



# Rheumatoid nodules: evaluation of the therapeutic response to intralesional fluorouracil and triamcinolone \*

## Nódulos reumatoides: avaliação comparativa da resposta terapêutica com triancinolona e fluoruracil intralesional

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**Abstract:** Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis and are present in around 20-25% of patients. Their etiology is unknown and although the nodules may undergo spontaneous remission during the treatment of rheumatoid arthritis, they usually constitute a therapeutic challenge. The present paper describes a case in which the response of rheumatoid nodules was evaluated by ultrasound following infiltration of triamcinolone acetonide and 5-fluorouracil.

**Keywords:** Arthritis, rheumatoid; Fluorouracil; Rheumatoid nodule; Triamcinolone acetonide

**Resumo:** Os nódulos reumatoides correspondem à manifestação extra-articular mais comum da artrite reumatoide, ocorrendo em cerca de 20-25% dos pacientes. A etiologia é desconhecida. Apesar de os nódulos poderem apresentar remissão espontânea durante o tratamento, eles, em geral, representam um desafio terapêutico. Apresenta-se um caso no qual se avaliou a resposta dos nódulos reumatoides por meio de ultrassonografia após infiltração de triancinolona e 5-fluoruracil.

**Palavras-chave:** Artrite reumatoide; Fluoruracil; Nódulo reumatoide; Triancinolona acetona

Rheumatoid nodules represent the most common extra-articular manifestation of rheumatoid arthritis, occurring in around 20-25% of patients.<sup>1-4</sup> Clinically, they present as subcutaneous nodules measuring 2 mm to 5 cm in size. They may be single or multiple and are usually located on the extensor surfaces of the forearms, metacarpophalangeal and proximal interphalangeal joints.<sup>3,4</sup> The lesions are generally asymptomatic but may complicate with infections and ulceration.<sup>1-4</sup>

The nodules may undergo spontaneous remission during treatment for rheumatoid arthritis with drugs such as colchicine, hydroxychloroquine and D-penicillamine.<sup>1-5</sup> There are few treatment options,

which include surgical excision and infiltration with corticoids; however, satisfactory results have recently been reported with fluorouracil.<sup>1,2</sup> Tumor necrosis factor inhibitors were not found to be effective.<sup>6,7</sup> There have been reports of an acceleration in cutaneous nodulosis with the use of infliximab, of the appearance of nodules during treatment with etanercept and worsening of nodules with methotrexate.<sup>5,8</sup>

The present study describes the case of a 58-year old male with rheumatoid arthritis. In January 2008, he developed painful, hardened nodules, initially on the palm of his right hand and later on the interphalangeal joints of both of his hands, on his elbows and buttocks. He was in use of prednisone (5

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mg/day), meloxicam, chloroquine and acetylsalicylic acid. The doses of the medication were not altered during treatment of the nodules.

The patient had rheumatoid factor 1:40 IU/ml, antinuclear factor 1:80 with a speckled pattern, negative serology for HIV and syphilis. Chest x-ray revealed bone degenerative changes of the thoracic spine and no alterations in the pulmonary parenchyma. Biopsy of one of the nodules performed in March 2008 was suggestive of a rheumatoid nodule.

Three rheumatoid nodules were selected for treatment with the objective of evaluating the best therapeutic response: a nodule on the proximal interphalangeal joint of the fifth finger on the right hand (nodule #1), a nodule on the interphalangeal joint of the forefinger of the right hand (nodule #2) and a

nodule on the proximal interphalangeal joint of the fourth finger of the left hand (nodule #3). The volume of the nodules was evaluated by ultrasonography (Figure 1).

Nodule #1 was treated with two infiltrations of 2 ml of triamcinolone 20 mg/ml. Nodule #2 was treated with two infiltrations of 2 ml of fluorouracil 25 mg/ml. Nodule #3 was treated with two infiltrations of 2 ml of lidocaine 2%. In all three cases, the two infiltrations were administered within the space of one month. Ultrasonography was performed on the lesions selected for treatment prior to the first infiltration (week 0), one month after the first infiltration (week 4) and two months after the second infiltration (week 12) to determine therapeutic response by measuring the volume of the lesions. All the exams were conducted by the same ultrasonographer.

