REVIEW PROF-527

RHEUMATOID ARTHRITIS ;
CUTANEOUS MANIFESTATIONS

Dr. Atiya Mahboob
Assistant Professor,
Department of Dermatology, Division of Medicine,
Sheikh Zahid Medical Complex, Lahore.

Dr. Farrukh Iqbal
Associate Professor, Department of Medicine,
Sheikh Zahid Medical Complex, Lahore.

Dr. Munir Akthar Saleemi
Assistant Professor,
Department of Preventive Pediatrics,
King Edward Medical College, Lahore.

Dr. Zafar Iqbal
Professor & Head of Department of Medicine,
Sheikh Zahid Medical Complex, Lahore.

INTRODUCTION

Rheumatoid arthritis (R.A) is an intense inflammatory process involving all organ systems. Although articular involvement is the most prominent manifestation of the disease, inflamation of other tissues including skin is common[1]. Lesions in the eyes, heart and lungs can be serious and may lead to significant disability or even death.

R.A is a disease with worldwide distribution, affecting all ethnic groups. Women are effected more often than men. All age groups can be affected, but there is an increasing incidence with advancing age[2].

R.A has been relatively ignored by dermatologists. It is the intention of this review to show the contribution and role which can be played by dermatologist in the diagnosis and management of the disease.

R.A can be separated into juvenile and adult forms. These two disease are usually quite distinct. The manifestations and prognosis of these disorders are different. The skin lesions in both forms are characteristic and may be valuable in diagnosis.

JUVENILE TYPE

Cutaneous Manifestations

1 Rash of Still's disease
2 Subcutaneous nodules
3 Vasculitis.

Rash of Still's Disease

The rash of still's disease is quite characteristic. It occurs in 25% of all patients with juvenile R.A[2]. The incidence decreases with age. The rash consists of small, non-itching, salmon-pink, erythmatous macules or papules, 3mm or less in diameter, on the trunk, limbs and face. The margin is irregular and there may be central and surrounding pallor. The lesions are smaller than the erythema marginatum of rheumatic

fever and do spread. The rash tends to occur at midday and in the evening, associated with increased temperature of the environment and with fever[3]. It is usually accompanied by splenomegaly, lymphadenopathy and a raised erythrocyte sedimentation rate. The rash and fever accompany or follow arthritis, but occasionally may precede other manifestations by up to nine years. The duration of the rash is variable, and it may occur intermittently over many years[2]. It has no relation with prognosis[4]. The rash, fever and arthritis may continue for years[3]. There may be residual ankylosis in the carpus, tarsus and neck as well as distal interphalangeal joint involvement and occasion destructive lesions.

ADULT TYPE

Dermatologic conditions reported in patients with rheumatoid arthritis

1 **Necrobiotic conditions**
Rheumatoid nodules
Linear necrobiotic subcutaneous bands
Superficial ulcerating Rheumatoid necrobiosis

2 **Rheumatoid vasculitis**
Severe: Systemic arthritis
Moderate: Syndrome of allergic vasculitis
Mild: Cutaneous vasculitis
Miscellaneous: Erythema elevatum diutinum.
Segmental hyalinizing vasculitis

3 **Leg ulcers**
Pyoderma gangrenosum
Felty syndrome
Vasculitic ulcers
Venous static ulcers
Pressure ulcers

4 **Autoimmune bullous dermatoses**
Bullous pemphigoid
Cicatricial pemphigoid
Pemphigus vulgaris
Dermatitis herpetiformis
Subcorneal pustular dermatitis
Epidermolysis bullosa acquisita

5 **Miscellaneous conditions**
Rheumatoid neutrophilic dermatitis
Transparent skin
Hyperpigmentation
Yellow nail syndrome
Palmer erythema
Still's like transient macular erythema
Erythromelalgia
Localized hyperhidrosis
Mondor's disease
Pustular panniculitis
Erythema multiforme
Urticaria
Erythema nodosum
Alopecia areata

6 **Overlap syndromes**

7 **Nail changes**

8 **Eheumatoid arthritis and cancer risk**

9 **Cutaneous changes due to drugs used for rheumatoid arthritis.**

1. NECROBIOTIC CONDITIONS

(i). Rheumatoid Nopdules (R.N).

