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Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab

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ABSTRACT

Rituximab is a chimeric monoclonal therapeutic antibody which causes depletion of CD20-positive B cells. Apart from its apparent efficacy in the treatment of non-Hodgkin lymphoma and of several rheumatic diseases, it is associated with adverse events including the induction of autoimmune phenomena. We describe here the development of psoriatic skin lesions in a patient with rheumatoid arthritis after the second course of treatment with rituximab. This report supports the hypothesis that autoimmune phenomena may occur by biologic agents and there is a link between B-cell depletion and the induction of psoriatic skin lesions, which were confirmed histologically. However, further studies are needed in order to identify the underlying mechanism, as well as the risk factors associated with rituximab-induced psoriatic skin lesions.

Introduction

Rituximab is a chimeric monoclonal antibody of human and mouse origin that binds to CD20 antigen presented on the cell surface of mature B cells and causes apoptosis of these cells. It targets and selectively depletes CD20-positive B cells without targeting stem cells or existing plasma cells (1). Rituximab was initially approved for the treatment of B-cell non-Hodgkin's lymphoma (NHL) (2), but has recently also been approved for treating patients with rheumatoid arthritis (RA) (3, 4). In RA it is used after an inadequate response to anti tumour necrosis factor (TNF) alpha therapy, showing a significant clinical efficacy and radiological improvement (5, 6).

The drug has been investigated in a variety of other autoimmune disorders in which B cells have been suggested to play a role. In addition to its approved indications, rituximab has been used successfully in systemic lupus erythematosus (SLE) (7), ANCA associated vasculitis (8), small vessel vasculitis (9), dermatomyositis (10), bullous dermatoses, including pemphigus vulgaris (11) and paraneoplastic pemphigus (12). However, there have been no large randomised controlled trials concerning these off-label uses of rituximab and the results of efficacy are based on the description of several case reports or pilot trials with small samples (13).

Despite a good overall efficacy profile and an acceptable toxicity profile rituximab can induce a number of adverse events (3-5, 14), including autoimmune phenomena. Such autoimmune phenomena are the development of human antichimeric antibodies and the induction of immune-mediated skin lesions such as psoriasiform lesions (15) or even psoriatic arthritis (PsA) (16). In this report we present a patient with RA who was treated with rituximab and developed psoriatic skin lesions during the second course of therapy.

Case presentation

A 55-year-old woman, with a 15-year history of symmetric polyarthritis involving primarily the small joints of the hands bilaterally visited our rheumatology clinic. She was currently not taking any disease modifying antirheumatic drugs, just paracetamol and occasionally non-steroidal anti-inflammatory drugs (NSAIDs). She had been also refractory to methotrexate (MTX), infliximab and anakinra. She did not report Raynaud's phenomenon, psoriatic skin rashes, mouth ulcers or uveitis. Laboratory tests showed hemoglobin 8.5 gr/dl, with features of anemia of chronic disease (low serum iron and normal ferritin levels). The C-reactive protein was 55 mg/l (normal values <6 mg/l) and the erythrocyte sedimentation rate was 72 mm/h. Serum IgM rheumatoid factor (RF) was positive at a titer of 1/1280 (latex fixation test), and anticyclic citrullinated peptide antibodies (CCP) were also positive at high titer 1,102 U/ml (normal value <100 U/ml). Hand and wrist radiographs showed osteopenia and severe erosive changes in the wrists, metacarpophalangeal and proximal interphalangeal joints bilaterally. The disease activity score for 28 joint indices (DAS-28) was 6.52. The patient was treated with rituximab (1,000 mg iv), and methylpredinsone (100 mg iv). The same treatment regimen was repeated after 14 days. In addition, MTX (10 mg/week), folic acid (1 mg/day) and small doses of prednisone (7.5 mg/

