EXTENDED REPORT

Cutaneous abnormalities in rheumatoid arthritis compared with non-inflammatory rheumatic conditions

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Ann Rheum Dis 2006;65:1341–1345. doi: 10.1136/ard.2005.048934

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Accepted 4 February 2006
Published Online First
13 February 2006

Background: Cutaneous abnormalities are common in rheumatoid arthritis, but exact prevalence estimates are yet to be established. Some abnormalities may be independent and coincidental, whereas others may relate to rheumatoid arthritis or its treatment.

Objectives: To determine the exact nature and point prevalence of cutaneous abnormalities in patients with rheumatoid arthritis compared with those in patients with non-inflammatory rheumatic disease.

Methods: 349 consecutive outpatients for rheumatology (205 with rheumatoid arthritis and 144 with non-inflammatory rheumatic conditions) were examined for skin and nail signs by a dermatologist. Histories of rheumatology, dermatology, drugs and allergy were noted in detail.

Results: Skin abnormalities were reported by more patients with rheumatoid arthritis (61%) than non-inflammatory controls (47%). More patients with rheumatoid arthritis (39%) than controls (10%) attributed their skin abnormality to drugs. Cutaneous abnormalities observed by the dermatologist were also more common in patients with rheumatoid arthritis (76%) than in the group with non-inflammatory disease (60%). Specifically, bruising, athlete's foot, scars, rheumatoid nodules and vasculitic lesions were more common in patients with rheumatoid arthritis than in controls. The presence of bruising was predicted only by current steroid use. The presence of any other specific cutaneous abnormalities was not predicted by any of the variables assessed. In the whole group, current steroid use and having rheumatoid arthritis were the only important predictors of having any cutaneous abnormality.

Conclusions: Self-reported and observed cutaneous abnormalities are more common in patients with rheumatoid arthritis than in controls with non-inflammatory disease. These include cutaneous abnormalities related to side effects of drugs or to rheumatoid arthritis itself and other abnormalities previously believed to be independent but which may be of clinical importance.

Many diseases treated by rheumatologists involve systems beyond the musculoskeletal system. This unique aspect of the specialty requires rheumatologists to have a rounded basic knowledge, if not expertise, in some other areas. Dermatology is one of these, as many rheumatic conditions such as systemic lupus erythematosus (SLE), psoriatic arthritis and the vasculitides have well-recognised cutaneous features.

Rheumatoid arthritis is the most common inflammatory arthritis,¹ and is associated with several cutaneous features, including rheumatoid nodules, vasculitis, ulcers, palmar erythema and Raynaud's phenomenon.² Rheumatoid nodules are one of the seven diagnostic criteria for rheumatoid arthritis³ and occur predominantly in seropositive patients.⁴ Vasculitis, also reported mainly in seropositive patients,⁴ is a poor prognostic factor of rheumatoid arthritis outcome.⁵ Other rare or less well-recognised conditions include skin atrophy, amyloidosis, lipoid nodules, vesicular disease, granuloma annulare and yellow-nail syndrome.⁴ However, the spectrum of skin conditions in rheumatoid arthritis is much broader, and skin abnormality is a common complaint in the rheumatology outpatient department. On administering a comorbidity questionnaire, 5% of continental European patients with relatively early rheumatoid arthritis reported a skin abnormality, and in half of these the onset was after the diagnosis of rheumatoid arthritis.⁶ Cutaneous abnormalities in rheumatoid arthritis may reflect the disease process itself, its treatment, immune abnormalities or a miscellany of conditions that are also found in the normal population.⁷

The dermatological aspects of rheumatoid arthritis have received relatively little attention in the medical literature. Case reports of rare findings relating to drug-induced cutaneous abnormalities are common,^{8–11} but there are no large, prospective studies documenting skin disease in patients with rheumatoid arthritis. In addition, the pattern of skin involvement in rheumatoid arthritis may be changing to shadow the evolution of treatment practices—for example, the early use of disease-modifying anti-rheumatic drugs (DMARDs), alone or in combination,^{12–16} and the introduction of new treatments such as the biologicals⁹ or some cyclo-oxygenase-2 inhibitors.^{17–19}

In the present study, we aimed to determine the prevalence and characteristics of dermatological disorders in contemporary patients with rheumatoid arthritis and compare this with a group of patients with non-inflammatory rheumatic conditions.

