Rheumatology

4

Oculocutaneous Manifestations of Rheumatic Diseases

Series Editor:
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Oculocutaneous Manifestations of Rheumatic Diseases

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With 53 figures and 9 tables

S. Karger · Basel · München · Paris · London · New York · Sydney 1973

Rheumatology

An Annual Review

Vol. 1: VIII + 243 p., 35 fig., 14 tab. (1967)
ISBN 3–8055–0619–8

Vol. 2: VI + 134 p., 15 fig., 43 tab. (1969)
ISBN 3–8055–0620–1

Vol. 3: VIII + 224 p., 10 fig., 2 tab. (1970)
ISBN 3–8055–0622–8

S. Karger · Basel · München · Paris · London · New York · Sydney
Arnold-Böcklin-Strasse 25, CH-4011 Basel (Switzerland)

Printed in Switzerland by Buchdruckerei Lüdin AG, Liestal
ISBN 3–8055–1594–4

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An Annual Review
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S. Karger · Basel · München · Paris · London · New York · Sydney

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Oculocutaneous Manifestations of Rheumatic Diseases
Rheumatology, vol. 4, pp. 1–12 (Karger, Basel 1973)

Introduction: Of Syndromes and Interfaces

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The inclusion of joint involvement segregates the rheumatic diseases from other multisystem disorders. The descriptive nosology reflects the bias introduced by making joint disease central to a rheumatologic appraisal of illness. Nevertheless, the majority of problems involving joints are strictly local phenomena, reflecting a wide variety of causes but generally unassociated with systemic disease. Among these are the degenerative and regenerative processes following single or repetitive mechanical traumata; stresses induced by alterations in alignment, postural and weight problems, and aging factors; and a host of alterations representing local reflections of metabolic disturbances. The unsatisfactory label, degenerative joint disease, which some still call osteoarthritis or osteoarthrosis, encompasses the majority of these disorders, including the joint diseases of ochronosis, chondrocalcinosis, and acromegaly. It has been estimated that almost everyone over 55 years of age evinces some features of osteoarthritis at least at some of his joints. When several joints are involved, as many separate mechanisms may underly the changes. Philip Wood [54] has cautioned against regarding these as diseases of the musculoskeletal system, as their concurrence may well be fortuitous, and they are not reflections of systemic disease (as generalized arteriosclerosis or the various enteropathies represent involvement of a system rather than of its isolated parts). The excitement generated by the description of generalized osteoarthrosis by Kellgren and Moore [28] reflected, in part, the desire of rheumatologists to think of disease in systemic terms rather than coincident isolated occurrences.

The minority of diseases – but a sizable minority – of rheumatologic concern are multisystem disorders, in which joint involvement represents part of the visible expression of the disease, although it is by no means

always necessary for diagnosis. The diseases in this group were named and recognized long before a relationship among them became apparent; the basic group includes rheumatoid arthritis, systemic lupus erythematosus (SLE), progressive systemic sclerosis, and polyarteritis nodosa. Later refinements have added dermatomyositis, Sjögren's syndrome, Behçet's syndrome, Goodpasture's syndrome, midline granuloma, Wegener's granulomatosis, Reiter's disease, Felty's syndrome, and other terms denoting frequent syndromic groupings. FEINSTEIN [14] has warned that these diagnoses, based on the preeminence of pathology in 19th century medical science, hamper our contemporary interpretations. The terms force us to categorize a patient's manifestations by one name, and to marvel that additional findings suggesting another such diagnosis are also present. Our classification thus creates a Procrustean bed and forces introduction of concepts of overlap or diffuseness of manifestations that may, in fact, not be justified.

The search for basic mechanisms underlying disease manifestations has fastened on immunologic clues. The path from *horror autotoxicus* to autoimmunity has at times developed a solipsismal inclination. The more recent appreciation that viruses may alter the process of self-recognition has led to theories of pathogenesis that begin with viral initiation and lead through antigen-antibody complexes, kinin activation, and elaboration of lysosomal enzymes responsible for inflammation to the ultimate production of autoimmune disease [3]. While these schemes of pathogenesis are nonspecific enough to account for the manifestations that can be appreciated clinically, they have thus far failed to explain the predilection for specific areas of the body by these diseases. Diseases that involve the joints so frequently also involve the skin, mucous membranes, eyes, blood-forming organs, and lympho-reticulo-endothelial system concurrently. Many medical reports clearly reflect the dichotomy between the descriptions of clinical expression with a failure to understand cause and the elaboration of causes without understanding the clinical expression. The need to classify either under an antiquated terminology has done most to impede appreciation of the problems.

