Mucocutaneous Manifestations in Patients with Rheumatoid Arthritis: A Cross-sectional Study from Eastern India

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Abstract

Background: Cutaneous manifestations are fairly common in rheumatoid arthritis (RA) and they can help in early diagnosis, prompt treatment, and hence reduced morbidity from the disease. Aims: The objective of the present study was to find out the different patterns of dermatoses in a group of patients with RA from Eastern India. Methodology: Consecutive patients fulfilling the American Rheumatism Association 1987 revised criteria for the classification of RA and who had different dermatoses were included in this cross-sectional study done over a period of 8 years in a tertiary care hospital in Eastern India. Thorough clinical examination and appropriate laboratory investigations were performed as needed. Data were recorded in a predesigned schedule, and appropriate statistical analysis was done. Results: We studied 111 evaluable patients with an age range of 19–71 years and a female to male ratio of 7:1. The mean disease duration of RA was 6.5 years. Cutaneous infections as a group was the most common mucocutaneous manifestation (34.2%) followed by xerosis including ichthyotic skin changes (27%), pigmented purpuric dermatoses (14.4%), leg ulcer (9.9%), periungual telangiectasia (9.9%), rheumatoid nodules (RNs) (8.1%), purpura and ecchymoses (7.2%), small vessel vasculitis (7.2%), corn and callosities (6.3%), palmar erythema (4.5%), and neutrophilic dermatosis (4.5%). Raynaud’s phenomenon was found in 3.6% patients and panniculitis in (3.6%) patients. Rheumatoid factor (RF) and anti-cyclic citrullinated peptides antibody were positive in 74.8% and 88.3% patients, respectively. No statistically significant difference of incidence of leg ulcer, small vessel vasculitis, RN, or Raynaud’s phenomenon could be noted between RF positive and negative groups. Limitations: Being an institution-based study, the study findings may not reflect the true situation in the community which remained a limitation of this study. Conclusion: While some of the features of this study were analogous to Western data, other features showed discordance which may be due to ethnic variations among the patients with RA.

Key Words: Mucocutaneous, rheumatoid arthritis, rheumatoid nodule

Introduction

Rheumatoid arthritis (RA) is a potentially serious, immune-mediated, chronic inflammatory disease predominantly affecting joints. However, extrarticular manifestations of RA, including skin disease, are relatively common and occur in nearly 40% of patients with RA over a lifetime of the disease course. A large number of specific and nonspecific mucocutaneous manifestations are associated with RA. Understanding the cutaneous manifestations of RA may lead to early diagnosis, prompt treatment, and hence lower morbidity and mortality of the affected persons. The disease severity as well as the prevalence extraarticular manifestations, dermatologic involvement tends to occur in patients with more severe RA. Understanding the cutaneous manifestations of RA may lead to early diagnosis, prompt treatment, and hence lower morbidity and mortality of the affected persons. The disease severity as well as the prevalence...
of extraarticular manifestations shows geographic variations. PubMed and MEDLINE database search revealed that apart from a few studies on Western population, there is a dearth of data on this subject, particularly on Indian population which prompted us to undertake the present study. The objective of the present study was to find out the different patterns of dermatoses in a group of patients with RA from Eastern India.

**Methodology**

This cross-sectional study was carried out at the Department of Dermatology, Venereology, and Leprosy of a tertiary care hospital in Eastern India over a period of 8 years (from March 2008 to February 2016). The study was approved by the Institutional Ethics Committee. Consecutive patients irrespective of gender and age who fulfilled the American Rheumatism Association 1987 revised criteria for the classification of RA and had different dermatoses were included in this study. Exclusion criteria were other autoimmune disorders, rheumatic diseases other than RA, juvenile RA, arthritis that was not unambiguously classifiable, concomitant medical problems which would confound the interpretation of the information gathered by this protocol, and nonconsenting patients. Figure 1 shows flowchart of recruitment of the patients in this study. Skin findings of each patient were evaluated by at least two dermatologists. Detailed history and clinical findings of these patients were recorded in a pretested, predesigned, and semi-structured schedule. Rheumatoid factor (RF) and anticyclic citrullinated peptides (CCP) antibody tests were done in all patients. Other appropriate laboratory investigations including histopathology and radiological examination were done as needed. We used descriptive statistics for data enumeration and Student’s t-test and Chi-square test for comparative data analysis. Statistical analysis was done using GraphPad Prism version 5 (GraphPad Software Inc., San Diego, CA, USA; 2007) software and Microsoft Excel.