PARTICIPANTS AND METHODS

Participants

A prospective, cross-sectional, observational study was conducted on consecutive patients attending adult rheumatology outpatient clinics of the Dudley Group of Hospitals NHS Trust (West Midlands, UK) between June and August 2001. Patients with rheumatoid arthritis had a clinical diagnosis of rheumatoid arthritis and also fulfilled the

Abbreviations: DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor

Table 1 Demographic and medical characteristics of participants

Variable	Group				Test of difference	p Value
	Patients with rheumatoid arthritis (n = 205)		Controls with non-inflammatory disease (n = 144)			
	Mean	SD	Mean	SD		
Age (years)	61.52	12.88	59.72	15.27	$t_{347} = 1.20$	0.23
Disease duration (years)	11.74	9.91	8.78	(8.13)	$t_{346}^* = 2.95$	<0.01
	n	Percentage	n	Percentage		
Women	152	74	91	63	$\chi^2_1 = 4.80$	<0.05
Receiving oral steroids	85	41	3	2	Fisher's exact	<0.001
Positive RF	133	65	—	—	—	—
Receiving NSAIDs	36	18	31	22	$\chi^2_1 = 0.86$	0.35
Hypertension	71	35	35	24	$\chi^2_1 = 4.27$	<0.05
Recurrent infections	35	17	7	5	$\chi^2_1 = 11.92$	<0.001

NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor.

*One participant had a missing disease duration, hence the reduced degrees of freedom.

retrospective application of the 1987 revised American College of Rheumatology criteria for rheumatoid arthritis.³ Patients with other forms of inflammatory arthritis were excluded. As a normal healthy control would not be matched for exposure to the healthcare system or might not have accurate medical records, consecutive patients attending the same clinic for non-inflammatory rheumatic conditions were recruited as a comparison group. A total of 349 patients were recruited: 205 (57%) had rheumatoid arthritis and 144 were controls with non-inflammatory disease. In all, 117 (81%) of the controls had osteoarthritis, 26 (18%) had soft-tissue rheumatism, 19 (13%) had mechanical back pain, 15 (10%) had osteoporosis, 14 (10%) had fibromyalgia, 10 (7%) had gout and 19 (13%) had miscellaneous other conditions (diagnoses not mutually exclusive). Among these controls, there were three patients receiving oral prednisolone for polymyalgia rheumatica.

Procedure

Patients who consented gave a structured interview and were given a clinical examination by a single dermatologist (EL), who, with a rheumatologist, also reviewed their case notes in detail and completed a specifically designed proforma with the following data: demographics (age and sex), rheumatological diagnoses, disease duration, presence of rheumatoid factor, history of drug-induced skin eruptions, drug history, medical history, dermatological history and current skin or nail symptoms. Current dermatological treatment was recorded and defined as a treatment prescribed or advised by a dermatologist or other doctor. Previous skin biopsy results were noted. Patients were asked for their opinion on how any current skin complaints related to their rheumatological disease or treatment. When patients declared a DMARD-induced skin eruption, this was cross-referenced with the case notes. Current dermatological diagnoses were based on clinical examination.

Statistical analyses

Data were analysed using SPSS. Group differences were examined using t test for continuous variables or χ^2 test for categorical variables; Fisher's exact test was used if one or more cells had $n < 5$. Multivariate analyses included logistic regression with conditional forward entry.

RESULTS

Table 1 gives the demographic and medical characteristics of patients with rheumatoid arthritis and controls with non-inflammatory disease. We found no significant differences in

age or disease duration, but a greater proportion of patients with rheumatoid arthritis than controls were women ($p < 0.05$). Of the patients with rheumatoid arthritis, 133 (65%) were seropositive and 174 (84%) were currently prescribed one or more DMARDs. None of the controls were taking DMARDs. Of the patients with rheumatoid arthritis, 41% were taking oral steroids compared with 2% of the controls ($p < 0.001$). About 20% of patients from both groups were taking regular non-steroidal anti-inflammatory drugs (NSAIDs). We found no significant differences between patients with rheumatoid arthritis and controls with non-inflammatory disease regarding the prevalence of documented cardiovascular disease, lung diseases, peptic ulcers, diabetes mellitus, hypothyroidism, hyperlipidaemia, hepatobiliary disease, renal disease, venous thrombosis or thromboembolism. However, hypertension was more common in patients with rheumatoid arthritis (35%) than in controls (24%; $p < 0.05$), as were recurrent infections (17% v 5%; $p < 0.01$).

