

Clinicopathological Conference: *Complications of Rheumatoid Arthritis*

Discussants:

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CLINICAL RECORD

This 61 year-old white male was admitted to the Medical College of Virginia Hospital on 10/29/64 for further treatment of rheumatoid arthritis.

History

He had had severe arthritis for approximately 14 years. Joint symptoms had begun in his right shoulder with pain, swelling, and redness, and had gradually progressed to involve numerous joints. He did not require medication initially, but approximately four years after the onset of symptoms, he needed medication for relief of pain and deformity. He was treated initially with salicylates and later, with prednisone and Butazolidin. He had been hospitalized in 1961 because of severe muscle pain in his left lower leg. Physical examination then showed a blood pressure of 180/110, pulse 80 per min, and temperature, 98 F. The chief positive physical findings were limited to the extremities and included arthritic changes in the carpal-metacarpal joints of both hands and stiffness in both knees. Dorsalis pedis pulses were good, and the lower extremities showed some hyperemia and warmth. There was loss of muscle strength in the upper and lower extremities, and a loss of vibratory sense in the toes.

All tendon reflexes were present.

Laboratory work in 1961 showed hemoglobin 16.2 g/100 ml, white cell count 18,350/mm³ (88% polymorphonuclears, and 12% lymphocytes). The latex test was reactive. Two LE cell preparations were negative. Total proteins were 6.3 g/100 ml (albumin 3.1, and globulin 3.2 g/100 ml). Serum transaminase was 18 units. Serum uric acid was 5.8 mg/100 ml. Sheep cell test for rheumatoid arthritis was positive with a titer 1:220, and a sensitized human cell test was positive, with a titer of 1:1280. The spinal fluid protein was 40 mg/100 ml, and a cell count revealed 1 lymphocyte; CSF pressure was normal. Muscle testing showed extensive loss of strength in the leg and foot, and an electromyogram showed almost complete denervation of all muscles supplied by the left common peroneal nerve. There was early evidence of degeneration of the right common peroneal nerve. An electrocardiogram was negative. It was felt at this time that the patient had an acute exacerbation of rheumatoid arthritis and an associated prednisone-induced neuropathy. The patient gradually responded to treatment with intramuscular injections of gold, salicylates, heavy sedation, and physical therapy.

He had been doing quite well until about four weeks before the present admission, when he had an

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exacerbation of his arthritis and became bedridden with severe joint pain. He complained of poor appetite, weight loss and weakness. Two weeks before admission he had developed cough, fever, and sore throat, for which he was admitted to another hospital and treated with antibiotics, including chloramphenicol. He was subsequently transferred to Sheltering Arms Hospital.

Physical Examination

Blood pressure 124/80, pulse 80/min, temperature 98 F, and respiration, 20 breaths/min. He was malnourished and pale. He was lying rigidly in bed, unable to move without pain. There were numerous decubitus ulcers on the occipital protuberance. The fundi revealed an increase in the tortuosity of vessels, with some narrowing. The neck was quite rigid. The mucous membranes of the mouth were dry. The chest was clear to percussion, but breath sounds were diminished throughout and there were moist rales at both bases. The heart was not enlarged to palpation. There was venous distention over the abdominal wall. The liver edge was palpable at the costal margin. The extremities showed severe arthritic deformities. There were "swan neck" deformities of the fingers and ulnar deviation bilaterally. There were bilateral ulnar rheumatoid nodules. The wrists, knees and ankles were swollen bilaterally, and motion was limited in both shoulders. There were multiple small, skin erosions over the bony prominences and large decubitus ulcers over the heels, ankles, sacrum, elbows, upper arms, wrists and back of the head.

Laboratory Data

Hemoglobin 9.0 g/100 ml, hematocrit 29%, MCV 97, MCH, 30; MCHC, 31; white cell count 4,900/mm (40% neutrophils, 1% eosinophils, 53% lymphocytes, and 6% monocytes). A urinalysis was

normal. Blood sugar was 108 mg/100 ml and BUN was 114 mg/100 ml. Serum electrophoretic pattern showed a marked decrease in the albumin, but there was no evidence of an abnormal globulin spike. Repeated blood cultures were negative. Stools were negative for blood on one occasion.

