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SHORT COMMUNICATION

Lupus attributable to anti-TNF therapy and revealed by interstitial granulomatous dermatitis

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Abstract Interstitial granulomatous dermatitis belongs to the group of aseptic cutaneous granulomas. It is a histopathological entity encountered in various pathological situations, such as polyarthritis including rheumatoid arthritis, but also systemic lupus erythematosus. It may also occur after systemic administration of medication, thus representing a drug-induced, interstitial granulomatous outbreak. This has recently been described after anti-TNF therapy was taken. We are reporting the case of a patient treated using adalimumab for rheumatoid arthritis and having developed interstitial granulomatous dermatitis during treatment, which revealed lupus erythematosus attributable to the biotherapy. The clinical appearance of interstitial granulomatous dermatitis can vary, and the diagnosis is confirmed by anatomo-pathological examination. Drug-induced interstitial granulomatous outbreaks have specific histological criteria, and secondary cases involving anti-TNF medication have been described. Cases of lupus attributable to anti-TNF therapy have also been described, and they have specific biological characteristics. Like idiopathic lupus, they may be associated with interstitial granulomatous dermatitis, but the association of an anti-TNF-induced lupus and this type of granulomatous has not, to our knowledge, been described before. We are reporting one case, which emphasises the importance of carrying out a complete and systematic aetiological assessment for all cases of interstitial granulomatous dermatitis, including where there is systemic disease or following medical treatment, either of which may provide an evident cause for the granulomatosis. In particular, the outbreak of interstitial granulomatous dermatitis during anti-TNF treatment should lead to screening for a drug-induced lupus, which would require the patient to stop such treatment.

Keywords Interstitial granulomatous dermatitis · Palisaded neutrophilic and granulomatous dermatitis · Induced lupus · Anti-TNF therapy · Rheumatoid arthritis · Systemic lupus erythematosus

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Introduction

Interstitial granulomatous dermatitis (IGD) is a rare non-infectious granulomatosis, of unknown mechanism, described for the first time in 1965 [1], occurring in various pathological situations: arthritis (mainly sero-positive or sero-negative rheumatoid arthritis), connective tissue diseases, particularly systemic lupus erythematosus, systemic vasculitis (mainly granulomatous) or lymphoproliferative syndrome [2–4]. It may also be a side effect of systemic treatment [5, 6].

We will describe a remarkable clinical case where IGD revealed lupus attributable to anti-TNF treatment, in the context of rheumatoid arthritis.

Clinical case

Mrs A., aged 61, had, as her main antecedent, sero-negative destructive rheumatoid arthritis successively treated, since 1999, with methotrexate and hydroxychloroquine, sulfazalazine, leflunomide then etanercept in 2006. Etanercept ceased to be effective in August 2008, resulting in a change for adalimumab, promptly effective.

In April 2009, myalgia appeared in the shoulders and hips, along with asthenia. Clinical examination found synovitis in some finger extensors, painful joints and rheumatoid nodules, amounting to rheumatoid arthritis. Purplish infiltrated erythematous plaques in the ischiatic area, the peri-anal area and the flanks were, however, unusual (Fig. 1). These lesions persisted for a month, which resulted in the adalimumab treatment being withdrawn.

Histological examination of a cutaneous lesion revealed that the surface epidermis had slightly thickened and was covered with a compact orthokeratosis. In the dermis, histiocytary inflammatory infiltrates formed reticular bands and were often palisaded around collagen bundles. These infiltrates were found with small lymphocytes, without plasma cells or eosinophil granules. The immunohistochemical examination revealed a discreet T-lymphocytary (CD3+) infiltrate, a few B lymphocytes (CD20+), with a preponderance of macrophagic histiocytary infiltrate (CD163+). The morphological appearance strongly recalled interstitial granulomatous dermatitis (Figs 2, 3).

Biologically, there was an increase in the number of anti-nuclear antibodies (ANF) to 1/320 on rat liver cells and on Hep-2 cells (1/160 and 1/80, respectively, in 2006), and an increase in anti-native DNA antibodies to 139 UI/ml. The sedimentation rate was 32 mm and the CRP 22 mg/l. The complement dosage (CH50, C3 and C4), creatine kinase, myoglobin and aldolase were normal, and the results for anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Scl 70, anti-JO1 antibodies, rheumatoid factor and anti-CCP antibodies were negative. The anti-cardiolipin and anti-phospholipid antibodies were at the upper end of the normal range. Except ANF, all this parameters were normal or negative in 2006. The diagnosis reached on the basis of these clinical and biological criteria, and on the chronology, was an anti-TNF-induced lupus, revealed by IGD, permanently contraindicating any anti-TNF therapy. Treatment was thus continued solely on the basis of general corticotherapy and leflunomide, which resulted in a reduction in the skin lesions, and myalgia and asthenia, in less than 3 months. Five months after withdrawal of adalimumab, the ANF were only positive on the rat liver cells (1/80), the anti-native DNA antibodies had fallen to 67 UI/ml and the sedimentation rate was 12 mm.

