Rheumatoid Arthritis: an Immune Disease in Search of an Etiology

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ABSTRACT

The current knowledge of the immunologic and etiologic factors which play a role in rheumatoid arthritis is reviewed and extrapolated to the systemic effects of rheumatoid disease. The disease process is viewed as the incidental result of an atypical immuno-inflammatory mechanism initiated by an unidentified antigenic stimulus.

Introduction

Rheumatoid arthritis with its associated systemic manifestations is one of the unusual disorders of man in which the process leading to the clinical symptoms is reasonably well understood, but the initiating cause remains unknown. The typical manifestations of rheumatoid disease, recurrent joint inflammation leading to destructive joint changes, are associated with a variable incidence of nonarticular pathology. General, nonspecific manifestations such as low-grade fever, tachycardia, weight loss, anemia, generalized lymphadenopathy and splenomegaly are suggestive of a chronic inflammatory process. Reflections of these general alterations are found in common laboratory evidence which may include a normochromic, normocytic anemia, increased erythrocyte sedimentation rate, decreased concentration of serum albumin and elevation of the concentrations of the serum globulins, especially of the immunoglobulins.

More specific types of non-articular disease may be widely distributed: (1) granulomatous subcutaneous nodules reminiscent of similar nodules in a variety of immunologic diseases and in experimentally-induced immunologic reactions are relatively common. In severe cases, such reactive processes can be found in almost any organ; (2) acute vasculitis, which may involve arteries or veins, is occasionally found and may lead to vascular obliteration and obstruction to blood flow; (3) painful neuropathy with either burning paresthesia or local anesthesia is a feature of active disease; (4) various pulmonary lesions, including pleurisy with effusion, chronic interstitial fibrosis and a massive reactive form of pneumoconiosis (Caplan’s syndrome) have been associated with progressive rheumatoid arthritis; (5) the eye may be the site of a keratoconjunctivitis of a dry or sicca type similar to that found in Sjogren’s syndrome; (6) renal lesions may develop of either a vasculitis type or a form of proliferative glomerulo-nephritis, mainly of endothelial cells; (7) amyloidosis is a common feature of almost all cases of chronic rheumatoid disease; (8) a specific constellation of abnormalities is seen in Felty’s syndrome: rheumatoid arthritis, splenomegaly with neutropenia and leg ulcers; (9) apart from
the specific joint manifestations of rheumatoid arthritis, a separate skeletal entity primarily involving the bones of the hand in an osteoporotic process to the point of disappearance of the bony tissues (osteolysis) may evolve; and (10) inflammatory disease of the aortic valve ring leading to aortic insufficiency is occasionally seen as a severe clinical problem in association with joint disease.

The existence of such a wide range of tissue and organ involvement serves to emphasize the fact that the pathogenetic process is not restricted to the classical joint problems and demands that the disease be examined from a more generalized point of view than has been the usual case to date. The dramatic crippling effects of joint involvement have attracted the major attention of investigators, and a large body of significant information has been accumulated by study of the joint components. For an understanding of the generalized phenomenon of rheumatoid disease, the data obtained from the study of the joints must be susceptible of extrapolation to explain the pathogenesis of the nonarticular lesions.

Immunological Factors

The existence of a group of pathologic lesions in rheumatoid disease similar to those seen in natural and experimental immunologic injury have led to an intensive study of the immunologic factors involved in their development. Vasculitis, "fibrinoid necrosis," lymphoid hyperplasia and the granulomatous nature of subcutaneous and, occasionally, of visceral nodules have suggested that the evolution of the disease may be based upon an immunopathologic mechanism. However, it is becoming clear that the lesions and their immunologically definable components probably do not represent the initiating phenomenon. Rheumatoid disease can now be considered as a two-phase process: an initiating event followed by a group of atypical immunologic reactions which result in tissue damage which are incidental by-products of the immunologic process.

Serious investigation into the immune status of rheumatoid disease began with the discovery of an agglutinatable protein in the serum of rheumatoid patients by Waaler. In discussing the Rheumatoid Factor (RhF), the caution was included by Waaler that the RhF was not found in all cases of rheumatoid arthritis, although it was considered to be the critical agent of the disease. With the development of methods of increased specificity and sensitivity for the detection of RhF, seropositivity was demonstrated in a much higher percentage of cases that Waaler had originally found. The RhF is now definable as the IgM anti-γ-globulin detected by agglutination procedures. The variations of immunoglobulin classes with anti-γ-globulin activity requires a careful distinction among them to discriminate the classic RhF activity. Varieties of RhF immunoglobulins are discussed elsewhere. Seropositive rheumatoid arthritis refers to patients whose serum contains the usual IgM rheumatoid factor. The specific activity of RhF is directed against denatured IgG.