For the rheumatologist, the propensity of a disease to produce arthritis is the unifying feature for a number of disorders. As for most other symptom complexes, the causes appear to be multifactorial. The correct interpretation depends on additional features. Involvement of multiple systems, demonstrable inflammation of small blood vessels, and immune responses implying alterations of self-recognition lend themselves to quantitative and qualitative assessment, and, when plotted along a curve, create a spectrum of disease

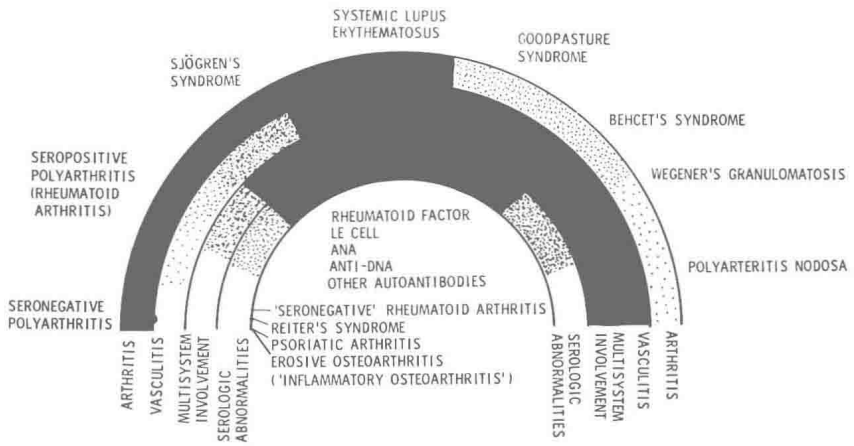

Fig. 1. The clinical spectrum of rheumatic diseases.

(fig. 1). Such a spectrum, while holistic in concept, implies neither a single cause nor a common pathogenesis. Instead, it suggests that the clinical manifestations in appropriate mixes permit syndromic diagnosis, rather than giving rise to speculations of overlap and new diseases[1].

At the beginning of the spectrum, polyarthritis alone, without associated manifestations in the other spheres, but of truly inflammatory nature, permits inclusion of what are now called seronegative rheumatoid arthritis, inflammatory osteoarthritis, Reiter's syndrome, and psoriatic arthritis. Of course, Reiter's syndrome and psoriatic arthritis are accompanied by waxing and waning skin changes, mucosal lesions, and transient ocular phenomena; major serologic abnormalities are lacking, as generally is involvement of internal organs. However, with rare exceptions, they appear to represent concurrent phenomena of limited extent rather than multisystem diseases. Seronegative rheumatoid arthritis [2] represents a quarter of the patients who bear the diagnosis of rheumatoid arthritis, and differs sufficiently in course and prognosis to warrant being thought of as a separate syndromic grouping. Inflammatory osteoarthritis [10] implies the acute onset of polyarthritis of small joints of the hands, frequently with associated arthritis at other joints, which results ultimately in degenerative features called erosive osteoarthritis on the basis of roentgenographic demonstrations. In a signifi-

1 A schema based on proportions of angiitis and granulomatosis, and related to autoimmune features, adumbrating several of these disorders, was also proposed by ALARCON, SEGOVIA and BROWN [Proc. Staff Meet. Mayo Clinic *39:* 205–222, 1964].

cant minority, further inflammation of joints and tendon sheaths and serologic and roentgenographic evidence permit the supposition that rheumatoid arthritis has supervened [11]. The proportion of patients so involved (15.3%) suggests a possible role in pathogenesis for the earlier inflammatory osteoarthritis.