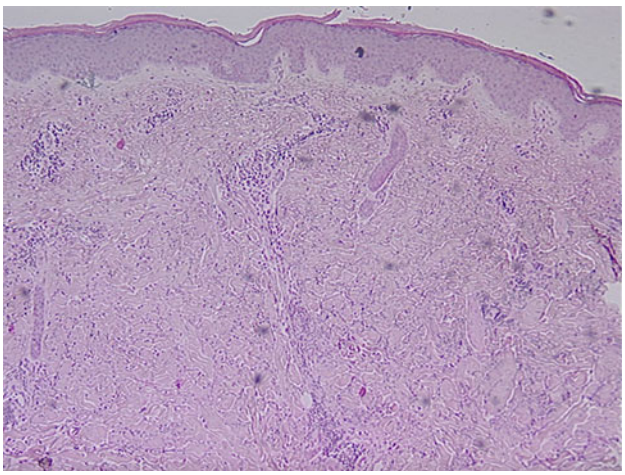

Fig. 2 Cutaneous biopsy (×25). Infiltration of the dermis by low-density histiocytary inflammatory elements forming reticular bands with palisading

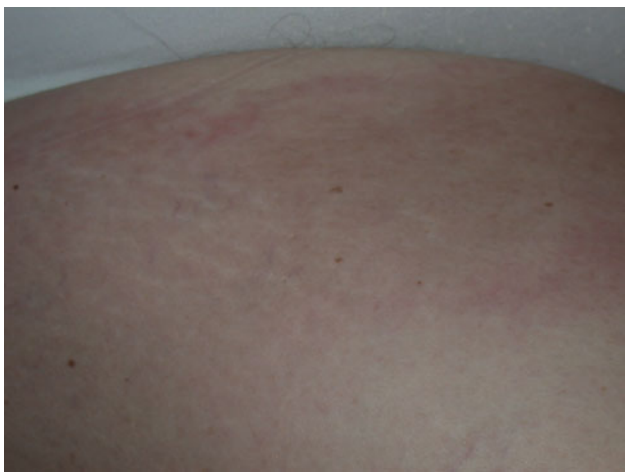

Fig. 1 *Purplish* infiltrated erythematous plaques in the area of the *left* ischium

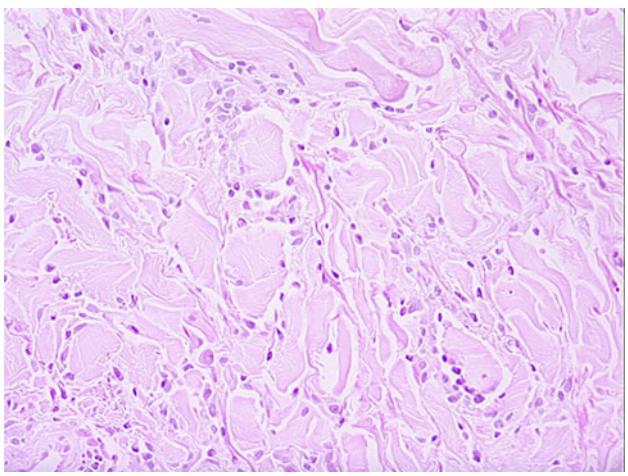

Fig. 3 Cutaneous biopsy (×100). Presence of small lymphocytes and histiocytes forming rosettes around collagen bundles

Discussion

Interstitial granulomatous dermatitis is a recently described anatomo-clinical entity. Clinically, it takes the form of annular, erythemato-cyanic papules or plaques, clearly indurated and infiltrated, with a tendency to necrosis or umbilication, often asymptomatic. It affects symmetrically the members, and above all their extremities, the buttocks, skin folds, the face and the neck [3, 4, 7]. Histologically, there are small foci of collagen fibre necrosis, surrounded by polynuclear neutrophils during the early stages or by histiocytes forming rosettes or regular palisading around the necrotic zone at a later stage [2, 4, 7]. Its clinical and histological presentation can vary, explaining the various names used in literature: Churg–Strauss granulomatosis, cutaneous extravascular necrotizing granuloma, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis and interstitial granulomatous dermatitis with arthritis or Ackerman's syndrome. The general term of palisaded neutrophilic and granulomatous dermatitis (PNGD) was put forward by Chu et al. [4] to describe this entity characterised by histological criteria that are constant but that change over time and that may, for each patient, correspond to clinical and aetiological specificities.