The subcutaneous nodules in one of the most characteristic findings in a patients with R.A. R.N are present in 20 to 30%[5,6] of patients with R.A and often help in the clinical diagnosis. Characteristically present as firm, skin coloured, non-tender, dome-shaped masses in the subcutaneous tissue. The most frequent sites for involvement are the extensor surfaces of forearms and elbows. Any subcutaneous site especially those exposed to trauma such as dorsa of hands, knees, knuckles, feet, buttocks, scalp, back, sacrum and heels can be affected. In addition, histologically typical R.N have been reported from abdominal wall, heart, larynx, lungs, pleura, splenic capsule, peritoneum, sclera (scleromalacia), bridge of the nose, pinna of ear, ischial tuberosity, Achilles tendon, nervous system and muscles[6]. They vary in

size from 2mm to greater than 5cm in diameter. Lesions develop insidiously and usually persist. They may regress or increase in size. They ulcerate with repetitive trauma. If the lesions are exposed to persistent pressure and shear forces, the overlying skin may break down, resulting in introduction of pathogenic organisms and deep infections[7]. A fistulous tract may form from an infected nodule and results in chronic draining sinus. Nodules adjacent to bone or tendon may cause erosions resulting in pain and subsequent tendon reptures[5]. Due to R.N in sclera, these become atrophic and may perforate (scleromalacia perforans) leading to complete blindness.

The presence of R.N clinically correlates with more severe erosive disease, high titres of rheumatoid factor and rheumatoid vasculitis[8,9,10]. A few patients with nodules have a negative conventional test for rhematoid factor, but these patients usually show an 1gM rheumatoid factor with binding sites saturated with 1gG or serological evidence for rheumatoid facor[11]. Sometimes these nodules may precede R.A by some years[12].

A variant of rheumatoid disease termed "rheumatoid nodulosis" has been described in which nodules occurred with palindromic rheumatism and little evidence of synovitis[13]. Nodules are multiple and small and occur mainly on hands and feet. Rheumatoid nodulosis may after many years, turn into rheumatoid disease with joint involvement.

Benign rheumatoid like nodules occur in healthy children under 18 years without clinical or serological evidence of rheumatoid or other disease[14]. These occur particularly on pretibial areas, feet and scalp and histologically indistingusihable from nodule occurring with R.A. They may develop rapidly and resolve spontaneously.

Histologically, R.N are characterized by dense deposits of fibrin like material within the subcutaneous tissue and /or dermis, surrounded by palisading histiocytes[15]. Both 1gM and 1gG have been shown by immunofluorescence studies to be present in blood vessels at the outer zone of R.N[5,16]. The presence of rheumatoid factor and complement in R.N has also been subsequently documented by immunofluorescence microscopy[17,18]. Plasma cells in the outer zone appear to produce both 1gM and 1gG rheumatoid factor[19].

R.N are not specific for R.A, in one survey upto 5% – 70% of patients with systemic lupus erythematosus had subcutaneous nodules[20]. Patients with scleroderma have also been reported to develop small subcutaneous nodules[21]. R.N have also been rarely reported in seronegative ankylosing spondylitis[5].

(ii). Linear Necrotic Subcutaneous Bands

Elongated subcutaneous bands 3-5 mm wide and 10cm or more in length, have been described in patients with R.A with nodules. These bands are firm, non-tender and adherent to the skin. They extend from the axilla to the iliac crest. Histologically, the bands show changes similar to the nodules[22].

(iii). Superficial Ulcerating Rheumatoid Necrosis (SURN)

These are chronic, superficial, ulcerating, discrete lesions on lower legs bilaterally present in patients with "classic" R.A with typical R.N. These nodules histologically reveal necrobiotic granulomas[23].

2. RHEUMATOID VASCULITIS

The presence of vascular lesions in R.A has been increasingly recognized. There is spectrum of dermatological lesions seen in rheumatoid vasculitis (R.V).

(i). Severe Rheumatoid Vasculitis

Severe vasculitis is a serious complication of R.A in which systemic vasculitis of small medium sized arteries produces wide spread systemic damage[24,25,26]. Cutaneous vasculitic lesions (excluding R.N) are present in over 85% of patients[24,25].

The most common vasculitic lesions in rheumatoid patients are digital infarcts[2]. These are found on the nail folds, finger pulp and at the edges of nails[27]: These are small, pale papulesat pressure points, darken to a reddish color and slowly develop central brown staining. A few lesions may result in small scars with superficial flaking. The infracts of the pulp of the fingers may show small, painful purpuric nodules (By waters lesions). Palpable purpura, involving the distal extremities or non-specific macular erythematous eruption, involving primarily the trunk is present in some patients[26].

In other patients, a more severe vasculitis is seen. Infarction with peripheral gangrene can occur in the digits and may extend to involve segmental portion of the hands, feet or legs[28].

