CASE REPORT

Methotrexate delayed wound healing of a pyogenic granuloma in a child with juvenile idiopathic arthritis

Methotrexato atrasou a cicatrização de um granuloma piogênico em criança com artrite idiopática juvenil

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease affecting children [1]. The disease causes a variety of symptoms, including: arthritis, fever and transient rash [2]. Symptoms are related to the breakdown of the innate immune mechanisms [2,3,4]. JIA treatments’ main goals are pain and inflammation control. Corticoid and/or non-steroidal anti-inflammatory drug administration are the primary treatment [1,5]. Methotrexate is a second line medication; it has many side effects, including oral ulcers [1,6,7].

Pyogenic granuloma is an inflammatory reactive lesion that affects the conjunctive
tissue. In the oral cavity, the site of involvement can be varied and patterned by many factors; it often involves the gingiva. It presents as a slow or fast growing lump and color dependents on the vascularity of the lesion [8,9,10,11,12].

This is a case report of a patient affected by JIA treated with methotrexate, presenting pyogenic granuloma in lower lip. For the best of our knowledge other cases of pyogenic granuloma in patients with JIA in use of methotrexate have not been described in the literature.

**CASE REPORT**

A nine-year-old Asian girl with JIA treated with methotrexate presented ulcerated lesion in the lower lip. The lesion was nodular and circumscribed, exhibiting a red surface, covered by a thin white pseudomembrane, with spontaneous bleeding (Figure 1-a). Local dental trauma was observed due to nibbling habit. Excisional biopsy was performed (Figure 1-b) and histopathology showed benign proliferative lesion, constituted by an ulcerated surface covered by fibrin-hemorrhagic exudate, and a highly vascular proliferation that resembled a granulation tissue, confirming the diagnosis of pyogenic granuloma (Figure 2).

After 15 days, a delay in wound healing was observed (Figure 1-c). Therefore, physician was contacted, and temporally suspension of the drug was made, culminating to complete wound healing of the biopsied site (Figure 1-d, e and f).
DISCUSSION

Local trauma, evident as usual lip chewing, worsened by anterior diastema and bad oral hygiene practices were seen in our case. Association between chronic trauma and poor hygiene care is well established in literature as an etiological factor in pyogenic granuloma [9,13].

The methotrexate is one of the drugs used for the treatment of JIA. This medicine may be given alone or in combination with other therapies. A prospective study of patterns of treatment for patients with JIA was performed by Davies et al. [14]. It was evaluated according to the type of initial presentation of pediatric reumatology considering the five groups: oligoarthritis (oJIA), polyarthritis (pJIA), systemic (sJIA), arthritis enthesitis-related (ERA) and psoriatic arthritis (PsA). Considering the synthetic disease-modifying anti-rheumatic drugs (sDMARD), in the vast majority, methotrexate was prescribed to 35% of patients with oJIA, 94% with pJIA, 93% with sJIA, 74% with PsA and 56% of ERA patients. In the overall assessment, sDMARD were used in 610 of 1051 patients evaluated, equivalent to 58%.

Many adverse effects are attributed to anti-metabolic drugs [6,15]. Del Pozo et al. [16] described skin ulcers as consequence of methotrexate toxicity. Euvrard et al. [17] described a case of pyogenic granuloma in the lateral border of the tongue in a 12-year-old girl submitted to immunotherapy. These authors observed that adverse effects of the drug were related to patient age more than to the immunosuppression therapy period. In the same article, pyogenic granuloma was included as a side effect of immunosuppressive treatment, affecting 6.2% of children in therapy.

The methotrexate is an antimetabolic which may interfere in purine and pyrimidine formation, essential molecules in DNA synthesis and cell proliferation, interfering also in angiogenesis [7], both important events in healing process, and it should be emphasized the cytotoxic effect over oral mucosa cells [6]. Methotrexate induces the release of adenosine that participates in the mediation of several mechanisms such as the induction of apoptosis, anti-inflammatory action and immune response [18].

Oral ulcers are quite common in young patients submitted to methotrexate administration in therapeutic doses in rheumatic diseases [6]. It is an important side effect, because it is responsible for up to 10% of breaking treatment [7]. The cytotoxic effects of the drug are dose dependent and may also be associated with specific characteristics of each patient [19].

Methotrexate is also used as a chemotherapeutic drug. A study by Li et al. [20] evaluated the viscoelasticity of 4 types of cells (myoblasts and cell line fibroblasts from mice, lung cancer cells and embryonic kidney cells, both human) under the effect of methotrexate, and they found that the drug inhibited the proliferation of cells and, moreover, had no effect on cell viscosity, with decrease in relaxation times.

A study was conducted by Dojcinov et al. [21], in which 26 patients with mucocutaneous ulcerative lesions with Epstein Barr virus (EBV) and associated with different types of immunosuppression were evaluated. These patients used drugs to control immunosuppression, including azathioprine, methotrexate and cyclosporin-A. As occurred in our case, the study reports spontaneous remission of mucocutaneous ulcer after discontinuation of methotrexate for rheumatoid arthritis in an EBV-positive patient.

CONCLUSION

Wound healing after methotrexate temporary suspension allowed concluding that the drug delayed surgical wound healing was a consequence of drug cytotoxicity.
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REFERENCES


