Rheumatoid Arthritis and Erythema Multiforme: A Possible Pathogenetic Link for T-Cell-Mediated Autoimmune and Reactive Skin Diseases?

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Received: July 28, 2012
Accepted: July 15, 2013

SUMMARY We present a case of a woman with a 14-year history of rheumatoid arthritis, who showed simultaneously and gradually appearing, annular, erythematous, itchy patches and exacerbation of the joint symptoms, of one month duration, after pregnancy. Clinical and histologic features led us to the diagnosis of erythema multiforme. While it is not possible to exclude that the co-occurrence of the two conditions is coincidental, our case suggests the possibility that erythema multiforme is a sign of an ample alteration of the immune system that may occur in patients with systemic immune diseases as a consequence of the action of various triggering factors, such as molecular mimicry between endogenous and exogenous antigens or pregnancy, which is notoriously a period of complex and still largely unexplored alterations in the immune system reactivity.

KEY WORDS: rheumatoid arthritis, erythema multiforme, molecular mimicry, pregnancy

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint inflammation. The pathogenesis is still unknown but it seems to be autoimmune in nature (1). Trigger factors such as infectious agents (2) could act over a genetic predisposition, determined by HLA genes, producing a large dysregulation of the immune system (1). The presence of rheumatoid factors, circulating immune complexes and the defective suppressor T-cell function (3) demonstrate that both humoral and cell-mediated systems are involved.

Rheumatoid arthritis is not exclusively a joint disease but it can involve, during its evolution, all the organs; cutaneous disease is often present in patients with RA (4,5).

We present a case of RA associated with erythema multiforme (EM), also trying to investigate the possible pathogenetic link between the two disorders.

CASE REPORT

A 30-year-old woman, with a 14-year history of RA, presented to our dermatology department for simultaneously and gradually appearing, annular, erythematous, itchy patches and exacerbation of the joint symptoms, of one-month duration.

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2013;21(3):185-188

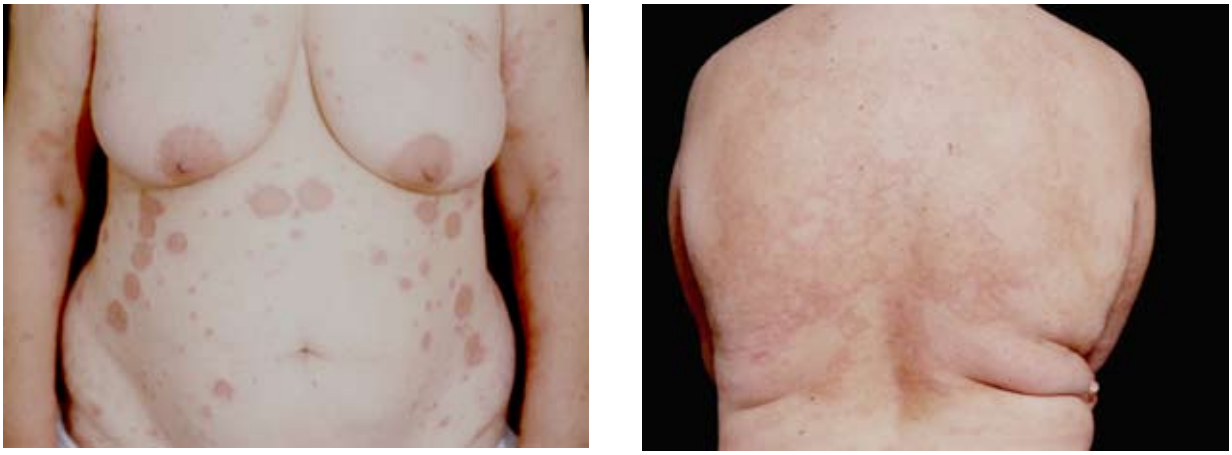

Figure 1 a-b. Annular, erythematous, itchy patches of coalescing target-like lesions with vesicular borders.

She reported that since the age of 16 years, after episodes of joint pain, RA was diagnosed on the basis of ARA criteria and successfully controlled for a long period with corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs) and intermittent hydroxychloroquine administration. One year before her presentation, having not experienced symptoms for a long time and being pregnant, she had stopped the treatment upon her physician's advice, but one month after delivery her cutaneous and joint symptoms reappeared.