Upon transfer to MCV for rehabilitation therapy, the physical examination was unchanged. Laboratory work showed a hemoglobin of 6.5 g/100 ml. Examination of the peripheral smear revealed normocytic, normochromic red cells with adequate platelets and slight toxic changes in the granulocytes. A bone marrow aspirate showed a) a marked erythroid hypoplasia; b) plentiful myeloid elements, with an increase in promyelocytes, a few myeloblasts, and many megakaryocytes; c) plasmacytosis, with a few binucleated, trinucleated, and multinucleated cells and a rare one showing flame cytoplasm, and d) moderate increase in R-E and mitotic cells. A urine culture on 12/2/64 grew *Klebsiella-Aerobacter* group in a concentration of over 1,000,000 organisms/ml. X-ray of the chest showed minimal degenerative changes in the dorsal spine but the lungs were clear bilaterally and the heart was thought to be of normal size. An electrocardiogram showed non-specific T-wave changes.

Physical therapy was instituted with passive and active range of motion exercises while in the Hubbard tank. Attempts were made to clear up the decubitus ulcers. The patient was unable to cooperate sufficiently in the performance of his exercises as the slightest movement caused him to cry out with pain. He received several transfusions and was placed on chloramphenicol, but continued to run a fever. Physical therapy had to be discontinued because of increasing pain which was only partially relieved by aspirin. He was unable to eat without choking, and fluids were necessary. His temperature rose to

103 F on 12/6/64. He grew progressively weaker, coughed more but was less and less able to expectorate. He expired on 12/7/64.

CLINICAL DISCUSSION

Dr. P. Franklin Mullinax: After suffering for many years with arthritis, this patient was hospitalized because of severe leg muscle pain and was found to have a peripheral neuropathy with both sensory and motor involvement. Laboratory studies revealed leukocytosis, hyperglobulinemia, and high titers of rheumatoid factors. Four years later, an exacerbation of arthritis left him bedridden. At the time of hospitalization, he was severely debilitated and had multiple decubitus ulcers, skin hemorrhages, pronounced deformities and rheumatoid nodules. Clearly, he had advanced rheumatoid arthritis with widespread articular and extra-articular involvement.

Fortunately, rheumatoid arthritis usually takes a milder, more reasonable course. Before commenting further on this patient's disease, I shall summarize certain features of the natural history of rheumatoid arthritis. Up to 20% of persons will, at some time in their life, have episodes of polyarthritis, probable rheumatoid arthritis. Most of these, because of the mildness of their disease, or because of psychic strength, will never consult a physician. In patients with disease severe enough to require hospitalization, the prognosis is not so sanguine. Follow-up studies of 250 patients hospitalized for treatment of rheumatoid arthritis revealed that 10 years later, 53% were improved, 13% were unchanged and 34% were worse (Short, Bauer and Reynolds, 1957). Patients evaluated 20 years after the initial hospitalization were graded as follows: 35% improved; 27% unchanged; 63% worse.

It is usually said that rheumatoid arthritis cripples but doesn't kill. Actually longevity is decreased in

patients with rheumatoid arthritis, particularly in those with onset before the age of 25. A 30-year follow-up showed that one-third of rheumatoid arthritis patients had died, whereas, in a control population, only 13% had died. Prominent causes of death were pneumonia, chronic pyelonephritis, and nephrolithiasis. Occasionally patients die from lesions more specifically associated with rheumatoid arthritis, particularly granulomas of the heart, generalized arteritis, and amyloidosis. I believe that the patient being discussed today had at least one of these more specific complications of rheumatoid arthritis.

We can, to a certain degree, identify the persons who are going to develop the severe lesions of rheumatoid arthritis. These are the patients who have rheumatoid nodules, high titers of rheumatoid factors, unremitting disease for over two years, and onset in the later decades.