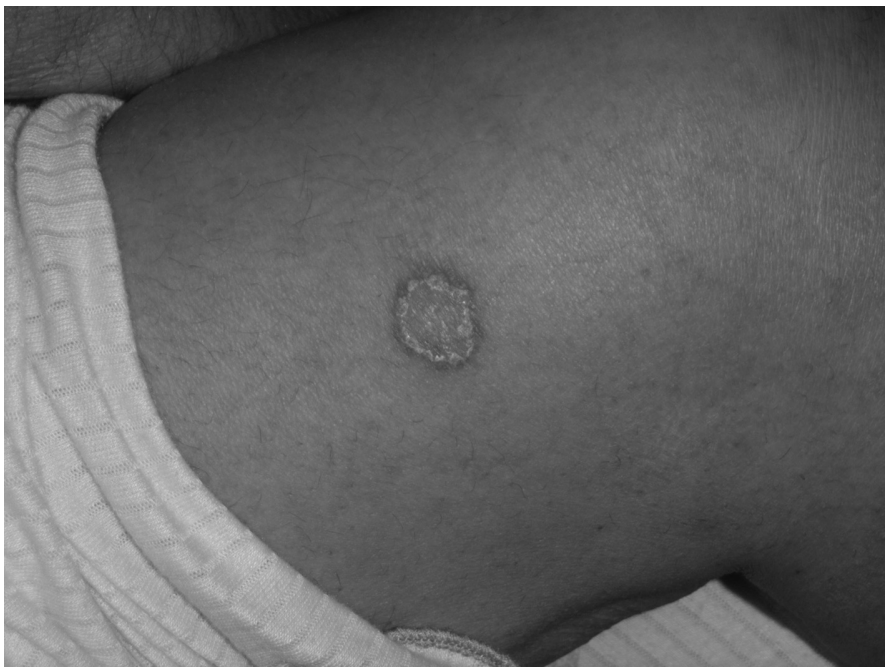

Fig. 1. Psoriatic skin lesion affecting the right thigh.

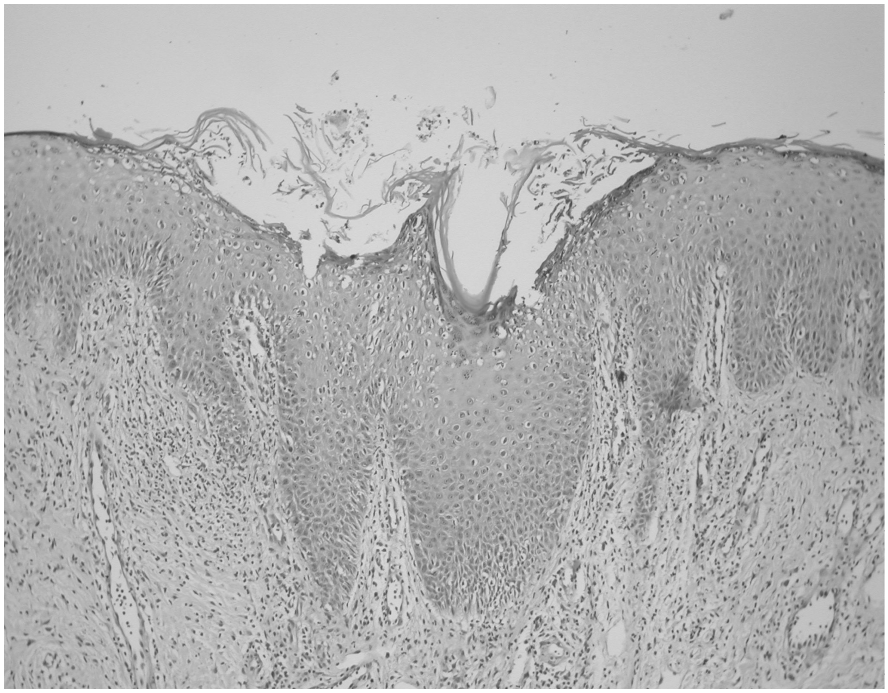

Fig. 2. The skin biopsy revealed epidermal hyperplasia with focal subcorneal pustule formation. There was a perivascular lymphocytic infiltration with scattered neutrophils and eosinophils in the upper dermis. Subcorneal pustules and mild epidermal hyperplasia (H-E x 100 and x 400).