Table 2 shows the DMARD history of patients with rheumatoid arthritis, the most common current prescription being methotrexate, with significantly more patients with rheumatoid arthritis currently taking it than in the past ($p < 0.001$). Significantly fewer patients with rheumatoid arthritis were currently taking gold, penicillamine and sulfasalazine than in the past (all $p < 0.001$). None of the participants with rheumatoid arthritis was being treated with anti-tumour necrosis factor (TNF) α .

Dermatological history

Table 1 also summarises dermatological history and tests of difference between patients with rheumatoid arthritis and controls with non-inflammatory disease. A similar low proportion of patients with rheumatoid arthritis (4%) and controls (2%) were currently under dermatological follow-up (difference not significant (NS)), but more participants from both groups had been under the care of a dermatologist in the past (18% v 17%; NS). The current usage of dermatological treatment was recorded in 11% of patients with rheumatoid arthritis and 10% of controls (NS), compared with previous usage in 27% versus 33% (NS).

Previous skin biopsy had been carried out on 10 patients with rheumatoid arthritis (5%) and 12 controls (8%; $\chi^2_1 = 1.71$, $p = 0.19$; Fisher's exact, $p = 0.08$), with a variety of diagnoses. In the group of patients with rheumatoid arthritis, there were three patients with basal cell carcinoma and one each with eczema, exfoliative dermatitis, hyperplastic scar, malignant melanoma, pemphigus vulgaris and non-specific changes. In the group of controls, there was one patient each with actinic keratosis, angiokeratoma, basal cell

Table 2 Past and present usage of DMARDs in participants with rheumatoid arthritis

Drugs (not mutually exclusive)	Currently taking (n = 205)		Previously taken (n = 205)		Test of difference	p Value
	n	Percentage	n	Percentage		
Azathioprine	4.0	2.0	5.0	2.0	Fisher's exact	0.25
Ciclosporin	2.0	1.0	7.0	3.0	Fisher's exact	0.07
Gold	14.0	7.0	61.0	30.0	$\chi^2_1 = 36.05$	<0.001
Hydroxychloroquine	30.0	15.0	35.0	17.0	$\chi^2_1 = 0.46$	0.50
Leflunomide	2.0	1.0	6.0	3.0	Fisher's exact	0.11
Methotrexate	96.0	47.0	37.0	18.0	$\chi^2_1 = 38.74$	<0.001
Penicillamine	7	3.0	26.0	13.0	$\chi^2_1 = 11.90$	<0.001
Sulfasalazine	66.0	32.0	99	48	$\chi^2_1 = 11.05$	<0.001

DMARD, disease-modifying antirheumatic drug.

carcinoma, bullous pemphigoid, histiocytoma, oral lichen planus, psoriasis, solar keratosis and squamous cell carcinoma, and three with non-specific changes. Given the very small numbers, no tests of difference were carried out.

Current skin changes and symptoms

In all, 61% of patients with rheumatoid arthritis reported current skin abnormality, compared with 47% of controls with non-inflammatory disease ($p < 0.05$). Of these, 8% of those with rheumatoid arthritis and 7% of controls believed that their skin abnormality related to their rheumatological condition (NS). However, significantly more patients with rheumatoid arthritis (38%) than controls (10%) thought that their skin abnormality related to their drug treatment ($p < 0.001$). Of patients who reported having a cutaneous abnormality, 38% of those with rheumatoid arthritis and 49% of the controls were currently symptomatic (NS); 25% of the patients with rheumatoid arthritis and 16% of the controls were bothered by their skin abnormality (NS). The most common symptom was pruritus, which occurred in 34% of patients with rheumatoid arthritis and 40% of controls (NS). Nail signs were found in significantly more patients with rheumatoid arthritis (52%) than in controls (35%; $p < 0.01$), with dilated nail-fold capillaries ($p < 0.05$), ridging ($p < 0.01$) and onycholysis ($p < 0.01$), all being more common in patients with rheumatoid arthritis than in controls. Nail pitting and subungual keratomas were rare in both groups.