Rheumatoid factors and their possible involvement in the vascular lesions of rheumatoid arthritis are worthy of note. You will recall that the rheumatoid factors are, usually, 19S macroglobulins which act like antibodies to normal 7S γ -globulin. The 19S rheumatoid factors can combine with the 7S γ -globulin and form a heavy (22S) complex. Recent experimental work emphasizes the role of antigen-antibody complexes in causing vascular lesions. It is possible that the 22S and heavier complexes in rheumatoid sera are similarly responsible for vascular lesions (Baum et al., 1964). Rheumatoid factors can be evoked experimentally in rabbits by repeated injections of killed *E. coli* (Abruzzo and Christian, 1961). How or why these rheumatoid factors appear is not known.

I have suggested that the rheumatoid factors may be involved in the vasculitis of rheumatoid arthritis. I believe that the vascular lesions are not an occasional occurrence found only in patients with

severe disease, but rather that vasculitis may underlie all the lesions of rheumatoid arthritis, even the mildest of synovitis. Evidence for this concept was presented by Sokoloff and Bunim (1957). Putting these thoughts together, I have assembled a tentative concept (table 1) of the pathogenesis of rheumatoid arthritis. According to this view, chronic, but at present, inapparent, infection stimulates in an unknown way the formation of rheumatoid factors; these in turn combine with γ -globulin and produce complexes which precipitate, drop out of the circulation, and produce vasculitis. When the complexes are deposited in smaller vessels such as those in the synovium, local vasculitis and synovitis appear. With involvement of larger vessels, a picture reminiscent of polyarteritis nodosa ensues. This schema is based on some facts, as well as on speculation. The facts are that high titers of rheumatoid factors are associated with severe, unremitting disease, and that the heavier complexes are seen in the sera of patients with the more severe disease. The suggested interrelations are speculative.

Four years prior to his terminal admission, this patient had a severe motor neuropathy, as shown by electromyographic evidence of virtually complete denervation of muscles supplied by the left common peroneal nerve. From a diagnostic point of view, this is the central event in the patient's illness. The occurrence of motor neuropathy in a patient with severe arthritis who is receiving steroids is highly suggestive of active arteritis of a degree sufficiently great to be pathologically described as polyarteritis (Irby et al., 1958; Bleehe et al., 1963). Again, I would simply say that this represents an intensification of the usual arteritis which is the hallmark of rheumatoid arthritis. Once this widespread arterial involvement occurs, one can expect that extensive, including visceral, lesions will develop

(Schmid et al., 1961).

I am suggesting that rheumatoid arthritis is one of the causes of polyarteritis and that this was the problem in the present case. Table 2 presents a classification of polyarteritis. Anatomically, Rose (1957) has simply classified cases into those with or without lung involvement. Polyarteritis with lung involvement is characterized by eosinophilia and granulomas, particularly along the respiratory tract, whereas cases without lung involvement are not.

For years we have heard much of hypersensitivity and arteritis. It is, therefore, reasonable to further classify polyarteritis into lesions caused by antigen-antibody interactions and complexes, and those that are not. Unfortunately we are not yet able to say in which patients with lesions of polyarteritis are the antigen-antibody complexes the responsible agent.

Table 3 shows the sites affected in cases of polyarteritis without lung involvement. The patient under discussion obviously had involvement of muscle, joint, nerves and skin. Inexplicably, rheumatoid polyarteritis usually does not involve renal vessels.

Our patient had many problems associated with splenic enlargement: rheumatoid arthritis with high rheumatoid factor titers, pronounced arteritis, and possibly amyloidosis. I wonder if the spleen was not enlarged.