**Results**

We studied 111 evaluable patients. The age range was 19–71 years with a mean of 41.1 ± 13.8 standard deviation (SD). The majority of the patients were female (n = 97; 87.4%) with a female to male ratio of 7:1. The mean age in years was 39.5 ± 13.0 SD for females and 52 ± 13.7 SD for males. The mean disease duration (in years) of RA was 6.5 ± 4.9. The mean disease duration (in years) was 6.8 ± 5.2 for females and 4.8 ± 2.2 SD for males. Only one patient had a positive family history for RA. Among mucocutaneous manifestations Table 1, cutaneous infections as a group were the most common condition, noted in 38 (34.2%) patients. Among infections, superficial fungal infections were present in 32 (28.8%) patients, including 15 (13.5%) with cutaneous dermatophytosis, 7 (6.3%) with tinea unguium, 6 (5.4%) with palmoplantar candidiasis, and 4 (3.6%) with oral candidiasis. Pyoderma was present in 4 (3.6%), and herpes zoster was present in 2 (1.8%) patients. This was followed by xerosis including ichthyotic skin changes, noted in 30 (27%), and pigmented purpuric dermatoses in 16 (14.4%) patients.

Leg ulcer Figure 2 was present in 11 (9.9%) patients including 8 (7.2%) cases of venous ulcers, 2 (1.8%) with arterial ulcers, and one patient with pyoderma gangrenosum (PG). Periungal telangiectasia was noted in 11 (9.9%) patients.

Rheumatoid nodule (RN) Figure 3 was seen in 9 (8.1%), purpura and ecchymoses in 8 (7.2%), small vessel vasculitis Figure 4 in 8 (7.2%), corn and callosities in 7 (6.3%), and palmar erythema Figure 5 and skin atrophy Figure 6 in 5 (4.5%) patients each.

![Figure 1: Flow chart showing recruitment of the patients](image1.png)

![Figure 2: Bilateral leg ulcers](image2.png)
Five patients (4.5%) had neutrophilic dermatosis including 2 (1.8%) patients of PG [Figure 7], 1 (0.9%) neutrophilic papular dermatosis, and 2 (1.8%) with sweet syndrome. Iatrogenic manifestations, seen in 5 (4.5%) patients, were in the forms of steroid-induced acneiform eruption (3, 2.7%) and methotrexate (MTX)-induced mucositis (2, 1.8%) [Figure 8].

Raynaud’s phenomenon was found in 4 (3.6%) patients. Panniculitis was noted in 4 (3.6%) patients. Chronic urticaria and erythema multiforme were seen in 3 (2.7%) patients each. Granuloma pyogenicum [Figure 9], hemorrhagic vesicle, livedoid vasculopathy [Figure 10], and generalized hyperpigmentation were noted in two (1.8%) patients each. Digital gangrene [Figure 4] was seen in one patient. RF was positive in 83 (74.8%) patients. Anti-CCP antibody was positive in 98 (88.3%) patients. Out of the 11 leg ulcer patients, 9 (8.1%) were RF positive while two (1.8%) were RF negative. All the patients with RA nodule were RF positive. Out of 7 patients with small vessel vasculitis, 5 were RF positive. All the patients with Raynaud’s phenomenon were RF positive. However, using Fisher’s exact test, no statistically significant difference of incidence of leg ulcer, palpable purpura (small vessel vasculitis), RN, or Raynaud’s phenomenon could be noted between RF positive and negative groups.
Discussion

RA is a systemic inflammatory disorder that primarily affects the joints, but frequently exhibit extraarticular, including cutaneous, manifestations.

A large burden of cutaneous disease may be a sign of RA disease activity and requires for more aggressive treatment. RA may have a plethora of cutaneous manifestations. The mechanisms of cutaneous affection include activation of inflammatory cells (neutrophils, lymphocytes, and macrophages), vasculopathy, vasculitis, acral deformity, and drugs. Specific skin lesions associated with RA comprise of RNs, granulomatous, and neutrophilic dermatitis in the context of immune complex diseases, and rheumatoid vasculitis. While RNs are almost exclusively seen in patients with RA, granulomatous and neutrophilic dermatitis in immune complex diseases may accompany other systemic autoimmune diseases, lymphoproliferative disorders or may be drug-induced. Likewise, rheumatoid vasculitis does not show any apparent clinical or histological difference from other forms of vasculitis. Numerous other nonspecific lesions (including iatrogenic lesions) have also been described in RA patients.