Current dermatological diagnosis

There was a wide variety of current dermatological diagnoses, as made by the dermatologist after clinical examination (table 3). Overall, detected skin changes were more common in patients with rheumatoid arthritis (76%) than in controls (60%; $p < 0.05$). The most common abnormalities in both groups (all p values NS between patients with rheumatoid arthritis and controls) were palmar erythema (19% v 18%), eczema (6% v 6%) and xerosis (6% v 6%). The conditions that had a significantly higher prevalence in patients with rheumatoid arthritis than in controls were bruising (16% v 5%; $p < 0.01$), athlete's foot (7% v 2%; $p < 0.05$), scars (4% v 0%; $p < 0.01$), rheumatoid nodules (19% v 0%; $p < 0.001$) and vasculitis (4% v 0%; $p < 0.01$).

Rheumatoid nodules were present in 39 patients with rheumatoid arthritis (19%), and 35 (90%) of these patients were rheumatoid factor positive. In this study, none of the cutaneous abnormalities (including palmar erythema or vasculitis) was more common in rheumatoid factor-positive than in rheumatoid factor-negative patients. Patients with nodules were more likely to be prescribed methotrexate (64%; $p < 0.05$). In all, 35% patients were prescribed sulfasalazine (NS), and 20% of patients with nodules were prescribed these drugs in combination.

Table 3 Current dermatological diagnoses of participants (all by Fisher's exact test)

	Patients with rheumatoid arthritis (%)	Controls with non-inflammatory disease (%)	p Value
Current skin diagnosis*			
Raynaud's phenomenon	0	1.4	
Cutaneous amyloid	0.5	0	
Follicular hyperkeratosis	0.5	0	
Folliculitis	0.5	0	
Herpes zoster	0.5	0	
Lipoma	0.5	2.1	
Dermatological petechiae	0.5	1.4	
Acne	1.0	0	
Calosity	1.0	0.7	
Milia	1.0	0	
Psoriasis	1.0	4.2	<0.05
Sebaceous cyst	1.0	0	
Seborrhoeic dermatitis	1.0	2.1	
Xanthelasma	1.0	0.7	
Intetigo	1.5	4.2	
Rosacea	1.5	0.7	
Vitiligo	1.5	0	
Bowen's disease	2.0	0	
Fixed drug eruption	2.0	0	
Skin mottling	2.0	3.5	
Melanocytic nevus	2.0	0	
Papular or nodular prurigo	2.0	0	
Varicose veins	2.0	6.3	<0.05
Lentigo simplex	2.4	0	
Viral wart	2.9	2.1	
Dyypuytrens contracture	3.4	2.1	
Actinic keratosis	3.9	2.1	
Skin atrophy	3.9	0.7	
Scars	3.9	0	<0.05
Vasculitic skin changes	4.4	0	<0.05
Eczema	5.9	6.3	
Xerosis or ichthyosis	5.9	5.6	
Telangiectasis	6.8	4.9	
Athlete's foot	7.3	2.1	<0.05
Eczema of leg	7.3	8.3	
Cushingoid facies	9.8	0	<0.001
Bruising	16.1	4.9	<0.01
Palmar erythema	19.0	18.1	
Rheumatoid nodules	19.0	0	<0.001
Nail signs or diagnosis			
Dilated nail-fold capillaries	3.4	0	<0.05
Nail ridging	33.2	18.8	<0.01
Onycholysis	15.6	5.65	<0.01
Subungual keratoma	1.9	3.4	
Nail pitting	2.4	1.4	

*In increasing frequency in patients with rheumatoid arthritis.