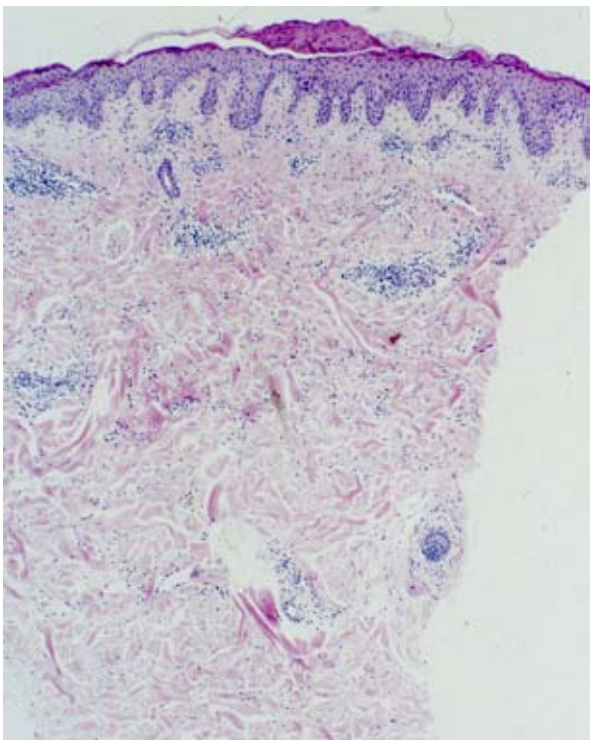

Figure 2. Histopathologic examination showing no modification of the epidermis and lymphocytic perivascular inflammatory infiltrate in the dermis. (HE; X20)

Clinical examination revealed numerous, coalescing target-like lesions with vesicular borders, acrally distributed (Fig. 1a-b). There were no mucosal lesions and no chilblain-like lesions on the extremities. The patient's general condition was good.

Laboratory tests were all normal except for erythrocyte sedimentation rate (24 mm/h; normal <14) and leukocyte count (18800/mm^3; normal 4500-9000). Rheumatoid factor was positive and ANA were negative (titer 1:20).

Histopathologic examination of a biopsy taken from lesional skin showed no modification of the epidermal layers. A lymphocytic perivascular inflammatory infiltrate was visible in the dermis (Fig. 2). Direct immunofluorescence was negative.

X-ray of the hands showed erosive arthritis of the proximal interphalangeal joints of the third and fourth fingers and of the distal metacarpophalangeal joint of the second finger in the left hand and similar abnormalities involving the metacarpophalangeal joints of the second and fourth fingers of the right hand. Note typical gull-wing configuration of the involved joints (Fig. 3). Posteroanterior radiography of the wrists demonstrated carpal bone osteopenia and marked narrowing of the articular spaces involving both radiocarpal and intercarpal joints. Note typical erosion of the ulnar styloids, which show a bulbous appearance due to reparative periostitis.

The diagnosis of EM in our patient with RA was made based on clinical and histologic features, excluding lupus erythematous, drug eruptions, urticarial vasculitis, necrotizing vasculitis, figurate erythemas and toxic erythemas on differential diagnosis.

The patient was subsequently treated with oral corticosteroids (methylprednisolone 32 mg/day) for 2 weeks, with gradual and progressive improvement of cutaneous lesions.

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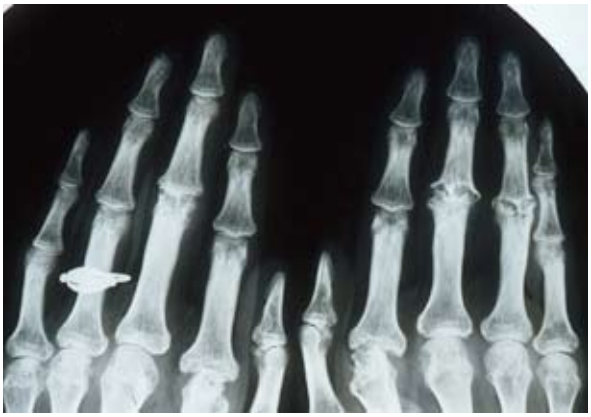

Figure 3. X-ray of the hands shows erosive arthritis; typical gull-wing configuration of the involved joints.