Amyloidosis, secondary amyloid, is found in up to 40% of patients with rheumatoid arthritis. The amyloid deposits may not be responsible for significant clinical disease, but the deposits are frequently found around smaller vessels. This case presents several features which lead me to suspect amyloidosis, and I suggest that minor lesions of amyloid, possibly visible only with the crystal violet stain, will be found at autopsy. First, he had long-standing rheumatoid arthritis. Second, the bone marrow specimen revealed pronounced involvement or stimula-

tion of his reticuloendothelial system and marked plasmacytosis, together with the serum globulin abnormalities. Finally, decubitus ulcers with chronic infection are among the most common causes of amyloidosis.

Though there is a great deal of overlap, it is generally true that secondary amyloidosis involves the liver, spleen, and particularly the kidneys, whereas primary amyloidosis involves heart, tongue, peripheral nerves and gastrointestinal tract. There is usually rather marked proteinuria, which this patient did not have. Hypertension, usually not present with amyloid renal disease, can even disappear subsequently to amyloid involvement. Out patient's hypertension did go away.

I should spell out what I believe to be the essence of the logic in this particular case history. A patient with severe rheumatoid arthritis developed a profound motor neuropathy. This occurrence strongly suggests arteritis of the vessels supplying that nerve. When an arteritis occurs, it can be reasonably predicted that arteritis and granulomas will occur elsewhere. There is little in the case history that requires postulation of lesions other than those of rheumatoid arthritis.

In summary then, I suggest that this patient had malignant rheumatoid arthritis with arteritis and granulomas of that disease; and that he had clinically insignificant deposits of amyloid.

Dr. W. Robert Irby (associate professor of medicine, MCV): I first saw this patient in July, 1961. At that time I thought he had peripheral neuropathy associated with steroid-treated rheumatoid arthritis. I was able to get him off the steroids and he left the hospital on salicylates. I did not see him again until November, 1964, when he was in his terminal illness. The anemia, abnormal plasma cells, and severe bone pain, suggested multiple myeloma, but I could not substantiate that diagnosis.

TABLE 1
Pathogenesis of Rheumatoid Arthritis (? ? ?)

1. Microbial infection (viral or bacterial)
→ → rheumatoid factors
2. Rheumatoid factors (19S) + normal
γ-globulin ⇌ complex (22S)
3. Complex → arteritis
4. Arteritis → synovitis, granulomas

TABLE 2
Classification of Polyarteritis

- A. Anatomic
 - 1) With lung involvement
 - 2) Without lung involvement
- B. Pathogenetic
 - 1) Caused by antigen-antibody complexes
 - 2) Not caused by antigen-antibody complexes

TABLE 3
Polyarteritis Without Lung Involvement:
Incidence of Affection of Other Sites*

Organ or System	% of Cases
Gastrointestinal tract	70
Liver	54
Muscle	46
Joints	27
Spleen	12
Peripheral nerves	36
Skin	27
No lesions post mortem	15
*Rose, 1957	

Dr. John H. Moon: Dr. Mullinax, you equated the rheumatoid factor with the production of arthritis, but I recall that Harris and Vaughan (1961) transfused sera with high titers of rheumatoid factor into normal individuals without demonstrable change.

Dr. Mullinax: There is a great argument not only in relation to diseases of hypersensitivity, but in immunology in general, as to the role of circulating anti-bodies in the production of delayed hypersensitivity (tuberculin-like) reactions. It was long thought that delayed sensitivity could not be transferred by serum and that, therefore, circulating antibodies are not involved. There is suggestive evidence now that one can effect such a transfer, but one needs a chronic perfusion. For instance, in the tuberculin reaction, one needs a perfusion of skin for two days. If Harris and Vaughan had perfused into the patient the equivalent of the amount of blood that would flow through in two days, then I would be convinced that they had done a conclusive experiment.

Dr. Elam C. Toone (professor of medicine, MCV): In reaching the opinion about the animals' receiving the *E. coli*, how was the rheumatoid factor determined? Did these animals develop a polyarthritis? Was the rheumatoid factor determined by the latex, the sensitized human cells, sheep cells, or electrophoretic pattern?