day) were added. The rituximab therapy resulted in a substantial clinical and laboratory response. A reduction in the DAS-28 score was noticed. The IgM RF also decreased (1/160), as well as the anti-CCP antibodies (283 U/ml). However, 6 months later, a second course of rituximab was prescribed because of morning stiffness and joint pain. Ten days after the first infusion of the second course of rituximab, the patient developed psoriatic skin lesions over her arms and thighs (Fig. 1). The patient was evaluated by a dermatologist and a skin biopsy confirmed the diagnosis of psoriasis. The histopathological report showed epidermal hyperplasia with focal subcorneal pustule formation. There was a perivascular lymphocytic infiltration with scattered neutrophils and eosinophils in the upper dermis (Fig. 2).

Discussion

Psoriasis is a common, chronic inflammatory disease known to be mediated by T cells (17). This autoantibody-negative autoimmune disease may or may not be associated with PsA. Rituximab is not, yet at the moment, approved for the treatment of autoantibody-negative diseases.

Dass *et al*. (15) reported three cases with either seropositive or seronegative RA or SLE who developed psoriasis after rituximab administration, while Mielke *et al*. (16) reported the onset of psoriasis with psoriatic arthropathy during rituximab treatment of NHL in a woman. However, in the case reported by Mielke *et al*. (16), it was suspected that the NHL and its therapy (chemotherapy-CHOP) could have contributed to the development of the psoriasis and the psoriatic arthritis. More confusion is provided by another case report of a middle-aged woman with psoriasis who experienced a partial sustained remission of her psoriasis after the treatment with rituximab for NHL (18).

These data about autoimmune phenomena induced by rituximab administration for the treatment of rheumatic diseases, have also been described with the anti-TNF-alpha therapies (19-21). It seems that the induction of autoimmune phenomena is a common feature of biologic agents. Furthermore, in the present case we are dealing with another paradoxical phenomenon; that of the induction of a known T-mediated disease (psoriasis) after the depletion of the B-cell population. Three possible explanations of this interesting adverse event can be given for rheumatic disease patients treated with rituximab. First, it may be induced by the dysregulation of the B-cell/T-cell interaction and the disruption of the expansion of autoreactive T-cell populations following the B-cell depletion therapy (22). Secondly, the susceptibility to infections (bacterial or viral) has been described as a trigger for psoriatic plaque

development (23). There is an increase of infection rates of rituximab treated patients (3-5). A third explanation could be that the psoriatic lesions may result from a T-cell dependent immune reaction against murine components of the therapeutic monoclonal and not by inducing anti-chimeric antibodies (16).

In all cases reported until now (15, 16), including ours, apart from one patient who presented widespread psoriasis over the trunk and the extremities, the psoriatic skin lesions were less diffuse. None of them had clinical evidence of psoriasis before or at the time of the initiation of rituximab therapy and none was reported to have had or developed disease or other conditions associated with psoriasis (23). The diagnosis of RA in our patient was certain, since the patient had definite seropositive RA (for both IgM RF and anti-CCP antibodies), fulfilling the criteria of the American College of Rheumatology (24). The induction of psoriasis by rituximab therapy cannot also be doubted, since the psoriatic skin lesions were confirmed by skin biopsy.

B-cell depletion therapy, an effective treatment for some subtypes of NHL, is a novel drug in the rheumatologic field and its current indications include only RA. It has also been used in other autoimmune disorders, but limited data are available from randomised controlled trials. Because the use of rituximab is becoming more widespread, a greater understanding of possible drug related adverse events is being recognised. The present case, together with the previous reported, supports the hypothesis of a link between B-cell depletion and the induction of psoriatic skin lesions. Apart from the known adverse events of this useful drug of our therapeutic armamentarium, physicians should be aware of the potential development of new autoimmune phenomena when dealing with patients treated with rituximab. More research is needed for a better understanding of the elusive underlying pathophysiological mechanism.

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