Seropositive rheumatoid arthritis differs from seronegative rheumatoid arthritis by the demonstration of rheumatoid factor in the serum. But multisystem involvement, a more deforming arthritis, serum protein abnormalities, and vasculitis (usually localized to rheumatoid nodules and synovium) also develop. When the serologic abnormalities become multiple, and the clinical manifestations include abnormalities in all the mucous and serous glands, the name, Sjögren's syndrome, has been applied. Sjögren's syndrome, however, is obviously only quantitatively, not qualitatively, different from seropositive polyarthritis. Excluding the sicca syndrome (the abnormal secretion of mucous and serous glands, especially in the eye and mouth), the clinical features of Sjögren's syndrome are also remarkably similar to those of SLE, with which it was often identified in earlier writings [23]. While it is obviously a mistake to think of patients who have the manifestations of Sjögren's syndrome as facing the same prognosis generally ascribed to SLE, it may also be incorrect to marvel at the concurrence of features commonly used for segregation of these syndromes [19, 43] (note the use of the term syndrome, as the absence of proven causation and the difficulty to draw exact boundaries should enjoin us from thinking of these disorders as proven diseases). The fact that SLE may present with dramatic inflammation of the salivary glands, seemingly acute, and that the roentgenographic and histologic investigation of these glands discovers chronic features usually identified with Sjögren's syndrome is only one example of this difficulty of clinical segregation [27]. In this schema, Sjögren's syndrome represents the interface between seropositive polyarthritis (RA), in which morbidity is a greater worry than mortality, and SLE, in which mortality is the greater worry. This spectrum also permits inclusion of those patients whose responses to treatment add additional features of multisystem involvement and vasculitis to their diseases; most notable are those patients with seropositive polyarthritis who are treated with corticosteroids [20]. A similar interface between the complex diagnosis of SLE and an illness characterized predominantly by clinical features resulting from polyvasculitis – polyarteritis nodosa – may be represented by Behçet's syndrome. This disorder, which only lately has been included among the connective tissue disorders, seems to represent a stage between SLE and polyarteritis nodosa.

There may still be some who think of Sjögren's syndrome as a rare disorder, featuring dryness of the eyes and mouth, and accompanying an arthritis not unlike classical rheumatoid arthritis. They may recognize in it Mikulicz's disease, identified as visible parotid swelling accompanying sarcoidosis. A modern concept of Sjögren's syndrome [7] is far broader, and includes many features formerly segregated into the diagnoses, RA and SLE, with features liberally borrowed from other so-called autoimmune disorders. As will be seen in later chapters, keratoconjunctivitis sicca and xerostomia are still the most important diagnostic features, the former confirmed by slit lamp examination after rose bengal or fluorescein staining and the Schirmer tests [13], the latter by measuring the amount of saliva secreted in 5 min into a cup placed over the opening of the parotid duct, before and after stimulation of the gland by paraffin-chewing, or by sialography [36] or technetium scintigraphy [51]. However, other mucous and serous glands throughout the body are involved as well. Nasal dryness and crusting reflects similar dryness or abnormal secretion in the larynx and tracheobronchial tree. Bronchiectasis and pulmonary fibrosis may follow. Atrophy of the oesophogeal mucosa is found [25]. Achlorhydria and achylia are characteristic [48, 53]; nevertheless, these are patients who not only are likely to be treated with corticosteroids but are likely also to develop gastric ulceration during such treatment. Atrophy afflicts rectal and vaginal mucosa as well, in the latter case resulting in dyspareunia. In the skin, appendages may atrophy, resulting in patchy alopecia, dryness, and pruritus [16]. Purpuric lesions and Raynaud's phenomenon suggest vascular involvement, and peripheral neuropathy, especially mononeuritis multiplex, results from ischemia produced by vasculitis of nutrient vessels of nerves [51]. Myopathy is usually focal [8]. While interstitial nephritis usually represents an incidental finding [47], an occasional patient develops renal tubular acidosis [41, 46]. Accompanying these lesions is an arthritis generally described as indistinguishable from classic rheumatoid arthritis, often with mutilating features, and accompanied by rheumatoid nodules. However, the arthritis is not an essential feature of the syndrome [7].