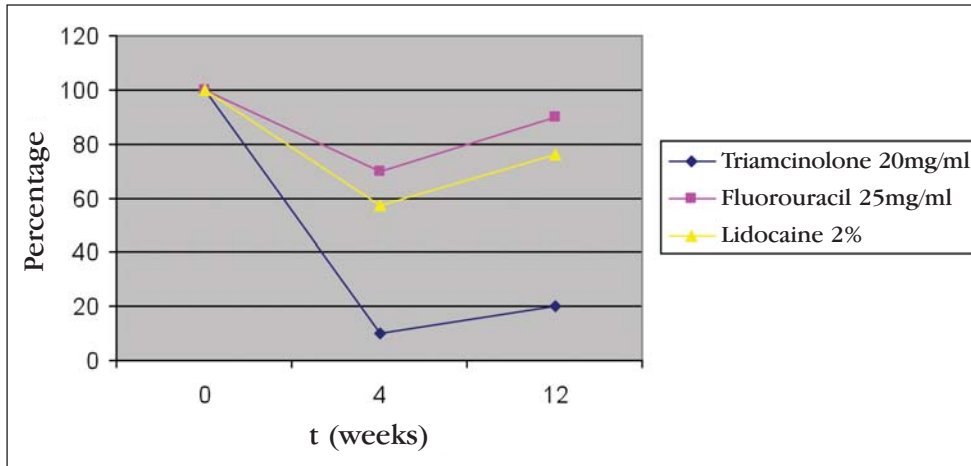
The nodule that received the two infiltrations of triamcinolone 20 mg/ml was the one in which the reduction in volume was greatest (80%). The nodule treated with fluorouracil 25 mg/ml underwent an initial reduction in volume of 30%; however, at the end of the two infiltrations, this reduction was less evident, only 10% of the initial volume, which could indeed be attributed to the intrinsic variability of the imaging method. The nodule treated with lidocaine 2% had a final reduction in volume of 24% over the period of observation, which may be related to the fact that, according to the patient, secretion had drained from this nodule between the first and second infiltration, resulting in a consequent reduction in its volume (Graph 1). With respect to tolerability, the patient reported mild discomfort during infiltration with fluorouracil and lidocaine that was not reported with triamcinolone.

Various studies have already demonstrated that corticoids injected into nodules lead to a greater reduction in their volume compared to placebo.<sup>9,10</sup> Baan, Haagsgma and van de Laar (2005) reported a reduction of 94% in the median volume of nodules in a group treated with triamcinolone compared to a placebo group in which the reduction was 34%. This is close to the reduction found in the nodule treated with lidocaine 2% (24%).<sup>2</sup> These authors believe that the placebo may have exerted an actual effect in reducing the nodules.

Fluorouracil is an antimetabolic drug that blocks the cell cycle by inhibiting thymidylate synthetase, thymidine, DNA and RNA. It inhibits the proliferation of fibroblasts and the formation of collagen in vivo and in vitro.<sup>1</sup> Fluorouracil has already been shown to be effective and safe for the treatment of keloids and hypertrophic scars. The antiproliferative effects of this drug encouraged investigators to experiment its use in rheumatoid nodules. Amini, Baum



FIGURE 1: Rheumatoid nodules evaluated by ultrasonography: periarticular hypochoic nodules



**GRAPH 1:** Reduction in nodule volume presented as a percentage of the initial volume

and Weiss (2009) reported complete disappearance of the nodules, unlike the results found in the present study. This discrepancy may be related to the corticoid used by these investigators in association with fluorouracil which, even in low concentrations, may have contributed to reducing the size of the lesions.<sup>1</sup> These authors justified the use of the corticoid as being necessary to avoid a possible inflammatory reaction resulting from the use of fluorouracil. However, in the present case, fluorouracil was used alone and no local inflammatory reaction was found.

Rheumatoid nodules may be measured by ultrasonography and this measurement may be used to fol-

low-up these lesions.<sup>9</sup> Evaluation of the nodules using this imaging technique permits a more accurate calculation of the volume and the percentage of reduction of the nodules compared to clinical evaluation; however, the limitations of this imaging method cannot be ignored. Furthermore, the different sites of the lesions and their different sizes may have negatively affected the efficacy and comparison of the results.

In the case in question, the treatment that yielded the best results was the injection of the corticosteroid. Further studies are necessary to enable the real efficacy of fluorouracil to be evaluated for the treatment of rheumatoid nodules. □

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