The onset of systemic vasculitis is sudden and may have prominent generalized symptoms. This arteritis appears to be highly correlated with the presence of rheumatoid factor and R.N[6]. Neurological involvement is not infrequent; occurring in almost half of affected patients, and includes both motor and sensory neuropathies[25,28]. The mechanism of neuropathies is believed to be narcotizing vasculitis of vasavasorum[29]. Cerebrovascular accidents have also been reported[25]. Cardiac involvement can include pericarditis, arrhythmias and conduction disturbances[25]. Eye involvement, which affects less than 25% of patients in most series, includes scleritis and scleromalacia perforans[26,28]. Renal involvement is a rare complication of R.A. Proteinuria is found in over 25% to 40% of patients and may be due to amyloidosis or medications rather than R.V in many patients[28]. Arteritis of gastrointestinal tract gives rise to abdominal pain, which may be due to multiple ischemic ulcers, gangrene of the bowel, intra-peritoneal hemorrhages or splenic infarction[30]. Systemic features also include weight loss, splenomegaly, hepatomegaly, pulmonary disease, hypertension and anemia[25,28].

(ii). Syndrome of Allergic Vasculitis

Allergic vasculitis (A.V) or moderate R.V has been well described in the absence of the severe grade of R.V in patients with R.A[24]. A.V is a leukocytoclastic vasculitis involving post-capillary venules. The initial presentation is most often with cutaneous lesions, characteristically palpable purpura, on dependent sites such as lower legs. The lesion may become bullous, infracted or ulcerating and may be painful. Systemic signs and symptoms may include; malaise, mylagia, moderate fever, mild proteinuria and haematuria, arthralgias, gastrointestinal pain and /or bleeding, pleurisy or pulmonary infarcts, pericarditis, retinal haemorrhages and central or peripheral nervous system involvement[31,32]. Henoch-Schonlein purpura is believed to be subtype of A.V.

(iii). Cutaneous Vasculitis

Many patients with active R.A have shown a high incidence of cutaneous vasculitic lesions without systemic evidence of moderate or severe R.V[27]. Clinically these cutaneous lesions consist of often transitory nail fold thromboses, nail fold telangiectasias and small, brown infracted areas often slough to leave small scars. Petichial lesions on the fingers have also been noted. Livedo reticularis is well described in patients with R.A[33].

(iv). Miscellaneous Vasculitis

a) Erthema elevatum diutinum: It is characterized clinically by erythematous to yellowish

infiltrated plaque as well as papules and nodules, found primarily over extensor surfaces of the extremities. Histologically these lesions reveal a leukocytoclastic vasculitis, fibrosis, infiltration of histiocytes and eosinophils[34].

b) Segmental hyalinizing vasculitis: Clinically it is a chronic, localized, scarring condition of lower extremities. It begins with focal purpura progressing to stellate, configured infractive lesions. A localized fine, reticulated vasuclar livedo pattern surrounds the lesions[35].

(3). LEG ULCERS

In R.A ulcers may develop from trauma, pressure, dependence or vasculitis. Often the skin is atrophic and can tear and shear easily with minor trauma[2]. These ulcers usually heal rapidly.

(i). Pyoderma Gangernosum

This distinctive entity, characterized by acute necrotizing, rapidly expanding ulceration of skin with a typical undermined border. It can involve any cutaneous site but favours the abdomen and lower extremities. Lesions begin as erythematous papules that rapidly expand, becomes fluctuant and ulcerate. It is the continued rapid expansion of the lesions despite antibiotic therapy that helps in the diagnosis of pyoderma gangernosum. Lesions are often painful, heal with typical atrophic scar[36,37,38].

(ii). Felty's Syndrome

The association of R.A, granulocytopenia and splenomegaly is designated "Felty's Syndrome". Leg ulcers which are extremely refractory to therapy and therefore chronic, are a frequent feature of this syndrome. Ulcers are often at site of previous truma, few polymorphonuclear cells can be seen in samples taken from these lesions. Splenectomy is often necessary in the treatment of recurrent of intractable infection and/or chronic leg ulcers[39].

(iii). Vasculitic Ulcers

Vasculitis is an important cause of leg ulceration in R.A. In a recent series, vasculitis was considered to be a cause of leg ulcer in 18% of R.A patients[40].The skin may show purpuric and necrotic arteritic lesions which can be painful. The haemorrhagic areas appear without preceding trauma and vary in size from small petechiae of bruising and necrosis to several centimeters in diameter. Sometime, these areas develop blackish scars, which may breakdown and ulcerate. The ulcers are well defined with a surrounding bluish-red halo. Healing occurs with scarring and may be slow.

(iv). Venous & Static Ulcer

Venous leg ulcer occur particularly in women and is due to venus drainage disturbance. Their onset is related to dependency, immobility and difficulty in walking[41]. The legs become brawny with shiny skin.

(v). Pressure Ulcers

Debilitated patients with R.A are also subjected to risk of pressure sores because of immobility in bed or from the pressure appliances[42].