Consideration of the immunologic features of rheumatoid arthritis demands not only the identification of the reactants in the process, but also must include their relationship to the pathologic process in situ. The application of the immunoflourescent antibody technique to rheumatic disease led to the identification of reaction components in rheumatoid synovia: fibrin, fibrogen, fibrin combined with IgG and weak IgM staining, fibrogen-fibrin degradation products, IgG and IgM singly or in combination, complement or complement components and nucleoprotein. Differences in the distribution of IgM, including that portion of IgM having RhF activity, and IgG were noted in the tissues.

IgG DEPOSITION

Regarding IgG deposition, it is present in abundance with lesser amounts of, and occa-
sionally no, IgM. It is a major component of early rheumatoid synovitis in children and in adults with seronegative disease, in which case little or no IgM is detectable. Complement, when found, is consistently associated with IgG but not with IgM alone. IgG-complement deposition is found extracellularly, in and about blood vessels, sometimes associated with deposits of nucleo-protein and in type A (phagocytic cells) of the synovium.

**IgM DEPOSITION**

On the other hand, IgM deposition in synovia is seen only in adult, seropositive disease, is present with lesser amounts of IgG, and is seldom coupled with complement. Within the extracellular tissue of the synovium, amorphous deposits of RhF, usually in combination with IgG, can be found. Plasma cells found in rheumatoid synovia contain either IgG or IgM. Lymphoid cells in the inflammatory reaction do not stain positively for IgM.

**IMMUNOGLOBULIN**

In view of the large amount of immunoglobulin found in rheumatoid joint tissues, the source of the immunoglobulins has been the subject of study. Smiley et al showed that the rheumatoid synovium itself could synthesize immunoglobulins at a rate similar to that of lymph nodes and spleen. Seventy-nine percent of the immunoglobulin was IgG and the rest was either IgM or IgA. Less than 10 percent of the locally synthesized IgM had anti-γ-globulin specificity.

The local immunoglobulin synthesis apparently accounts for less than 25 percent of the total IgG in the joint and may represent an immunoglobulin produced against a specific antigen.

**LIGHT CHAIN COMPOSITION**

The IgG recovered from rheumatoid joints has a unique molecular structure with a light chain composition differing from that of IgG recovered from peripheral blood, suggesting that it arose from a different source by a process unique to the joint tissues and not shared by other immunoglobulin synthesizing tissues.

The light chain difference is distinct from the differential agglutinability of IgG's by RhF, a reaction which is dependent upon the Gm subgroups of IgG. The Gm determinants are confined to the γ heavy chain of IgG. The site of reactivity of RhF with IgG is on the γ chain and in the Fc papain digestion fragment.

It has been shown that denatured aggregated IgG is the material which reacts with RhF. Henney and Stanworth suggested that rupture of interchain disulfide bonds in the Fc portion of the IgG molecules during the denaturation process leads to new intermolecular bridges, aggregation and to exposure of reactive sites for RhF coupling.

**PHENOMENA ASSOCIATED WITH IgG**

The two phenomena, aggregation of IgG and complexing of aggregated IgG with RhF, have different results. Macroaggregates are relatively nontoxic and are removed by lymphatic drainage, whereas minimally aggregated IgG combined with RhF fixes complement and remains in the joint. Evidence for complement participation in the reaction is found both in the identification of complement in deposits in the synovium and in phagocytosed deposits in synovial fluid leukocytes and the remarkable depression of complement concentration in rheumatoid joints as compared with serum complement concentration and with complement concentration in non-rheumatoid joints. Aggregated IgG of itself does not fix complement, whereas aggregated IgG fixes complement in seropositive (RhF containing) plasma. The fixation is proportional to the concentration of RhF.

The immunologic events in rheumatoid joints can be related to the inflammatory and destructive process. The ingestion of im-
immune complexes by phagocytic cells of synovial origin (type A) and by leukocytes results in the release of lysosomal enzymes from these cells which have a variety of destructive activities directed against the synovial and joint cartilage tissues (neutral proteases, acid protease, collagenases). Furthermore, the complement activation portion of the system is chemotactic for leukocytes, amplifying the response of these cells and increasing the levels of released leucocytic lysosomal enzymes. Contributing to the acute joint problem are kinins, lymph node permeability factor (LNPF), histamine and 5-hydroxytryptamine, all powerful bioactive mediators of the inflammatory process and all present during the active phase of the joint disease.

JOINT CHANGES

The mass of information regarding the immunologic-inflammatory-destructive process in rheumatoid joints has given rise to several proposals to explain the relationships among the observations. The proposals are summarized by Zwaifler. The synovial membrane is structurally an ideal site for an immune response, containing lining phagocytic cells and a vascular stroma. Antigens localized in the articular cavity stimulate the production of antibodies which combine in the synovial membrane or synovial fluid and activate the complement sequence, generating biologically active substances including some potent chemo-tactic agents. These latter agents draw polymorphonuclear leucocytes into the joint where they ingest the immune complexes. In the process, the chemotactic agents release a variety of hydrolytic enzymes which induce the destructive and proliferative joint changes characteristic of rheumatoid arthritis. The generation of an immune IgM directed against aggregated, denatured IgG results in RhF-IgG complexes as well as IgG-antigen complexes. The reason and mechanism of the IgG denaturation process in vivo is not clearly understood.