DMARD-induced skin eruptions

Gold treatment was associated with drug-induced skin eruption in 29% of patients with rheumatoid arthritis, sulfasalazine in 8%, hydroxychloroquine in 6% and methotrexate in 3%. Reactions to less commonly prescribed drugs (azathioprine, leflunomide, penicillamine, ciclosporin or cyclophosphamide) occurred less often and numbers were too small to draw conclusions.

Predictors of observed cutaneous abnormalities

In logistic regression (entering age, sex, disease duration, diagnosis of rheumatoid arthritis, and use of steroids, NSAIDs and DMARDs), the only predictors of observed cutaneous abnormality were the diagnosis of rheumatoid arthritis (Wald's test 6.29; $p = 0.01$) and the use of oral prednisolone (Wald's test 10.38; $p = 0.01$).

In specific logistic regressions of particular cutaneous abnormalities, current use of steroids predicted bruising (Wald's test 22.90; $p < 0.001$), but age, sex, disease duration, diagnosis of rheumatoid arthritis and use of NSAIDs and DMARDs did not. Use of steroids did not predict the presence of any other cutaneous abnormalities.

DISCUSSION

Our study detected a high cumulative point prevalence of cutaneous abnormalities in patients with rheumatoid arthritis. Most (if not all) patients with rheumatoid arthritis are likely to have a cutaneous abnormality over the life course of their disease. Rheumatoid arthritis and use of steroids were major predictors of the presence of cutaneous abnormalities, irrespective of disease duration, age, comorbidity or sex. Most of these abnormalities would not be considered serious, but were symptomatic in more than a third of the patients, with a quarter reporting that they were troubled by them. Only a few patients attributed their cutaneous abnormality to their rheumatic disease (including nodules, which patients may not perceive as a skin abnormality), but drugs were implicated by nearly 40% of patients with rheumatoid arthritis.

Cutaneous toxicity from DMARDs is a relatively common reason for stopping drugs. Wilkinson *et al*²⁰ reviewed 114 patients with rheumatoid arthritis with suspected DMARD-induced rash: in 38% of cases the rash was attributed to drugs, in 33% it was directly related to rheumatoid arthritis and in the remainder the rash was unrelated or resolved spontaneously. The authors concluded that 82% of patients initially thought to have a skin reaction to a DMARD could safely continue the drug. In concordance with our findings, gold salts were the most commonly implicated drug treatment, although in our study DMARD-induced skin eruptions were based on the patient's opinion or the case-note entry rather than expert dermatology opinion at the time of the reaction. Over the past decade, treatment of rheumatoid arthritis has moved away from gold treatment, methotrexate has become the most commonly used DMARD, and new drugs, including leflunomide and the biologicals, have been introduced. Post-marketing surveillance of treatment with anti-TNF α has shown numerous case reports of skin diseases related to autoimmune diseases, in particular skin infection, atopic conditions, leucocytoclastic vasculitis, discoid lupus and even psoriasis.^{9 21 22} Leflunomide has been associated with focal epidermal necrosis¹¹, among other rashes.^{8 23} Our study predates the widespread use of treatment with anti-TNF α , and the number of patients taking leflunomide was small.

In SLE, a condition classically associated with skin, patients are aware of the potential rashes and are commonly treated with drugs (azathioprine, hydroxychloroquine, steroids and NSAIDs) that are also used in rheumatoid arthritis.

In a recent qualitative study²⁴ investigating self-consciousness and appearance, patients with SLE did not relate their skin problems, commonly including proneness to bruising,²⁵ to drugs. This highlights the difference in perceptions between these groups of patients, which may be important in the context of adherence to their prescribed treatments.²⁶ Dermatological disease affects the perception of a patient's body,²⁴ and when it occurs in people who are already experiencing changes in body image because of their rheumatoid arthritis, it may put additional strain on their coping mechanisms.²⁷ Greater attention by medical staff to skin problems and appropriate education of patients may help patients cope better with the overall effect of their medical conditions.