(4). AUTOIMMUNE BULLOUS DISEASES IN PATIENTS WITH RHEUMATOID ARTHRITIS

(i). Bullous Pemphigoid

Bullous pemphigoid (B.P) is an autoimmune bullous diseases and occurs particularly in the elderly. In this cutaneous disease, circulating complement fixing

immunoglobulins are directed against a constituent of the lamina lucida of the dermoepidermal junction zone. The first report of this association appeared in 1963[43]. While the association of B.P and R.A could occur by chance alone, it is interesting to speculate on mechanisms whereby a disease with documentable suppressor T cell dysfunction, such as R.A could be followed by a disease with anti-self directed antibodies as B.P.

(ii). Cicatrical Pemphigoid

Cicatricial pemphigoid (C.P) is a far less common variant of B.P, characterized by cutaneous and mucous membrane erosion which heal with scarring. In a report of four patients with coexistent C.P and R.A the authors speculated on a possible role for rheumatoid factor in initiating the autoimmune bullous disease[44].

(iii). Pemphigus Vulgaris & Pemphigus Foliaceus

Pemphigus vulgaris (P.V) and pemphigus foliaceus (P.F) are bullous diseases of autoimmune pathogensis with a high mortality in the pre-corticosteroid era. These diseases have been frequently reported in association with myasthenia gravis, thymona or patients treated with D-pencillamine for R.A or Wilson's disease[45,46]. The mechanism of induction of pemphigus by D-pencillamine, despite several theories, remains unknown[46,47]. Diaz et al postulated a break down in immune regulation to explain their findings in a patient with "multiple immune auto-reactivity"[48]

(iv). Dermatitis Herpetiformis

Dermatitis herpetiformis (D.H) an intensely puritic vesiculobullous disease has as association with secretory immunoglobulin I g A and bowel disease[49]. D.H has been reported in association with thyroid disease, systemic lupus erythematosus and ulcerative collitis, which may be related to HLA – B8 predisposition to autoimmune diseases in general[50]. D.H has been rarely reported in patients with R.A[51].

(v). Subcorneal Pustular Dermatosis

It is a distinctive condition first reported in England by Sneddon and Wilkinson in 1956[52]. Clinically these patients have fragile pustules, arranged in gyrate patterns, often around flexural surfaces and respond to sulfon class of medications (e.g; dapson). This disease in association with R.A has been reported[53,54].

(vi). Epidermolysis Bullosa Acquisita

It is an acquired bullous dermatosis with clinical features resembling the dystrophic forms of the mechanobullous disease, epidermolysis bullosa. The disease has been associated with an ever-enlarging group of disorders associated with autoimmune phenomena, including amyloidosis, thyroiditis, systemic lupus erythematosus, inflammatory bowel disease and R.A[55,56].

(5). MISCELLANEOUS CONDITIONS ASSOCIATED WITH RHEUMATOID ARTHITIS

(i). Rheumatoid Neutrophilic Dermatitis (R.N.D)

It is a rare cutaneous finding in patients with severe R.A or with high titre rheumatoid factor. Clinically firm erythematous papules or "urticarial-like" plaques distributed symmetrically on dorsa of hands, extensor aspects of the joints, back of neck and trunk, hips and proximal thighs. These are sometimes tender[57,58]. The lesions may be puritic leading to excoriations and crusts. Ulceration and vesiculation may occur. Vertical symmetrical infiltrated linear cords on the median axillary line have been reported[57]. Histology reveals

a dense dermal infiltrate with reutrophilic granulocytes, while leukocytoclasia may be seen, vasculitis is not observed. The pathogenesis of R.N.D is unclear, and few treatments are known[75].

(ii). Transparent Skin

Patients with R.A are well known to develop a generalized thinning of the skin which is most conspicuous over bony prominences particularly the metacarpal phalangeal joints[2]. It is most common in elderly and corticosteroid treated patients with rheumatoid disease even in steroid have not been used. Disuse or vasomotor instability have suggested as etiologic possibilities[59]. The clinical association of skin atrophy and osteoporosis has been recognized. Skin thickness and cortical bone thickness are directly related. These findings imply the presence of altered connective tissue metabolism and calcium balance in areas directly adjacent to chronic rheumatoid inflammation[60].

(iii). Yellow Skin

This has been shown to be due to inspissated sweat and is therefore removable by careful washing of the skin[61].

(iv). Hyperpigmentation

Generalized hyperpigmentation is poorly characterized in R.A patients, but is reported to occur occasionally[62]. It is more frequently a feature of juvenile R.A.