Patients with RA exhibit geographic and ethnic variations. In a previous Turkish study of RA with cutaneous manifestations, the mean age and disease duration were 55.3 years and 138.1 months, respectively. Another study from Germany showed that the mean age and mean disease duration was 62.81 years and 15.54 years, respectively. Contrary to this, the mean age of presentation (41.1 years) and the mean disease duration (6.5 years) were much less in the present series. However, in consonance with the previous studies, there was a female preponderance in the present series. The mean age of presentation was much less in females (39.5 years) in comparison to that of the males (52 years). Familial occurrence of RA is rare as only one patient of the current series had a positive family history for RA.

RN are the most common specific cutaneous manifestation in patients with RA. Classic RNs are movable subcutaneous firm or hard, usually asymptomatic, persistent nodules that usually develop on the extensor surface of the elbow, olecranon, and extensor tendons of the hands, proximal ulna, sacrum, occipital region, and sole. It is noteworthy that all of these areas are prone to friction. They may also occur internally in the spine, lung, heart valve, and gastrointestinal tract. The precise mechanism of RN formation remains elusive. Histopathologically, palisades of histiocytes surrounding a zone of necrobiosis are usually found. The occurrence of RN has ranged from 34% of outpatients with RA to 53% among 127 hospitalized patients, and as high as 75% in those with Felty syndrome. However,
a lower prevalence (9.3%) has been observed in Turkish patients.\[6\] Yamamoto et al. also described an extraordinarily lower frequency (<2%) in Japanese patients.\[13\]

A relatively lower occurrence (8.1%) has also been noted in the present study. In another Indian series, RN was found in 7.5% patients.\[14\] RF positivity was seen among 75% of the patients with RN.

Recently, RN formation has been reported following etanercept and adalimumab. RNs which crop up mostly in the hands and feet in patients without RFs or joint complaints include a condition known as rheumatoid nodulosis, or are otherwise known as benign RNs.\[8\]

RA patients receiving MTX treatment may occasionally develop multiple RN (accelerated nodulosis). The mean period from the beginning of MTX therapy to the onset of subcutaneous nodulosis is about 3 years. No such case has been noted in the present series.

Rheumatoid papules are an additional characteristic cutaneous manifestation associated with RA. Histological features of such papules demonstrate leukocytoclastic vasculitis and palisading granuloma with collagen degeneration, in the more superficial part of the dermis than is the case with RNs. Rarely, rheumatoid papules spontaneously fall of after crusting due to transepidermal elimination. Papular eruptions might also be induced by MTX therapy. Rheumatoid neutrophilic dermatitis clinically manifests as symmetrical erythematous papules, wheal-like erythema, nodules, plaques, and rarely, vesicles, over the extremities, and trunk.

Seropositive RA has been associated with PG in about 12% of cases.\[3\] A much lower occurrence (1.8%) of PG has been found in the present series.

Rheumatoid vasculitis, on the other hand, may at times be tricky to diagnose because of the wide variations of clinical presentations. In the present Chapel Hill Consensus. Conference nomenclature, primary vasculitides in RA is classified under “vasculitis associated with systemic disease.”\[15\] Whereas vessels of any caliber may be involved, the disease more frequently affects small and medium-sized vessels. Clinical manifestations depend on the types of vessels involved and may include palpable purpura, cutaneous ulcers, or hemorrhagic blisters among others. Mononeuritis multiplex is another typical feature of rheumatoid vasculitis. Small digital infarctions may go with other manifestations in clinical vasculitis or may occur alone as isolated digital arteritis.\[6,9,16\]

The incidence of RV has in fact been waning over the last two decades, possibly as a result of the more aggressive management of RA currently used. It remains an important complication of RA that needs to be prompt recognition and treated.\[17,18\] The precise etiology of clinical rheumatoid vasculitis is poorly understood. However, high titers of RF, cryoglobulins, decreased circulating complement, an increased prevalence of HLA-DR4, and the pathologic findings support an immune etiology. In a previous Indian series, RV was seen in 5.8% of patients.\[14\] A relatively higher occurrence (7.2%) was noted in the present study.

