasis, and more recently in Crohn's disease and uveitis[14].

The use of MTX at a weekly dosage is a well-established treatment in paediatric rheumatology[1]. The usual weekly dose of MTX as a DMARD is between 5 to 25 mg divided into three doses over a period of 12 hours[15].

In a study of 2170 patients with rheumatoid arthritis (RA), Grove et al[16] found MTX to be the most well tolerated of the DMARDs with 60 to 70% of patients continuing the drug for 5 to 7.5 years, which is significantly longer than other DMARDs[16,17]. MTX is an anti-metabolite of folate and an immune-modulating drug[14] (an anti-metabolite is a chemical with a similar structure to the substance required for normal biochemical reactions, yet different enough to interfere with the normal functions of cells). MTX





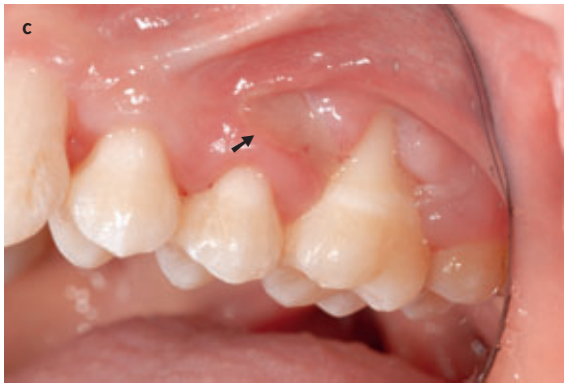


Fig 3a to c Intra-oral views. Figure 3c shows an area of ulceration (black arrow) and recession in the region of 26.

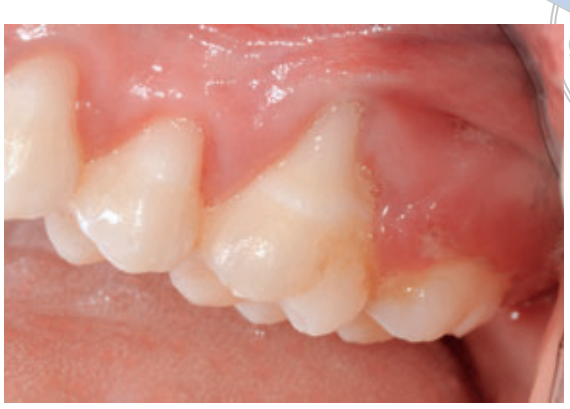


Fig 4 Intra-oral view taken at a review appointment after adjustment of medication.

competitively inhibits dihydrofolate reductase (DHFR), an enzyme responsible for converting folic acid to reduced folate cofactors (i.e. tetrahydrofolate). These reduced folate cofactors are required in many biochemical reactions such as in the synthesis of AMP, GMP, DNA, RNA and cell proliferation[13,18]. MTX enters the cell predominantly via the reduced folate carrier (RFC1). Once inside the cell, MTX undergoes polymerisation of its glutamic acid side chain, to form methotrexate-polyglutamate (MTX-PG)[13,19]. MTX-PG derivatives have the ability to inhibit other folate-dependant enzymes such as thymidylate synthetase (TS), which is required for pyrimidine nucleotide biosynthesis, and 5-aminoimidazole-4-carbamide-ribonucleotide transformylase (AICAR-T), which is required for purine nucleotide biosynthesis (Fig 5) [13,14,19].

Therefore, tissues that have a high rate of cellular metabolism, such as neoplasms, the lining of the alimentary canal, foetal cells and bone marrow are most sensitive to the effects of this drug[13,14]. MTX's effect on reducing DNA synthesis and cell turnover is, thus, responsible for both the therapeutic effects and the common side effects that occur.

MTX also has immunosuppressive properties and can exhibit anti-inflammatory activity. MTX-PG inhibits the action of AICAR-T leading to an accumulation of adenosine, a substrate in the purine metabolism cycle (Fig 5)[1,13,18,19]. Although the mechanism of action of MTX in rheumatoid disease is not fully understood, the literature suggests that this anti-inflammatory effect is related to the resultant extracellular adenosine release and its interaction with specific cell receptors[1,18,19]. P1 receptors specifically exert action on a variety of cell types including neutrophils, macrophages and endothelial cells[19]. Thus, MTX can modulate the secretion of interleukins, IFN-γ, TNF and histamine, which affects both chemotaxis and phagocytosis[13].

The adverse effects of low-dose MTX treatment, as suggested by Kalantzis et al[18] can be divided into three major groups (Table 2).