(v). Yellow Nail Syndrome (Y.N.S)

It is an unusual condition seen in patients with R.A and is characterized by a yellowish to greenish discoloration of the nails[63]. The structure of the nail is abnormal with a pronounced side to side curvature and a central hump. Ridging or onycholysis is sometimes evident and nail growth is extremely slow. Y.N.S in patients with R.A almost always is associated with peripheral edema and recurrent pleural effusions. Frequently bronchiectasis is also present[64]. There is no obvious possible mechanism to explain these associations. There is evidence of abnormalities of lymph drainage, perhaps related to ongoing vasculitis. The abnormalities of the nails may resolve with a sustained clinical remission or may persist indefinitely.

(vi). Palmer Erythema or Dawson's Palms

A vivid red discoloration of the palms – liver palms is a non – specific finding often present in R.A[2]. It is also present in chronic hepatic disease and is of unknown significance, but may be related to vasomotor instability. Raynaud's phenomenon is uncommon[65].

(vii). Erythromelalgia (erythermelalgia) or Labile Hyperthermia

It is a rare syndrome typified by pain in the extremities accompanied by objective evidence of increased blood flow (e.g; increased pulses, temperature, color) in response to heat exposure. Cases are labeled idiopathic or secondary erythromelalgia. Secondary cases have been reported with a number of systemic disorders, including systemis lupus erythematosus and R.A66. The patho-mechanism of erythromelalgia and its association with R.A are obscure.

(ix). Localized Hyperhidrosis of Palms and Soles

It has been rarely reported in association with R.A[67].

(x). Mondor's Disease

Mondor's disease, superficial thrombophlebitis of the chest wall, is an obscure condition rarely reported in patients with R.A[68].

(xi). Pustular Panniculitis

Extensive pustular panniculitis, particularly on the legs, may occur as a result of breakdown of red painful nodular lesions[69]. Histologic examination shows fat necrosis and neutrophilic dust in the subcutaneous tissue with surrounding fibrosis. This type of panniculitis may respond to dapsone and tetracycline.

(xii). Non-Inflammatory Purpura

It occurs frequently in patients with R.A. Capillary fragility may be increased due to systemic corticosteroid therapy or due to the thinning of the skin that occurs in R.A. Qualitative platelet defects can occur with nonsteroidal anti-inflammatory agents and could exacerbate the phenomenon[70].

(xiii). Miscellaneous

Patients with R.A may have any of the various reactive vascular dermatoses such as erythema multiforme, erythema nodosum, or urticaria either as a reaction to antirheumatic therapy or possibly simply in association with the R.A. The association of R.A with diseases of possible autoimmune pathogensis, such as vitiligo and alopecia areata need future investigations[70].

(6). OVERLAP SYNDROMES

Overlap syndromes between R.A and systemic lupus erythmatosus, dermatomyositis and/or scleroderma could present with cutaneous manifestations of any of the associated connective tissue – vascular diseases. Sjorgen's syndrome is another well-known association with R.A and keratoconjunctivitis sicca could result in periorbital cutaneous changes[70]. The patients with overlap synrome have the speckled type of anti-nuclear antibody together with a high titre of antibody to ENA (extractable nuclear antigen antibody) which is sensitive to digestion with ribonuclease (RNase) unlike the ENA antibody found in 50% of patients with SLE[71].

The presence of anti-RNP (ribonuclear protein) is usually associated with a good prognosis. In one series, the authors noted that 25% developed into SLE and a few patients with HLA – DR4 developed R.A[72].

(7). NAIL CHANGES IN RHEUMATOID ARTHRITIS

In addition to the nail changes seen in yellow nail syndrome[63], longitudinal ridging with beading is more common finding in patients with R.A than in controls in Hamilton as well as in Michal series[73,74]. Occasionally, infracts of the nail fold may result in grooving of the nail. Such lesions occurred in 34% of the males and 18% of females in 157 consecutive cases of R.A[75].

(8). RHEUMATOID ARTHRITIS & RISK OF CANCER

In one series, a follow – up study of cancer incidence in R.A was conducted within a cohort of 20,699 patients recorded in the Danish Hospital Discharge Registrar during 1977-87. There were consistent excesses of non – melanoma skin cancer. While risks for colorectal cancer and female breast cancer were reduced[76].

(9). CUTANEOUS CHANGES DUE TO DRUGS USED FOR RHEUMATOID ARTHRITIS

Details discussions cutaneous complications of anti-rheumatic therapy is not possible in this review. However there are some worth mentioning side effects of some anti-rheumatic drugs.

(i). Corticosterids

Many patients with R.A who have been treated with

steroids show typical purple discoloration of corticosteroid therapy. This mainly found on the posterior aspects of the forearms, although it may occur on the legs and elsewhere and is due to shearing of blood vessels in the dermis as the result of degeneration of the dermal collagen[77].

