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Rheumatoid Arthritis: An Association with Pemphigus Foliaceous

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We have observed a high incidence of pemphigus foliaceous, in the absence of therapy with penicillamine, within a small population of patients with rheumatoid arthritis. We suggest that penicillamine as well as inducing autoimmune disease might exacerbate subclinical pemphigus foliaceous in this group, accounting for those few patients whose skin disease fails to resolve following drug withdrawal. Pemphigus and rheumatoid arthritis have both been associated with HLA DR4, which was present in all three of our patients who were tested. ***Key words: Autoimmune disease; HLA type.***

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The annual incidence of pemphigus is estimated to be 0.1–0.5 per 100 000 population (1). We present our experience of the high incidence of pemphigus foliaceous in the setting of a clinic studying cutaneous reactions to drugs used to treat rheumatoid arthritis.

PATIENTS AND CASE REPORTS

All patients seen in a rheumatology clinic over a period of 18 months who developed a suspected cutaneous reaction to antirheumatic drugs were reviewed in a dermatology clinic. Where possible a specific dermatological diagnosis was made and in all patients, where consent was given, a skin biopsy for histology and immunofluorescence was obtained.

Over a period of 18 months, 92 patients were seen from a population of 695 patients who were attending clinics for monitoring of their second line therapy.

All four patients reported had classical and definite rheumatoid arthritis as defined by the American Rheumatism Association criteria.

Case 1

A 62-year-old man with rheumatoid arthritis for 31 years presented with a 2-week history of a rash on his upper chest and back (Fig. 1) which he described as blisters which then scabbed over. He had been entered 4 weeks before into a double-blind placebo-controlled trial of a new anti-rheumatic drug and when the code was broken he was found to be on placebo. His only other medication was diclofenac 50 mg prn. He had not previously been treated with penicillamine but had earlier discontinued treatemnt with sodium aurothiomalate bacause of the development of a rash. There was no history of other autoimmune disorders. Clinically he had 5–1 cm diameter crusted lesions on his upper chest. Histology was non specific showing an epidermal erosion but immunofluorescence of perilesional skin showed deposition of IgG and C3 in the upper epidermis. Indirect immunofluorescence was negative. Other investigations included erythrocyte sedimentation rate (ESR) 74 mm/h, C-reactive protein (CRP) 14 mg/l (normal range 0–9 mg/l), rheumatoid factor (RhF) 1:640) and antinuclear antibody (ANA) 1:320. He was treated with auranofin 3 mg bd with resolution of the pemphigus foliaceus over 3 months.

Case 2

A 62-year-old woman with rheumatoid arthritis for 4 years presented with a 6 month history of red patches on her shoulders which then blistered. Her medication consisted of parenteral sodium aurothiomalate 50 mg fortnightly, which she had been on for the previous year, and indomethacin SR 75 mg daily. She had not been treated with other second line therapy. Her medical history included hypothyroidism for which she was taking thyroxine 50 μg daily. On examination she had 3 1 cm diameter erythematous patches between her shoulders. Histology revealed subcorneal blister formation with acantholysis (Fig. 2). Direct immunofluorescence showed deposition of IgG between keratinocytes and indirect immunofluorescence was negative. Other investigations included ESR 66 mm/h, CRP 20 mg/1, RhF 1:640 and ANA 1:640. HLA type A10(25), A19(29), B5(51), B12(44) and DR4. She was treated with topical betamethasone valerate and continued on the same dose of gold with improvement in her pemphigus.

Case 3

A 61-year-old man with rheumatoid arthritis for 15 years presented with a 4-month history of a scaly red rash on his face, scalp and central chest. He had noted that the extent of the rash varied with the dose of penicillamine, currently 250 mg daily, which he had been on for 2 years. He had been on doses of penicillamine up to 625 mg in the past. His other medication was indomethacin 75 mg bd. There was no history of other autoimmune disorders. Clinically he had extensive erythema and scale with some erosions on the face and scalp with well demarcated lesions on the central chest. Histology was nonspecific with epidermal erosions. Direct immunofluorescence was positive with intercellular staining of the epidermis with IgG. Indirect immunofluorescence was negative. Other investigations included ESR 7 mm/h, CRP 36 mg/1, RhF 1:160 and ANA 1:80. HLA type A2, A9(24), B12(44), B15, DR4. He was treated with topical clobetasol butyrate and withdrawal of the penicillamine with gradual improvement over 4 months. No other second line therapy was given for his arthritis.

Case 4

A 44-year-old woman with rheumatoid arthritis for 25 years presented with an asymptomatic scaling eruption of her chest for 5 weeks. Her medication included penicillamine 500 mg daily which she had been

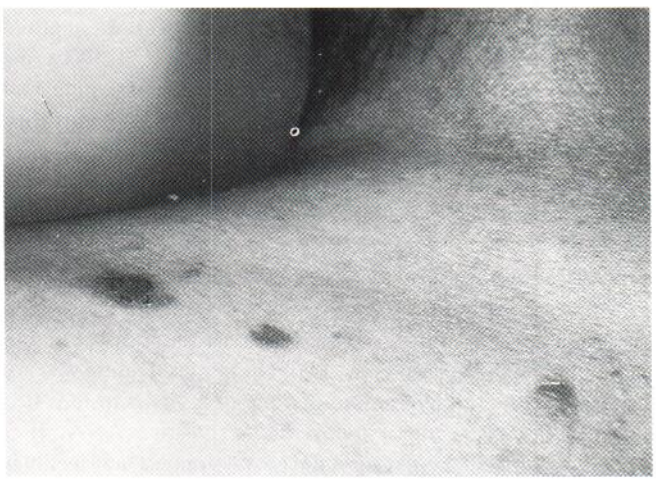

Fig. 1. Localised lesions of pemphigus foliaceous with erythema and scale on the upper back.