Dr. Mullinax: The rheumatoid factor determinations were done by several serologic techniques, including F 11 latex, sensitized sheep cells, and tanned sheep cells coated with a variety of γ -globulins, and γ -globulin precipitations and absorptions. All were positive. The reactive materials were exclusively macroglobulins. The lesions, which were not described, were said to be compatible with serum sickness. No arthritis was described.

Dr. Toone: I think chronic symmetrical polyarthritis is more germane to the diagnosis of rheuma-

toid arthritis than the presence of the rheumatoid factor. It is quite important to know how the factor was detected, because the tests vary in sensitivity and specificity. I feel that the rheumatoid factor probably appears after the polyarthritis, since we see patients with full-blown rheumatoid disease in whom the factor tests may remain negative for weeks or even years. A recent report by Dixon (1960) is pertinent to this point. In his summary, the following statements are made: "Sixty-one in-patients with severe, active polyarthritis associated, with a persistently negative sheep cell agglutination test (S.C.A.T.) for rheumatoid arthritis are reviewed. The average duration of follow-up was 5.4 years. Of the 61 patients reviewed, twelve were found at follow-up to have developed a positive S.C.A.T. All but two of these had distribution of arthritis typical of rheumatoid arthritis and six developed subcutaneous nodules. The course of their arthritis was not different from that seen in 23 patients in whom the arthritis was also typical but in whom the S.C.A.T. remained negative. Both mild and severe end-results were seen. A persistently negative S.C.A.T. was compatible with typical rheumatoid arthritis of progressive course and fatal outcome. Eleven patients had proven or probable diseases other than rheumatoid arthritis. . . . Eight patients showed a persistently negative S.C.A.T. (sheep cell test) and an atypical arthritis."

Other entities such as liver disease, bacterial endocarditis, etc., may produce the rheumatoid factor. Recently, we have found that of 20 patients who received kidney transplant, 14 (66%) developed evidence of rheumatoid factor, and only one developed a chronic polyarthritis which might have been of the rheumatoid type (Waller et al., 1965). Dr. Marion Waller has had a patient under observation for six or eight years who has had rheumatoid factor in high titer and in whom there has been no evi-

dence of rheumatoid arthritis or any other disease. This is just to illustrate that we really do not know the relationship of rheumatoid factor to either the cause or effect of the disease.

Clinical Diagnosis

1. Rheumatoid arthritis
2. ? Multiple myeloma
3. ? Septicemia
4. ? Steroid-induced gastric ulcer
5. ? Amyloidosis

Dr. Mullinax's Diagnosis

1. Malignant rheumatoid arthritis
2. Amyloidosis, mild

PATHOLOGIC DISCUSSION

Dr. Page Hudson: Most of us certainly do not think of rheumatoid arthritis as a fatal disease. When the term is mentioned we consider it only as an entity that involves peoples' joints. But, as Dr. Mullinax has pointed out, it involves vessels and connective tissues. Thus, every tissue, every organ in the body can be involved. Still rheumatoid arthritis is not a "fatal" disease ordinarily.

When confronted with the problem of death or a sudden severe illness following a "non-fatal" disease, we should consider five possibilities;

- 1) development of a different and unrelated disease;
- 2) emergence of a natural complication;
- 3) predisposition to another disease;
- 4) complication of therapy; or
- 5) reaching the "end of the spectrum."

For specific examples, first, this patient may have developed multiple myeloma which, as far as we know, is unrelated to rheumatoid arthritis. After all there were, as Dr. Irby reminded us, severe bone pain, anemia, and abundant, abnormal plasma cells. Secondly, amyloid is a well-recognized com-

plication of rheumatoid arthritis. Thirdly, due to the severe debilitation, secondary bacterial or fungal infection may have supervened. Next, complications of therapy are becoming more generally recognized. There are distinct hazards in the use of steroids, gold, Butazolidin, and even aspirin. Physical therapy is not without some danger in patients with rheumatoid arthritis. Fat and bone marrow embolism from manipulative procedures have caused death (Rosenberg et al., 1944; Gleason and Aufderheide, 1953). The fifth possibility is that the patient may have had an extreme form of the recognized disease. He might have been at the end of that spectrum of degrees of severity that all illnesses display.