(ii). Methotrexate

Rheumatoid nodulosis is characterized by multiple small subcutaneous granulomatous nodules typically located on the elbow in nearly 20% of patients with R.A. Accelerated rheumatoid nodulosis especially involving the hands and feet has recently been reported in patients receiving methotrexate therapy for R.A[78]. Similarly large hemorrhagic and necrotic cutaneous lesions developed after two low dose (5 mg) methotrexate injections in a patient suffering from long standing R.A[79].

(iii). Gold

In one study, 77 patients with R.A were investigated for contact allergy to gold in connection with treatment with gold preparation[80]. Contact allergy to gold was demonstrated in 10.4% of patients. In order to avoid early hypersensitivity reactions, skin tests should be carried out before gold therapy is instituted.

REFERENCES

1. Williams R,C. Rheumatoid arthritis as a systemic disease. In: Internal Medicine IV. Philadelphia. WB Saunder, 1974, p.8

2. Fitz patrick TB, Eisen AZ, Wolff K et al. Skin Manifestations of rheumatic disease. In: Fitz patrick TB, et al, editors: Dermatology in General Medicine, New York, 1993. McGraw-Hill Book Co; p.2192.

3. Isdale IC, Bywaters EGL. The rash of rheumatoid arthritis and Still's disease. Q J Med 25: 377; 1956.

4. Calabro JJ Marchesano JM. Juvenile rheumatoid arthritis. N Eng, J Med 277: 296; 1967.

5. Moore CP, Wilkens RF, The subcutaneous nodule. Significance in the diagnosis of rheumatic disease. Semin Arthritis Rheum 7: 63-79; 1977.

6. Hurd ER. Extra-articular manifestations of rheumatoid arthritis. Semin arthritis Rheum 8: 151-76; 1979.

7. Hart FD. Rheumatoid Arthritis: Extra-articular manifestations. Br Med I 3: 131; 1964.

8. Dorfman HD, Norman A, Smith RJ. Bone Erosion in relation to sub-cutaneous rheumatoid nodules. Arthritis Rheum 13: 69-73; 1970.

9. Rapoport RJ, Kozin F, Machel SE, Jordon RE. Cutaneous vascular immunofluorescence in rheumatoid arthritis: correlation with circulating immune complexes and vasculitis. Am J Med 68: 321-31; 1980.

10. Morgon ES, Cass RM, Jocox RF et al. A study of relation of seronegative and seropositive rheumatoid arthritis to each other and to necrotizing vasculitis. Am J Med 47: 23; 1964.

11. Bluestone R, Goldberg LS, Cracchiolo A. Hidden rheumatoid factor in seronegative nodular rheumatoid arthritis. Lancet 2: 877; 1964.

12. Lowney ED, Simons HM. Rheumatoid nodules of the skin. Arch Dermatol 88: 853-8; 1963.

13. Ginsberg MH, Genant HK, Yu Tf et al. Rheumatoid nodulosis: an unusual variant of rheumatoid disease. Arthritis Rheum 18: 49-68; 1975.

14. Bury HC, Caughery DE, Palmer DG. Benign rheumatoid nodules. Aust NZJ Med 9: 697-701; 1979.

15. Ackerman AB. Histologic diagnosis of inflammatory skin disease. Philadelphia, 1978, Lea and Febiger, 415-31.

16. Mellors RC, Heimer R, Cercos J et al. Cellular origin of rheumatoid factor. J Exp Med 110: 875-86; 1959.

17. Munthe E, Natvig JB. Characterization of 1gG complexes in elutes from rheumatoid tissue. J Clin Exp Med 8: 249-62; 1971.

18. Munthe E. Immunofluorescence studies on rheumatoid

tissue. Symposium on immunology, Stockholm March, 1969. Acta Pathol Microbiol Scnad 77: 348-9; 1969.

19. Natvig JB, Munthe E. Self associating 1gG rheumatoid factor represents a major response of plasma cells in rheumatoid inflammatory tissue. Ann NY Acad Sci 256: 88-95; 1975.

20. Haln BH, Yardley JH, Stevenes MB. Rheumatoid nodules in systemic lupus erythematosus. Ann Intern Med 72: 49-58; 1970.

21. Kennedy C, Leigh IM. Systemic sclerosis with subcutaneous nodules. Br J, Dermatol 101: 93-6; 1979.

22. Dykman CJ, Galens GJ, Good AE. Linear subcutaneous bands in rheumatoid arthritis. Ann Intern Med 63: 134-40; 1965.

23. Jorizzo JL, Olansky AJ, stanley RJ. Superficial ulcerating necrobiosis in rheumatoid arthritis. A variant of the necrobiosis lipoidica-rheumatoid nodule spectrum? Arch Dermatol 118: 255-9; 1982.