DISCUSSION

Erythema multiforme is an immune-mediated disease of uncertain etiology. An immune complex-related vasculitis was originally considered the main pathogenetic event, while modern studies have instead focused attention on the role of cell-mediated immunity (6). Herpes simplex virus and other infectious agents could play a role by altering DNA replication, thus causing apoptosis or expression of new membrane antigens on keratinocytes, with consequent activation of a cell-mediated cytotoxic response and cell necrosis (7). Drugs could induce a cell-mediated reaction as well as an immune complex vasculitis.

Rheumatoid arthritis is an immune-mediated systemic disease characterized by involvement of both cell-mediated and humoral response. These alterations are able to produce a wide spectrum of cutaneous eruptions, but, to the best of our knowledge, no reports of association of RA and EM are currently present in the literature.

On the basis of recent acquisitions on the pathogenesis, it could be supposed that, in RA patients, self-reactive lymphocytes recognize membrane antigens of keratinocytes, thus producing cutaneous eruption. Another possibility is that circulating immune complexes, often present in RA, precipitate on the basal membrane and attract leukocytes, thus inducing cutaneous damage. However, in our case, direct immunofluorescence of lesional skin did not reveal deposition of immunoglobulins or complement.

It is also noteworthy that EM is commonly related to drug administration, and our patient was treated for a long period with NSAIDs, drugs frequently reported as triggers of EM. In the case presented here, the low dose used by our patient and the long-standing administration (ten years) of these drugs make us doubtful of this hypothesis.

Based on the current knowledge, it is impossible to definitely include EM among, or exclude it from, the cutaneous manifestations of RA. Their coexistence in a patient might be purely coincidental, as a sign of genetic predisposition to autoimmune disorders, on which environmental factors and drugs can act as trigger factors, leading to cutaneous eruption.

The clinical appearance of EM, in the absence of any known precipitating factors and characteristic immune abnormalities, has been described in patients with lupus erythematosus (Rowell's syndrome), but probably this association is not specific (8,9). The laboratory criteria, in fact, were not present in all cases reported in the literature and, above all, they are not unique to Rowell's syndrome, as they are also present in lupus erythematosus and in RA (8,9). In our case, in particular, rheumatoid factor was positive, ANA negative and, after an extensive search, no provocative factors (drugs or infectious agents) were found. We think that EM could be a sign of an ample alteration of the immune system that may occur in patients with systemic immune diseases.

It remains to be verified whether a pathogenetic link between the two diseases really exists, and if their association changes the usual evolution of each single disorder; furthermore, the role of pregnancy in the cutaneous eruption observed in immune disorders should be investigated thoroughly.

Molecular mimicry has been postulated to explain autoimmunity that occurs simultaneously to, or immediately after, intervention of environmental triggers, mainly infectious agents. In this model, experimentally verified in several cases, structural similarity between non-self and self-antigens would, in predisposed subjects, turn a defensive immune reaction into an autoaggressive reaction (10). Infections, sometimes subclinical or not reported by patients, or drugs could, directly or indirectly, trigger EM in patients affected by systemic lupus erythematosus or RA *via* molecular mimicry.

The role of pregnancy in autoimmunity is much less well defined. As very well outlined in a recent review (11), the fetus has been considered for years as immunologically equivalent to a transplant trying to escape recognition by the immune system of the mother, and, consequently, pregnancy has been considered as a period of immune suppression, or a Th2 or anti-inflammatory state. However, more recent studies have revolutionized this concept, showing a cooperative interaction between the two symbiotic

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organisms, which modulates the maternal immune system but does not suppress it, and alternatingly induces, in the various phases of pregnancy, pro-inflammatory or anti-inflammatory state, with obvious consequences on the susceptibility to different diseases.

CONCLUSION

We believe that, in our case, pregnancy could have played a decisive role in determining the clinical picture observed; however, the exact mechanism remains unknown in its details and further studies are advisable to better define it.

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