Lymphoproliferative features include splenomegaly, hepatomegaly [22], generalized lymph node enlargement, and subacute thyroiditis of the Hashimoto variety [52]. Biopsy of lesions, especially of the salivary glands, discloses aggressive lymphocytosis [5, 45]. Their benignity is suggested by their confinement to glandular tissue; discrete extraglandular infiltrates bear the diagnosis pseudolymphoma, and if they display malignant features, lymphoma [21]. Dysproteinemia characterizes all patients bearing the diagnosis

of Sjögren's syndrome [17], and macroglobulinemia may be found on the malignant end of the spectrum [21]. It is not surprising, therefore, that a greater proportion of patients bearing the diagnosis of Sjögren's syndrome have rheumatoid factor in their serum than do patients bearing the diagnosis of rheumatoid arthritis, and that antibodies against nuclei, thyroglobulin, salivary duct cystoplasm, smooth muscle, skeletal muscle, gastric parietal cells, adrenal cortex, and mitochondria can also be found [17]. Any combination of anemia, leukopenia, and thrombocytopenia is possible, and an absolute increase in eosinophils is not unusual. Liver function tests are often abnormal, especially as they reflect protein synthesis, and malabsorption is reflected by deficiency of folic acid or vitamin B_{12} [49].

What contribution immunosuppressive agents, including the corticosteroids, make to the development of malignant lymphoproliferative disease is still moot. The severity of manifestations makes it likely that many patients will have received corticosteroids at some time during the course of the disease. Azathioprine seems to speed development of lymphoma in New Zealand Black mice [4], which are predisposed to connective tissue diseases terminating in lymphoma; a similar progression has been described in human patients treated with azathioprine for SLE or Sjögren's syndrome [21]. The causal role of azathioprine has been inferred by analogy and has yet to be proved.

In rheumatoid arthritis, the extra-articular features, awesome as they may be, are hubristically relegated to second place behind the striking articular manifestations by rheumatologists. Some very similar extra-articular manifestations achieve priority in the description of SLE, where the articular lesions are often of a lesser order. Sjögren's syndrome straddles both these diagnostic groupings.

Behçet's disease, known at least since the time of HIPPOCRATES, has recently attracted increasing attention. It, too, will be discussed in greater detail later. The oral ulcers, multiple ophthalmologic lesions (involving almost every anatomical portion of the eye), and genital ulcers, in conjunction, are considered diagnostic [6, 34]. A multitude of skin lesions, from pyoderma to erythema nodosum, may be found. However, the underlying vasculitis is reflected in gangrenous lesions of acral projections, and in migratory thrombosis of small and large veins. Inflammatory disorders of the central nervous system form part of the syndrome. Rheumatic symptoms range from arthralgias and myalgias to marked synovitis, usually without destructive lesions of the joints [32]. A wide variety of mucosal antibodies may be found [31], although tests for rheumatoid factor, antinuclear anti-

bodies, and LE cells generally are negative. The similarity of some of the lesions to Reiter's syndrome [9], others to SLE, and others still to polyarteritis nodosa has prompted its recent inclusion among the connective tissue diseases [6, 30], as a syndrome on the bridge between SLE and polyarteritis nodosa.

Wegener's granulomatosis and midline granuloma have more in common with polyarteritis nodosa, and Goodpasture's syndrome with SLE. There is no organ in the body that may not be involved by the majority of the disorders in this catalogue. Involvement may range from the subclinical, demonstrable only at *post mortem* examination (as pericarditis in many cases of rheumatoid arthritis and pancreatitis in Sjögren's syndrome) [24] to profound destruction (as of lung and kidney in Goodpasture's syndrome) [33].

Of particular interest is the observation that small lymphocytes and related cells, reticulum cells and plasma cells, and their products, are demonstrably increased except at the seronegative end of this disease spectrum. Lymphocytic aggregates and plasma cells capable of producing rheumatoid factor are found in the synovium in rheumatoid arthritis. Aggressive lymphocytic infiltrates populate the salivary glands in Sjögren's syndrome [50]. Relative lymphocytosis and a variety of immunoglobulins can be demonstrated throughout the central portion of this spectrum, and lymphocytic cuffs around small blood vessels in polyarteritis nodosa. A possible relationship to other lymphoproliferative diseases has therefore been hypothesized. In the NZB mouse, an animal bred to develop a disease resembling human SLE, the early administration of immunosuppressive drugs, presumably by interfering with the immune surveillance mechanism, results in malignant lymphomata. Human patients bearing established diagnoses of Sjögren's snydrome seem to be more susceptible to development of pseudolymphoma and reticulum cell sarcoma [7]. Patients receiving immunosuppressive therapy may be made more susceptible to malignant disease [13]. A laboratory model of Sjögren's syndrome was produced by crossing NZB mice with NZW F′ mice, resulting in spontaneous development of histopathologic and autoimmune features that are characteristic of the human syndrome [28a].