It is particularly associated with pathologies involving the circulation of immune complexes [2–4], but it may also be a side effect of medication, thus referred to as IGRS (interstitial granulomatous drug reaction), described in 1998 by Magro et al. [5]. The drugs that are most often incriminated are calcium blockers, converting enzyme inhibitors, beta-blockers, anti-lipemics, anti-histamines, anti-depressants or anti-convulsive medication. IGRS is clinically similar to IGD of other aetiological origin, but, histologically, the interstitial infiltrate seems denser in lymphocytes, which is sometimes of pseudolymphomatous appearance, while the polynuclear neutrophils are most often absent. Mucin deposits, atypical lymphocytes or eosinophils may be observed. In contrast, the appearance of necrobiosis or vascularity is rare [5–7]. Usually, the lesions disappear when the incriminated drug is withdrawn, persist if the treatment is maintained and may reappear if it is received again later on [3, 5, 7].

Recently, cases of IGRS during anti-TNF therapy have been described. Bremner et al. [3] described three cases of IGD occurring in patients suffering from rheumatoid arthritis treated using infliximab. In the first two cases, the treatment was continued, and the lesions only receded partially, under dapsone in one case and under general corticotherapy then dapsone and hydroxychloroquine in the other. In the third case, the lesions were aggravated after replacing etanercept with infiximab. Deng et al. [9] described five cases of IGD occurring during treatment with lenalidomide, infliximab, etanercept or adalimumab. The IGD lesions appeared between 1 month and 1 year after the start of treatment, and disappeared or improved, for four patients within 2 months on discontinuation of the biotherapy. In the final case, the treatment was not withdrawn but the lesions remained. The IGRS diagnosis is based on these eight cases, on chronological criteria and on the histological aspect of the lesions. However, the hyperlymphocytosis with rarefaction or total absence of the neutrophils described in the cases of IGRS was only found in five cases, including one case with mucin deposits. Nevertheless, in all cases, there is no mention of ANF dosage or anti-native DNA antibodies, so a drug-induced lupus cannot be excluded, given that the non-typical histological aspect of IGRS in half of the cases. Moreover, one case of IGD, which receded despite continuation of the incriminated anti-TNF therapy, has also been described [8]. In addition, one case of IGD receded under anti-TNF treatment administered for rheumatoid arthritis [9]. The very existence of IGD attributable to anti-TNF treatment can thus be called into question on the basis of these observations. It is therefore logical to ask whether or not, from among the described cases of IGD occurring during anti-TNF therapy for an auto-immune disease, certain cases are related to an underlying induced lupus, which was not looked into, given that the IGD was directly linked to the underlying disease or the biotherapy.

Drug-induced erythematosus lupus is well known. It is biologically characterised by the presence of anti-nuclear and anti-histone antibodies, whereas the anti-native DNA antibodies and the soluble anti-antigen antibodies, particularly anti-RNPs, are rare [10, 11]. Cases of anti-TNF-induced lupus have been described [12–15] with adalimumab, infliximab and etanercept. They are specific because soluble nuclear anti-antigens, and above all the anti-native DNA antibodies, are frequently positive, whereas the anti-histone antibodies are not as high as in cases of lupus induced by other drugs [10, 12, 14]. Anti-phospholipid antibodies are also frequent and add to the thrombotic risk encountered with anti-TNF therapy [11, 12]. After the start of treatment, the clinical lesions and biological anomalies occur, on average, between 3 and 16 months [11, 12], recede, respectively, within a few weeks and a few months when it is withdrawn [10, 11] and can reoccur if the molecule is reintroduced [15]. The anti-TNF drugs can only reveal an underlying lupus that actually existed before biotherapy. However, this notion remains controversial, as the lupus would normally have been sought out before the start of treatment, with the semiological imputability score for biotherapy being high [11].

In our case, there were clinico-biological characteristics specific to anti-TNF-induced lupus: typical cutaneous lesions (in areas other than the points of injection), with a

more marked increase in anti-native DNA antibodies than of anti-nuclear antibodies, and a moderate increase in anti-phospholipid antibodies, occurring within an identical timeframe as described in the literature. Furthermore, clinical and then biological anomalies receding when the treatment was withdrawn, with dynamics comparable to those described in the literature. Moreover, in our case, the sole diagnosis of biotherapy-induced IGD cannot be retained on the basis of the histology and the immunological anomalies. The hypothesis of IGD relating to rheumatoid arthritis alone was not retained, due to the high imputability of the anti-TNF treatment, for which the intrinsic imputability score, in particular the chronology, is significant and, above all, due to the absence of IGD when the inflammatory scores of the disease were high before the anti-TNF treatment.

Conclusion

Diagnosis of IGD usually include the realisation of a complete aetiological assessment, which is necessary even if there are already pre-existing pathologies and/or the taking of potentially imputable drugs, as this assessment may reveal another related, potentially serious pathology.

In particular, when it occurs during anti-TNF therapy, it seems to be wiser to investigate into an underlying induced lupus which, if confirmed, represents a formal contraindication to pursuance of the treatment.

Conflicts of interest None.

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