Extrapolation of Joint Findings to Systemic Rheumatoid Disease

The immunologic events indicated by studies of joint synovia and fluids can serve as a starting point to visualize the pathogenesis of the non-articular manifestations of rheumatoid disease. Should aggregated IgG or RhF complexed with IgG appear in the general circulation as soluble complexes, their fate can be predicted to be similar to that of other soluble immune complexes. Vascular wall deposition or deposition in connective tissue could induce changes comparable to those seen in Arthus-type reactions. The component analysis of rheumatoid vasculitis and glomerulonephritis suggests that the complement-bound immunoglobulins may be the basis for these reactions.

The regular appearance of amyloidosis in chronic rheumatoid arthritis probably represents deposition of excess immunoglobulin fragments. Electron microscopic studies of amyloid do not demonstrate any substantial difference among amyloids from rheumatoid arthritis and other chronic immunologically-associated diseases.

GRANULOMATOUS LESIONS

The granulomatous lesions of rheumatoid arthritis pose a more difficult problem. In this case, it must be assumed that there is a cell-mediated immune response in addition to the humoral-type response so well demonstrated in the joints. Two hypotheses can be offered: (1) the cell-mediated response is one directed against the atypical antibody complexes of rheumatoid disease, much as RhF is a humoral response to denatured aggregated IgG; and (2) the cell-mediated response is directed against an as yet unidentified antigen which is the common denominator for both the humoral and the cell-mediated immunity. Evidence to support either of these propositions is weak. A satisfactory answer to this question must also account for the depression of cell-
mediated immunity against classical antigens in chronic rheumatoid arthritis.

ANEMIA

The existence of anemia can be explained by either a nonspecific infectious anemia or as an autoimmune anemia owing to the association of antigen with red-cell surface or of aggregates of IgG with red-cell membranes. Autoimmune activity is a common feature of rheumatoid disease. A large number of isoantibodies are present in rheumatoid sera including antinuclear antibodies, antibodies to heart antigens, reticulin, kidney, prostate, skin and other organs. On the other hand, human red cells coated with immune globulin agglutinate when exposed to RhF, a system which does not require specific anti-erythrocyte antibody. The elucidation of this phenomenon requires further study. Similar arguments can be made in the case of the neutropenia of Felty’s syndrome.

Either the anemia or neutropenia may be interpreted as related to the splenic and lymphoid tissue enlargement by virtue of the clearing mechanism of these structures for damaged cells. To this should be added the lympho-proliferative process which accompanies the stimulation of systemic immunoglobulin synthesis.

Etiologic Agents in Rheumatoid Disease

There is little evidence that a virulent, contagious organism is the inciting agent for the induction of the complex immunodestructive processes of rheumatoid disease. Attention has rather been drawn to organisms of low pathogenicity or of a commensal type which might be able to induce the immune process in a small percentage of the total population at risk. Such an agent must be able to produce disease in only the human host. The implication is that the human is either the only natural host for the agent or that the human is uniquely capable of mounting the aberrant immune reactions resulting in rheumatoid disease in response to a more widely distributed agent.

Infectious agents under suspicion include viruses, L-forms of bacteria, mycoplasmataceae and intracellular bacterial parasites. Viral infections can produce an inflammatory arthritis, but the question of low-pathogenicity viral induction of rheumatoid disease is difficult to assess. The ubiquitous distribution of viral particles in human cells has confounded attempts to identify a relationship between these particles and the disease.

Isolation of mycoplasmas from rheumatoid joint fluids has been reported on several occasions but has not been found consistently. Some isolates did not grow on subculture; others showed a wide variety of types. As common tissue contaminants, they suffer from the same problems as do tissue viral particles in any attempt to assign them an initiating role.

Pleomorphic gram-negative organisms resembling diphtheroids have been isolated from a small percentage of joints with rheumatoid arthritis, with the implication that they represent L-forms of a corynebacterium. Otherwise unidentified intra-cellular structures presumed to be microorganisms have been seen in the endothelial cells of synovial vessels. There is some doubt regarding their nature.

Summary

The evolution of rheumatoid disease can be explained on the basis of an immunopathologic process in which the usual tissue insult is directed against joint tissues but which may also become generalized to the rest of the body. The initial cause remains unknown, although a number of infectious agents have been suggested as possible initiators of the process. The pathologic damage appears to be a non-specific process incidental to an immunologic response to an as yet unidentified antigen. It is a peculiar type of reaction in that
it appears to be a primary immune response almost indefinitely prolonged.

References