The first patient in whom heavy chain disease was diagnosed was found to have parotid gland infiltrates of small lymphocytes and reticulum cells, and reticulum cell infiltrate was seen in the base of a small ulcer on the posterior aspect of the tongue [18]. He developed a disease resembling lymphoma, a pattern subsequently found in other patients bearing this diagnosis. Subcategorization suggests that γ-chain disease results in rapidly

progressing lymphoma, α-chain disease in diffuse lymphosarcoma of the intestinal tract [39], and μ-chain disease in chronic lymphocytic leukemia [29]. The similarity of some of the clinical manifestations to connective tissue disorders has not gone unnoticed. A sequential relationship of heavy chain disease to rheumatoid arthritis has already been discovered [55]. The dread that immunosuppressive therapy currently being employed experimentally and in some cases, strictly therapeutically, for the treatment of the more rapidly progressive connective tissue diseases and rheumatoid arthritis may hasten the development of lymphomata is based on the above observations [42].

There is no longer much question that immune mechanisms participate in the pathogenesis of the lesions of these syndromes. An incomplete catalogue of such observations would include the LE cell, RA cell, and the Reiter's cell; serum hypocomplementemia in SLE, and a low level of complement in pleural fluid [26]; anticomplementary activity in SLE and rheumatoid arthritis, and low complement levels in synovial fluid in rheumatoid arthritis. Rheumatoid factors, antinuclear antibodies, antibodies against DNA in SLE and against extractable nuclear antigen in 'mixed connective tissue disease' [40], antithyroid and antisalivary antibodies in Sjögren's syndrome [15], antibodies against oral and esophogeal mucosa in Behçet's syndrome, and demonstrable selective elevations of the various immunoglobulins in any of the disorders, are further examples. Serologic abnormalities in relatives of patients so afflicted have raised the question whether similar environmental exposure or hereditary factors are responsible. Twin studies are currently attempting to answer that question. The occurrence of syndromes resembling SLE in mothers of children with chronic granulomatous disease, an inherited defect of leukocyte function, raises the possibility that viral invasion in the parent produces this genetic change [38]. Leukocyte bactericidal defects have also been described in lipochrome histiocytosis, which is sometimes accompanied by an illness resembling rheumatoid arthritis [35]. Similarly, a supposed lipid storage disease, multicentric reticulohistiocytosis, has clinical features suggestive of rheumatoid arthritis [12]. Altered sensitivity to infection is also a feature of hypogammaglobulinemia, in which state an illness resembling rheumatoid arthritis is likewise common. The search for infective agents, the relationship to lymphoproliferative disorders, and the systemic investigation of immunoglobulins thus far overshadow other studies and theories of the mechanisms of pathogenesis.

In many respects, the current theories are the legitimate descendents of the humoral theory of disease still atavistically present in the terms rheuma-

tism, rheumatic, rheumatoid, and rheumatology (rhea-flow). The four basic humours were supposed to be blood, bile, black bile, and mucus, whose altered relationship produced disease, and whose dropping (gutta-drop) produced gout. While no longer adhering to these antiquated concepts, we do accept the possibility that macroglobulins plugging end arteries might result in some of the lesions we have considered.

As later chapters will demonstrate, tissue-fixed antibodies can be found in many of the lesions of all the disorders associated with immune features in figure 1, in the basement membrane of skin, in the glomeruli, suspected around retinal blood vessels, in the synovium and the choroid plexus [1], and in other target organs. Sometimes, inclusions that can be interpreted as 'viral footprints' are found in conjunction, although there is no general agreement what these imply [44]. The advocates of viral initiation of Behçet's disease are losing ground to those who see it as a non-viral vasculitis. We have thus come full cycle to the beginning. There is hope, however, that better clinical definitions will result in more promising correlations with underlying mechanisms. The addition of malignant lymphoproliferative disorders to the spectrum of benign lymphoproliferation elucidated above would be in accord with the views tabulated by ANDERSON and TALAL [7]. This volume, then, raises the questions and collates the known data that relate the eyes, skin, and oral and genital mucosa to the syndromes of rheumatologic interest. It can be hoped that the explanations for these remarkable concurrences will not be far behind.

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