24. Glass D, Soter NA, Schur PH. Rheumatoid vasuclitis. Arthritis Rheum 19: 950-2; 1976.

25. Scott DGI, Bacon PA, Tribre CR. Systemic rheumatoid vasculitis. A clinical and laboratory study of 50 cases. Medicine 50: 288-97; 1981.

26. Bywaters EGL, Scott JT. The natural history of vascular lesions in rheumatoid arthritis. J Chron Dis 16: 905-14; 1963.

27. Bywaters EGL. Peripheral vascular obstruction in rheumatoid arthritis and its relationship to other vascular lesions. Ann Rheum Dis 16: 84-103; 1957.

28. Schmid FR, Hamilton MG, Gill RS. Arteritis in rheumatoid arthritis. Am J Med 30: 56-83; 1961.

29. Pallis CA, Scott JT. Peripheral neuropathy in rheumatoid arthritis. Br Med J 1: 1141; 1965.

30. Lindsay MK, Tavadia HB, Whyte AS et al. Acute Abdomen in rheumatoid arthritis due to necrotizing arteritis. Br Med J 2: 592-3; 1973.

31. Sams WM Jr, Throne EG, Small P et al. Leukocytoclastic vasculitis. Arch Dermatol 112: 219-26; 1976.

32. Soter NA. Necrotizing vasculitis of the skin. In: Fitz patrick TB et al, editors: Dermatology in General Medicine. New York, 1993, McGraw Hill Book Co; 1501-10.

33. Golding JR, Hamilton MG, Gill RS. Arteritis of rheumatoid arthritis. Br J Dermatol 77: 207-10; 1965.

34. Katz Sl, Gallin JI, Hertz KC et al. Erythema elevatum diutinum. Skin and systemic manifestations, immunological studies and successful treatment with dapsone. Medicine 56: 443-55; 1977.

35. Winkelmann RK, Schroeter AL, Kierland RR et al. Clinical Studies of livedoid vasculitis (segmental hyalinizing vasculatis). Mayo Clin Proc 49: 746-40; 1974.

36. Stolman LP, Rosenthal D, Yaworsky R et al. Pyoderma gangrenosum and rheumatoid arthritis. Arch Dermatol 111: 1020-3; 1975.

37. Perry HD. Pyoderma gangrenosum. South Med J 62: 899-908; 1969.

38. Lazarus GG, Goldsmith LA, Rocklin RE et al. Pyoderma gangrenosum, altered delayed hypersensitivity and polyarthritis. Arch 105: 46-51; 1972.

39. Laszlo J, Jones R, Silberman HR et al. Splenectomy for Felty's syndrome: Clinicopathological study of 27 patients. Arch Intern Med 138: 597-602; 1978.

40. Pun YLW, Barraclough DRE, Muirden KD. Leg ulcers in rheumatoid arthritis. Med J Aust, 153: 585-7; 1990.

41. Wilkinson M, Kirk J. Leg ulcers complicating rheumatoid arthritis. Scott Med J 10: 175-82; 1965.

42. Reuler JB, Cooney TG. The pressure sore: Pathophysiology and principles of management. Ann Intern Med 94: 661-6; 1981.

43. Lillicrap DA. Rheumatoid arthritis and pemphigoid. Proc R Soc. Med. 56: 921-2; 1963.

44. Spigel GT, Win-Kelmann RK. Cicatricial pemphigoid and rheumatoid arthritis. Arch Dermatol 114: 415-7;

1978.

45. Tagami H, Imamura S, Noguchi I, Nishitani H. Co existence of peculiar pemphigus, myasthenia gravis and malignant thymona. Dermatologica 152: 181-90; 1976.

46. Ahmad R, Grahan J, Jordan R et al; Pemphigus: Current concepts. Ann Intern Med 29: 396-405; 1980.

47. Marsden RA, Ryan TJ, Vanhegan R I et al. Pemphigus foliaceus induced by penicillamine Br Med J 2: 1423-4; 1976.

48. Diaz LA, Glamb RW, Silva J. A syndrome of multiple immune autoreactivity. Arch Dermatol 116; 77-9; 1980.

49. Katz SI, Hall L, Lawly T, Strober W. Dermatitis herpetiformis. The skin and the gut. Ann Intern Med. 93: 857-74; 1980.

50. Callen JP. Internal disorders associated with bullous disease of the skin. J Am Acad Dermatol 3: 107-19; 1980.

51. Kalimo K. Rheumatoid factor in sera of dermatitis herpetiformis patients. Br J Dermatol 98: 79-83; 1978.

52. Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. Br. J, Dermatol 68: 385-94; 1956.

53. Olsen TG, Write RC, Lesten A I. Subcorneal pustular dermatosis and crippling arthritis. Arch Dermatol 115: 185-8; 1979.