Rheumatoid nodules were present in 19% of patients with rheumatoid arthritis, which is similar to other reports,⁴ but not all patients with rheumatoid arthritis with nodules were rheumatoid factor positive. Methotrexate can induce nodulosis in patients with rheumatoid arthritis, but the mechanisms are unknown.²⁸ In this survey, patients with nodules were more likely to be taking methotrexate. It is unclear whether this was the result of the treatment or simply reflected the fact that rheumatoid nodules are a confounder for aggressive disease, for which the preferred treatment is currently methotrexate.²⁹ Indeed, a limitation of our study is that we did not record rheumatoid disease activity and hence were unable to correlate this with skin disease. Similarly, recording the dose and duration of treatment with oral prednisolone may have enabled further appreciation of the relationship of long-term steroids with skin disease, particularly bruising.

Contrary to other reports,³⁰ palmar erythema was not more common in patients with rheumatoid arthritis than in controls with non-inflammatory disease, and Raynaud's phenomenon was rare. Yellow-nail syndrome, an unusual condition characterised by yellow discoloration of fingernails and toenails, persistent lymphoedema and pulmonary pathology, has been described in patients with rheumatoid arthritis, but was not seen in our study. However, nail signs as a whole were increased in rheumatoid arthritis, particularly ridging and onycholysis. Longitudinal ridging has previously been reported to be a more common finding in patients with rheumatoid arthritis than in those with other rheumatic conditions.³¹ Skin atrophy occurs in those with rheumatoid arthritis mainly over areas of bony prominences such as the metacarpophalangeal joints or shoulders. This is distinct from "thin skin", although it also relates to use of steroids. Interestingly, correlations have been made between skin atrophy and cortical bone thickness.⁴ We identified skin atrophy in eight patients, all of whom were taking prednisolone. Although our study is the largest in this aspect, the number of rare conditions was still small, and results are therefore vulnerable to both type I and type II errors. Future studies on large cohorts (perhaps within the British Society for Rheumatology's Biologics Registry programme) could consider these issues more robustly.

Conditions previously not believed to be related to rheumatoid arthritis are also of interest. Athlete's foot was considerably more common in patients with rheumatoid arthritis than in controls. This has not been reported previously, but may be relevant to both treatment (immunosuppressants) and the disease (patients may be sufficiently disabled to prevent adequate foot hygiene, particularly in deformed feet with over-riding toes, for example). Skin breaks due to fungal infection may act as a point of entry for infection and thus predispose patients to cellulitis or more sinister effects after surgery of the lower limbs. This may also occur in the case of eczema of the leg, which was found in about 7% of both patients with rheumatoid arthritis and controls.

The term vasculitis when applied to rheumatoid arthritis encompasses a spectrum of disorders from "classic" rheumatoid vasculitis of various degrees of severity⁵ to other forms of cutaneous vasculitis, including erythema elevatum diutinum, livedo reticularis, pyoderma gangrenosum, cutaneous polyarteritis nodosa-like vasculitis, and leg ulcers of complex cause. Owing to the small number of cases in our study and the diagnosis being made on clinical grounds, we did not subdivide cases with vasculitis. Vasculitis may associate with the disease itself, but it has also been reported as a side effect of treatment, including NSAIDs^{5, 32} and biologicals.^{33, 34} In our study, vasculitis was clinically detected in 4% of patients with rheumatoid arthritis, a prevalence comparable with other studies,³⁵ and did not associate with any type of treatment. Although the prevalence of clinically overt rheumatoid vasculitis is believed to be falling,³⁶ subclinical vasculitis (detected on rectal, labial or skin biopsies) is common in patients with rheumatoid arthritis,^{37, 38} and may be of relevance in the context of the increased cardiovascular morbidity and mortality in patients with rheumatoid arthritis.^{39, 40}

In summary, skin problems are common in patients with rheumatoid arthritis. Their misdiagnosis may lead to mismanagement (eg, the unnecessary withdrawal of a potentially beneficial drug). Clearly, in clinical practice, allergy testing, skin biopsy or investigations on blood may help to clarify diagnoses or causes of cutaneous abnormalities, and future studies should consider these measures. This observational study suggests that rheumatologists need a good working knowledge of skin conditions. This has already been identified, as is evident from its inclusion in the current curriculum for higher specialist training in rheumatology in the UK, in which knowledge of skin abnormalities, as part of multisystem disease, is required. Coordination with dermatologists, either through combined clinics or through quick-access care pathways, may be a further way of improving the management of this common comorbidity.

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Competing interests: None.

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