The latter situation was the most likely one to Dr. Mullinax. He was quite correct except that the patient did not have amyloidosis.

The gross findings at autopsy were striking. The pericardial sac looked like white cake-icing and was tenaciously adherent to the heart (fig. 1). It was thick and hard, but not calcified. Pleural adhesions were marked over both the emphysematous lungs. The muscles were exceedingly pale and atrophic. The bones were soft and osteoporotic. Fibrous plaques with soft centers were apparent in the pleura, peritoneum, and other cavity lining membranes, including synovia. The spleen and lymph nodes were enlarged.

Dissection of the heart revealed greatly thickened, milky-white mitral valve leaflets and chordae tendineae. The distal thirds of the papillary muscle were extremely scarred. Despite these changes, the mitral valve and size of the cardiac chambers suggested that there had not been prominent functional mitral disease.

Microscopically, there was perivascular fibrosis in the heart as is often seen in inactive rheumatic fever. In addition, there were large aggregates of plasma cells in the papillary muscles, perhaps stuffed

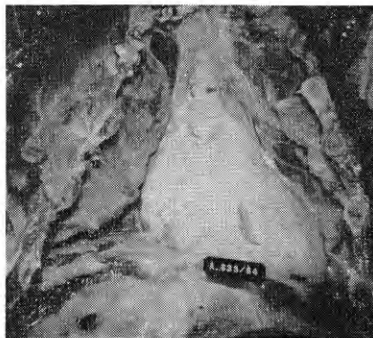


Fig. 1—The heart was encased in thick, white partly fibrous and partly gelatinous pericardial sac. The sac was totally adherent to the epicardium. There was no clinical evidence of constrictive heart disease.

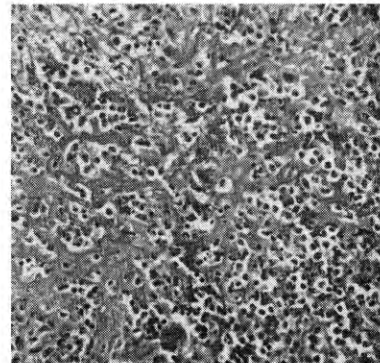


Fig. 3—Rheumatoid nodules from the epicardium; the radially oriented palisaded fibroblasts surround fibrin, inflammatory cells and necrotic debris (H&E, 100 \times).

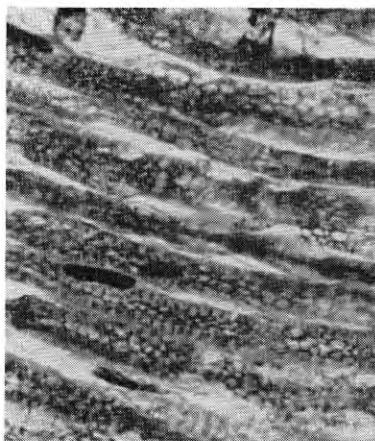


Fig. 2—Peripheral nerve showing myelin degeneration which gives the cytoplasm a foamy appearance. Multiple minute foci of lymphocytes were also seen about small vessels in nerve bundles (H&E, 450 \times).