54. Butt A, Burge SM. Sneedon-Wilkinson disease in association with rheumatoid arthritis. Br J Dermatol 132: 313-5; 1995.

55. Roenigk HH, Pearson RW. Epidermolysis bullosa acquisita. Arch Dermatol 117: 383; 1981.

56. Pearson RW. Some observations on epidermolysis bullosa and experimental blisters, in Montagna, Lobitz W editors: The epidermis New York, 1954, Academic Press Inc; 613-26.

57. Hirota TK, Keough GC, David BK et al. Rheumatoid neutrophilic dermatitis. Cutis 60(4): 203-5; 1997.

58. Sanchez JL, Cruz A. Rheumatoid neutrophilic dermatitis. J Am Acad Dermatol 22: 922; 1990.

59. McConkey B, Bligh AS, Fraser GM et al. Transparent skin and osteoporosis. Lancent 1: 693-5; 1963.

60. McConkey B, Fraser GM, Bligh AS. Transparent skin and osteoporosis. A study in patients with rheumatoid disease. Ann Rheum Dis 24: 219-23; 1965.

61. Spender JK. Some of the rarer complications of rheumatoid srthritis. Br Med J I: 905-7; 1982.

62. Bleehan SS, Ebling FJG, editors: Test book of dermatology, London, 1998, Blackwell Scientific publications, 1782.

63. Mattingly PC, Bossingham DH. Yellow nail syndrome in rheumatoid arthritis. Report of three cases. Ann Rheum Dis 38: 167-73; 1979.

64. Samman PD, Write WF. The yellow nail syndrome. Br J Dermatol 76: 153-7; 1964.

65. Carroll GJ et al. The prevalence of Raynaud's syndrome in rheumatoid arthritis. Ann Rheum Dis 40: 567; 1981.

66. Rayan TJ, Burnand K. Diseases of the veins and arteries. Leg ulcers, in Text book of Dermatology, 6th ed, edited by Rook et al. Oxford, Blackwell, 1998, 2236.

67. Dobson RL, Hyperhidrosis, in Demis DJ, Dobson RL, Mc Guire J, editors: Clinical dermatology, New York, 1981, Harper and Row, Pulishers inc., 9A-3,2.

68. Demis DJ. Mondor's disease (superficial thrombo phlebitis of the chest wall, in Demis DJ, Dobson RL, Mc Guire J, editors. Clinical dermatology; New York, 1981, Harper and Row, Publishers Inc., 7-35, 1-3.

69. Anstey A, Wilkinson JD, Wojnarowska F et al. Pustular Panniculitis in rheumatoid arthritis. J R Soc Med 84: 307-8; 1991.

70. Jorizzo JL, Daniels JC. Dermatologic conditions reported in patients with rheumatoid arthritis. J Am Acad Dermatol 8: 439-57; 1983.

71. Pettersson I, Wang G, Smith El et al. The use of immunoblotting and immunoprecipitation of small nuclear ribonucleoproteins in the analysis of sera of patients with mixed connective tissue disease and systemic lupus erythematosus. Arthritis Rheum 8: 986-

96; 1986.

72. Gendi NS, Welsh K I, van-Venrooij WJ et al. HLA type as a predictor of mixed connective tissue disease differentiation. Ten year clinical and immunogenetic follow up of 46 patients. Arthritis Rheum 38: 259-66; 1995.

73. Hamilton EDB. Nail studies in rheumatoid arthritis. Ann Rheum Dis 19: 167-73; 1960.

74. Michel C, Cribier B, Sibilia J et al. Nail abnormalities in rheumatoid arthritis. Br J Dermatol 137(6): 958-62; 1977.

75. Golding JR, Hamilton MG, Gill RS. Arteritis of rheumatoid arthritis. Br J Dermatol 77: 207-10; 1965.

76. Mellemkjaer L, Linet MS, Gridley G et al. Rheumatoid arthritis and cancer risk. Eur J Cancer 32A (10): 1753-7; 1996.

77. Rowell NR, Goodfield MJD, The connective tissue diseases, in Texbook of Dermatology 6th ed, edited by Rook et al. Oxford, Blackwell 1998, 2566-8.

78. Williams FM, Cohen PR, Arnett FC. Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. J Am Acad Dermatol 39: 359-62; 1998.

79. Simonart T, Durez P, Margauz J et al. Cutaneous necrotizing vasculitis after low dose methotrexate therapy for rheumatoid arthritis. A possible manifestation of methotrexate hypersensitivity. Clin Rheumatol 16: 623-5; 1997.

80. Moller H, Scensson A, Bjorkner B et al. Contact allery to gold and gold therapy in patients with rheumatoid arthritis. Acta Derm Venereol 77: 370-3; 1997.