On the other hand, chronic leg ulcers with or without edema are often documented in patients with RA. The etiology of leg ulcers in RA is multifactorial.

The predominant causes are chronic venous insufficiency, rarely peripheral artery disease, hypertension (Martorell’s ulcer), and diabetes mellitus, or a combination of these. It is worth mentioning that vasculitic leg ulcers are relatively rare in the setting of RA.\[6\] Other causes of leg ulcer include vasculopathy (nonvasculitic vascular disorders of various origins such as, coagulopathy, thrombosis of postcapillary veins, intimal proliferation of small arteries that lead to partial or complete vascular occlusion).\[6,8\]

In addition, another subgroup of patients may have ‘inactivity ulcers’ due to impaired mobility and ensuing lymphedema. Morphology and localization of ulcerations, as well as Doppler ultrasonography, present the vital clues for accurate diagnosis, ensuring proper treatment.\[19\] About 2.7% of patients of a previous series had leg ulcers.\[6\] A relatively higher percentage (9.9%) of patients of the present series had such problem.

Patients with RA have an increased baseline risk of infections when compared with the general population.\[6\] RA patients are often on immunosuppressives which make them further susceptible to develop secondary viral, bacterial, or fungal infections.\[20\] Ziemer et al. observed such infections in 7.5% of their patients.\[4\] A much higher percentage (34.2%) of patients of the current series had cutaneous infections.

Western data show that palmar erythema may be found in >60% of patients with RA and is associated with a
favorable prognosis. Contrary to this, we found a much less (4.8%) occurrence of palmar erythema.

We speculate that as all of the patients of the present series had type IV and V skin, the palmar erythema was less appreciable in them. In RA, the prevalence estimates of Raynaud’s phenomenon range from 2.7% to 17.2%. In the current series, 3.6% of patients had history suggestive of Raynaud’s phenomenon.

In addition to manifestations related to the disease, there are also diverse dermatologic features related to the medications used to treat RA. Anti-TNFα agents, in particular, have a wide variety of adverse effects including psoriasiform eruptions, granulomatous conditions, and cutaneous connective tissue disorders, great vessels arteritis. Justice et al. reported a case of widespread cutaneous herpes simplex virus type 1 infection following treatment with infliximab. Pustular psoriasis and MTX-related lymphoproliferative disorder with extensive vascular involvement have also been described recently.

The other cutaneous manifestations of RA may include skin atrophy, transparent skin, generalized hyperpigmentation, hyperhidrosis of the palms, erythema nodosum, alopecia, vitiligo, contact dermatitis, urticaria, tylosis, clavus, ingrown nail, among others. In a German study, 27.1% of patients had nail changes. Various nail abnormalities may include thickening, discoloration, splinter hemorrhages, curvature abnormalities, longitudinal nail beading, and surface abnormalities among others.

In a previous series involving German population, 1.9% of individuals had atrophic skin and 3.2%, xerosis. A relatively higher percentage of our study population had skin atrophy (4.5%) and xerosis (27%). In a previous series, 1% patients had an atopic skin disease, which is comparable to another study conducted by Kaptanoglu et al., in which 1.6% of RA patients had atopic dermatitis. However, there was no patient with atopic dermatitis in the present series. Overall, atopic skin diseases seem to be less common in RA patients than in the general population. In a previous series of patients with RA and skin lesions, 70% of the patients were RF positive. A comparable percentage (74.8%) of patients of the present series had positive RF. However, there was no statistically significant difference of occurrence of leg ulcer, palpable purpura, RN, or Raynaud’s phenomenon between the RF positive and negative groups in the current series.

**Limitation**

Being an institution-based study, the study results may not reflect the true situation in the community. Furthermore, there was no control group in the present descriptive case series.

**Conclusion**

The present study highlighted the patterns of mucocutaneous manifestations in an Indian population while some of the features of this study are comparable to Western data, other features showed discordance to existing data which might be attributed to ethnic variations. We would further like to emphasize that every physician caring for patients with RA should be aware of these relatively common dermatologic complications.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

- The present study highlighted the patterns of mucocutaneous manifestations in a group of patients from Eastern India.
- Whereas some of the features of this study are comparable to Western data, other features showed discordance to the existing data which may be due to ethnic variations of the patients with rheumatoid arthritis.

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