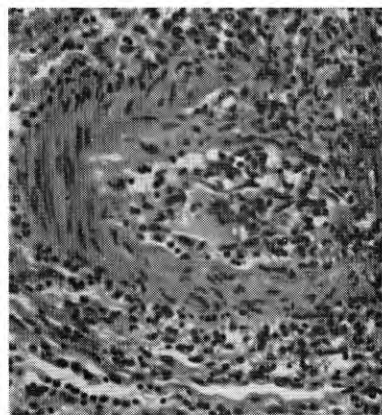


Fig. 4—Mesenteric artery showing partial destruction and almost complete occlusion. The intense inflammatory infiltrate consists of lymphocytes, eosinophils, polymorphonuclears, plasma cells and macrophages (H&E, 160 \times).

with Dr. Mullinax's "19S macroglobulin." Classical acute rheumatoid nodules were present in the epicardium, mitral valve, wall of the aorta, and in the right coronary artery which had been completely occluded by the reaction and superimposed thrombus. Recanalization of the coronary had occurred. No old infarct was seen. Cardiac lesions are relatively common in rheumatic arthritis patients, many of whom have no clinically discernible heart disease (Schoene and Risse, 1964). Some of the lesions are similar to those of rheumatic fever.

The terminal event was respiratory insufficiency due to a combination of chronic aspiration pneumonia and emphysema, with pulmonary fibrosis and mild interstitial pneumonia. Perhaps, too, limitation of pulmonary excursion by the massive adhesions was a factor. Recall that he was hospitalized elsewhere with pneumonia before his terminal admission here. A review of his last record at our hospital reveals, particularly from the nursing notes, the difficulty he must have had in swallowing. We can account for this by the myelin loss and inflammatory changes seen in many sections of nerve (fig. 2) including the glossopharyngeals and recurrent laryngeals. Also the muscles of deglutition revealed degenerative changes. In addition, sections of brain revealed occasional intense vasculitis and foci of encephalomalacia. Foreign body reaction around aspirated vegetable fibers was seen in all lung sections. Foci of acute and chronic inflammation within and about countless bronchioles were visible. Alveolar walls were thickened and fibrotic.

Pulmonary fibrosis and interstitial pneumonitis have frequently been described in cases of rheumatoid arthritis (Brannon et al., 1964). They do appear to be slightly more common in these patients than in patients with other chronic diseases. Possibly excepting "Caplan's nodules" seen in silicosis with rheumatoid arthritis, there is nothing really

approaching a specific pulmonary parenchymal alteration in this disease. The classic rheumatoid nodules (fig. 3) may be seen on the pleural surfaces and in the interlobar fissures. This is a different matter and was marked in this case. These well-known nodules were widespread in the peritoneum, joints, and subcutaneous tissue as well as in the pleura, pericardium, and vocal cords.

Continuing the description of the generalized disease, there was a mild acute glomerulonephritis with swollen glomeruli, enlarged cells, and thickened basement membranes. That this condition was of recent onset was suggested by the lack of clinically detected renal disease. In addition to glomerulonephritis, renal lesions that have been noted in the other cases include amyloidosis, phenacetin-induced interstitial nephritis with or without papillary necrosis, and segmental parenchymal damage secondary to vasculitis (Allander et al., 1963).

The bloody diarrhea the patient suffered was due to ulcerations caused by focal mesenteric vasculitis affecting both arteries and veins but particularly the smaller arteries (fig. 4). This complication of rheumatoid disease was apparently only recently described (Adler et al., 1962).

In addition to the plasma cells taking part in cellular infiltrates in many tissues, the bone marrow contained vast numbers of those antibody and rheumatoid factor producing cells. This is seen in many severe chronic diseases, particularly the granulomatous and autoimmune diseases, both terms being applicable to rheumatoid arthritis. Bi- and tri-nucleate plasma cells and other atypical forms may be seen in conditions where there is a stimulant to plasma cell formation.

Despite the extent of the disease in this patient, he did not have scalp or meningeal lesions which are also occasionally seen. He was also spared scleromalacia perforans, another sometime complication.

In conclusion, our patient demonstrated the most extreme, diffuse, and malignant form of rheumatoid arthritis. At the "end of the spectrum" of clinical and morphologic disease, he expired with respiratory insufficiency.

Pathologic Diagnosis

1. Rheumatoid arthritis, severe, with involvement of multiple organs and tissues.
2. Pulmonary insufficiency, with aspiration pneumonia, interstitial fibrosis, emphysema, and massive chronic pleuritis.

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