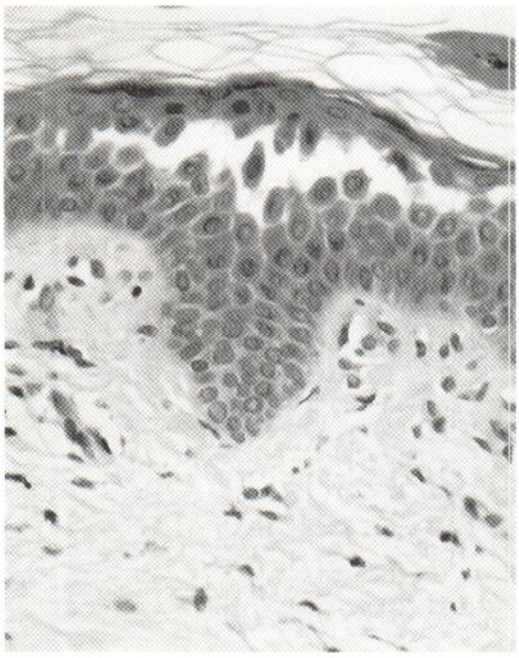

Fig. 2. Superficial epidermal split with acantholysis (H & E x200).

taking at that dose for 6 months and in total for 9 months. In addition, she had been taking sulphasalazine 500 mg daily for 8 years together with indomethacin 75 mg daily. Previous therapy for her arthritis included sodium aurothiomalate for 19 years. Clinical examination revealed discrete erythematous macules with a central erosion and peripheral scale. Histology revealed a superficial perivascular infiltrate with basal layer degeneration and the formation of colloid bodies. Direct immunofluorescence showed the deposition IgG, C3 and C4 between keratinocytes with the linear deposition of IgM along the basement membrane and within colloid bodies. Indirect immunofluorescence was negative. Other investigations included ESR 37, CRP 21, RhF 1:640 and ANA 1:320. HLA type A2, A19(31), B5, B16(39), DR4, DR8. Withdrawal of the penicillamine together with the use of topical fluocinolone acetonide resulted in resolution of the rash over 3 months.

DISCUSSION

Excluding the patients on penicillamine, the annual incidence of pemphigus foliaceous in this prospective group of rheumatoid arthritis patients is 1.9 per 1000 patients with rheumatoid arthritis requiring second line therapy. This is ~ 1000x the incidence in the normal population, strongly suggesting that this is a real association. We propose that rheumatoid arthritis be included with myasthenia gravis and thymoma (2–4) as a condition associated with pemphicus. The first two cases had mild disease and would not have independently sought a dermatological opinion and we suspect that this is the reason for this association not previously being recognised.

Direct immunofluorescence of normal skin in patients with rheumatoid arthritis may show perivascular deposits of immunoglobulin and complement (5) but epidermal staining was not reported in the relatively small sample of patients tested. It is notable that all of our patients had a positive ANA. It is recognised (6) that in drug-induced pemphigus intercellular antibodies circulate at a low titre and that other autoantibodies, including antinuclear, are a frequent finding. Whilst circulating intercellular antibodies may be found in other conditions, such as burns, the presence of positive direct immunofluorescence is thought to be specific to a diagnosis of pemphigus (1). The occurrence of rheumatoid arthritis with both bullous pemphigoid (7) and linear IgA disease (8) has been reported.

Pemphigus has been reported in association with HLA A10 in Japanese patients (9) as well as with HLA DR4 (10, 11) in Jewish patients. Rheumatoid arthritis is also associated with HLA DR4 (12) and this HLA association might explain the tendency of both diseases to occur in the same patient. In the three patients who agreed to testing all had HLA DR4 and two were homozygous for this allele. One patient had HLA A10 (25).

It is interesting that the patients on penicillamine had clinically more extensive disease despite negative indirect immunofluorescence which is usually used as a marker of disease activity (13). The original description of penicillamine induced pemphigus occurred in a patient with Wilson's disease (14) with positive immunofluorescence findings. However, whilst penicillamine can produce autoimmune disease it is also known to induce acantholysis in skin explants (15) and could therefore exacerbate pemphigus in patients with rheumatoid arthritis with mild or subclinical disease. This may also explain those reports of a bullous dermatosis with penicillamine with negative immunofluorescence findings (16, 17) and those reports of penicillamine induced pemphigus which fail to completely resolve following discontinuation of therapy (18).

The last patient had some features of cutaneous lupus erythematosus on routine histology. The immunofluorescence findings, however, combining features of both pemphigus and lupus erythematosus, were diagnostic of pemphigus erythematosus which has been reported following penicillamine therapy (19, 20).

In conclusion, we suggest that there is an association between rheumatoid arthritis and pemphigus foliaceous and that therapy with penicillamine, as well as causing pemphigus de novo, may exacerbate pre-existing disease.

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