Gastrointestinal effects are reported in over 70% of patients on low-dose MTX and include nausea, vomiting, abdominal discomfort, anorexia, weight

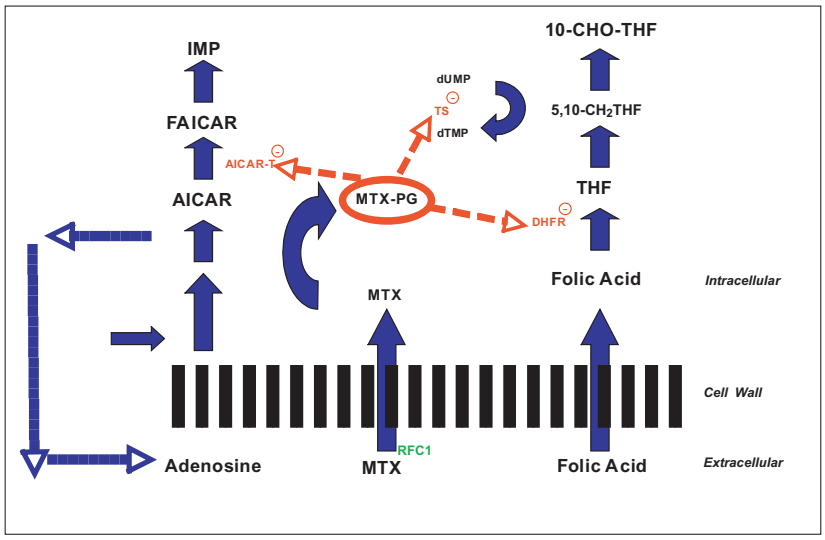


Fig 5 Diagrammatic representation of mechanism of action of MTX. Adapted from Turesson and Matteson[20]. Reproduced from Annals of the Rheumatic Diseases, B N Cronstein et al, 63(2):ii25-ii27, 2004 with permission from BMJ Publishing Group Ltd.

loss and diarrhoea[14,18,21,22]. For clinicians, the most pertinent side effects are oral stomatitis, ulceration and dysgeusia (taste disturbance), with a greater frequency of these occurring with high dose treatment[15,18]. Indeed Kalantzis et al[18] also reported that from a series of 18 relevant studies, oral ulceration developed in 14% of patients and 3% of patients withdrew from treatment primarily because of oral effects. These painful symptoms may affect mastication and can exacerbate any existing folate deficiency and lead to a deterioration in systemic health. As previously mentioned, many patients require the use of NSAIDS (such as piroxicam in this case) in conjunction with MTX, and this may theoretically increase serum levels of MTX and cause toxicity by displacing it from protein binding sites or by reducing renal clearance[15,23,24]. Table 3 shows several approaches to treating MTX-induced stomatitis and oral ulceration[18].

Table 2 The adverse effects of low-dose MTX treatment.

Effects	Features
Dose-dependent	Gastrointestinal and bone marrow toxicity
Idiosyncratic or allergic reactions	Pneumonitis
Effects of long-term treatment	Hepatic and cardiovascular disease

MTX is often given in conjunction with low dose oral folic acid, usually 5 mg daily. This reduces the incidence of myelosuppression, as described by Hunt et al[25], who performed a controlled trial in children with JIA and demonstrated that the addition of folic acid did not interfere with the clinical efficacy of oral MTX[26,27]. The effects of MTX can also be counteracted with folinic acid (leucovorin), a reduced form of folic acid that is not affected by enzymatic inhibition. Administration of folinic acid can deplete the intracellular supply of reduced folate and is useful in MTX overdose or for treating severe side effects in rheumatology and oncology[21,25,26].

■ Summary

It is clear that there may be several explanations for the gingival ulceration experienced by this patient. It is conceivable that the gingival condition may have been attributable to the JIA alone by extrapolating the emerging evidence that there may be an association between rheumatoid arthritis and periodontitis[28]. However, associations are currently limited to attachment loss rather than gingival ulceration. Furthermore, if the JIA had a causal relationship with the ulceration and subsequent recession, one would have expected the gingival health to improve as the arthritic condition stabilised through medication, yet the ulceration became worse following the MTX therapy. Therefore, the two most likely explanations that would account for both ulceration and resulting recession at the gingival margin are:

Table 3 Approaches to treating MTX-induced stomatitis and oral ulceration.

1. Folate supplementation
2. Use of topical treatments including analgesics, antiseptics, steroids and covering agents
3. Cessation of MTX
4. Reduction of MTX dose
5. Interruption of MTX for 2-3 weeks
6. Fortnightly MTX dosing
7. Changing to another DMARD or combination therapy

- MTX-induced ulceration (secondary to bone marrow suppression)
- aphthous ulceration exacerbated by MTX.

The authors suggest that the latter cause is the least plausible, as minor aphthous ulceration does not normally present at the gingival margin. Conversely, although major aphthous ulceration may theoretically cause recession, the gingival margin is an uncharacteristic locus of presentation. Moreover, the fact that reducing the MTX dose resulted in improvements in symptoms and that there were no further recorded episodes of gingival ulceration, points towards ulceration and recession being primarily a side effect of MTX, as the patient was initially administered with 20 mg of MTX daily. He was also taking piroxicam 10 mg daily, which can displace protein-bound MTX and increase serum concentrations and/or reduce renal clearance. If this were indeed the case, then the patient would require careful assessment with regard to his dose of medication, perhaps with haematological monitoring. It may also be argued that the MTX itself was not directly the cause, but rather the ulceration arose as a secondary complication to a consequent folic acid deficiency. This seems unlikely given there was only evidence of a normocytic anaemia (rather than a macrocytic anaemia, which characterises folate deficiency) and a reduced PCV, both of which are recognised side effects of MTX.

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