DEFORMING POLYARTHROPATHY WITH EXCESS DEPOSITION OF CHOLESTEROL

Report of a Case

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THE accumulation of cholesterol in rheumatoid nodules is well recognized.[1-4] However, there heretofore has been no report of deforming polyarthropathy in association with cholesterol in nodules and, in addition, with cholesterol-containing pleural and joint effusions, deposition of cholesterol in synovial membranes, and normal concentration of serum cholesterol. The above-mentioned lesions and mild hepatic cirrhosis of the postnecrotic type occurred in a patient who will be described and discussed in this report.

Case Report

A 54-year-old white man had been in good health until the age of 39 years when, after a severe, acute, infectious illness that had been diagnosed as pericarditis with effusion, he developed severe pain with redness, warmth, and swelling in nearly all of the joints. The acute illness subsided within six weeks, but joint manifestations persisted and were characterized by exacerbations and remissions that resulted in synovial and periarticular thickening, tendon contracture, ankylosis, subluxations, and atrophy of adjacent muscles of the hands, wrists, elbows, knees, ankles, and feet. He had been unable to work since the onset of illness in 1939.

Ten years after the onset of illness (1949) he was first admitted to the Cleveland Clinic Hospital. At that time he had pain, swelling, and tenderness of the fingers, wrists, elbows, shoulders, jaws, ankles, and feet, and mild blurring of vision. Extension of both wrists was limited to 20 degrees and there was a 15-degree flexion deformity of the right elbow. Moderate effusion was present in each knee joint and there was pain on motion. Nodules were present over the extensor surfaces of the wrists, elbows, and sacrum. The eyes showed mild patchy injection of the bulbar conjunctivae bilaterally, which was thought to represent scleritis. A roentgenogram of the chest revealed multiple nodular densities throughout both lung fields and a pleural reaction at the base of the right lung, associated with effusion (Fig. 1). Thoracentesis produced 650 ml. of cloudy yellow fluid

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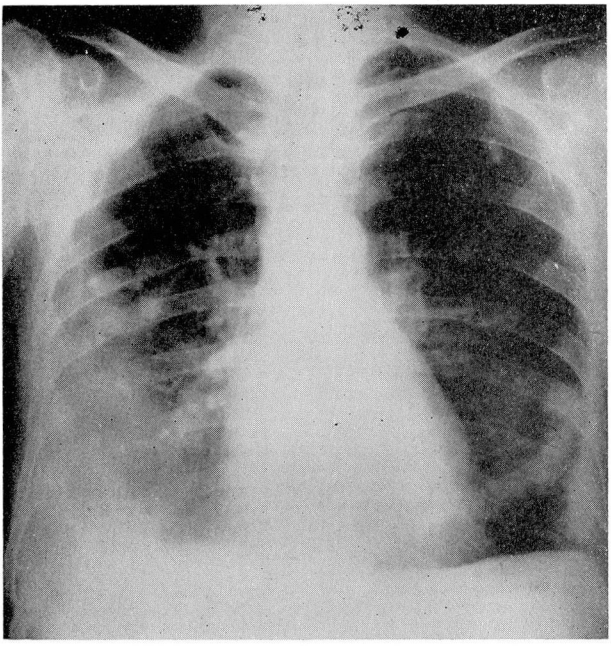


Fig. 1. Roentgenogram of chest in 1949.

that contained cholesterol crystals and fat globules. The protein content was 2.6 gm. per hundred milliliters. Direct smears and cultures were negative for tubercle bacilli and other organisms. Skin tests for histoplasmosis and coccidiomycosis were negative. The tuberculin skin test (Purified Protein Derivative # 1) was positive.

Other laboratory findings were as follows: Blood hemoglobin 11.0 gm. per hundred milliliters; red cell count 4,140,000 and white cell count 4,300 per cu. mm. with a differential count of 58 per cent neutrophils, 37 per cent lymphocytes, and 5 per cent eosinophils. No abnormalities were noted on routine urinalysis. The total serum protein was 7.1, with albumin 2.6 and globulin 4.5 gm. per hundred milliliters. Blood urea content was 13.6, blood uric acid 2.5, serum calcium 13.2, and serum phosphorus 3.5 mg. per hundred milliliters. Serum cholesterol was 136 mg. per hundred milliliters, and sedimentation rate was 0.45 mm. per minute (Rourke-Ernstene method[5]). Treatment consisted of physiotherapy and sodium salicylate 4 to 6 gm. daily. He was discharged from the hospital with minimal objective improvement.

On January 4, 1955, he was readmitted to the hospital because of progression of the arthritis and failing vision. At this time he was able to walk only short distances in the house. Mild activity resulted in swelling of both knees and the right ankle. In addition to the failing vision he noticed yellow plaques in both sclerae that were increasing in size. A mild, morning cough productive of a small amount of white sputum first appeared in the summer of 1954, and it persisted to the time of this examination. Exertional dyspnea, present for years, had increased during the past year.

Physical examination revealed a man who appeared chronically ill. The skin was pale except for bilateral palmar erythema. The conjunctivae were injected bilaterally

and elevated with large yellow plaques that extended to within 2 mm. of the limbus. Slit-lamp examination revealed an irregular ring of corneal opacities from the limbus to 2 or 3 mm. into the cornea. Superficial and deep vascularization was present. The fundi revealed many fine vitreous floaters in the media. The discs were flat and of good color. There was diminished expansion of the chest bilaterally with dullness and decreased breath sounds at the base of the left lung. Dullness and absence of sounds were noted over the lower two thirds of the right lung field. Examination of the heart revealed the left border of cardiac dullness to be 8.0 cm. from the midsternal line. Heart tones were normal. The veins were flat and the peripheral pulses were full and equal. There was one-plus pitting edema of the feet and ankles. The pulse rate was 100 per minute and regular, and the blood pressure was 110/70 mm. Hg. The liver was smooth and was palpated 3 cm. below the right costal margin in the midclavicular line. The spleen and kidneys were not palpable. Advanced arthritic changes, manifested by subluxation and ulnar deviation of the fingers, and almost complete ankylosis of both wrists with interosseous atrophy were present (Fig. 2). There were 15-degree flexion contractures of

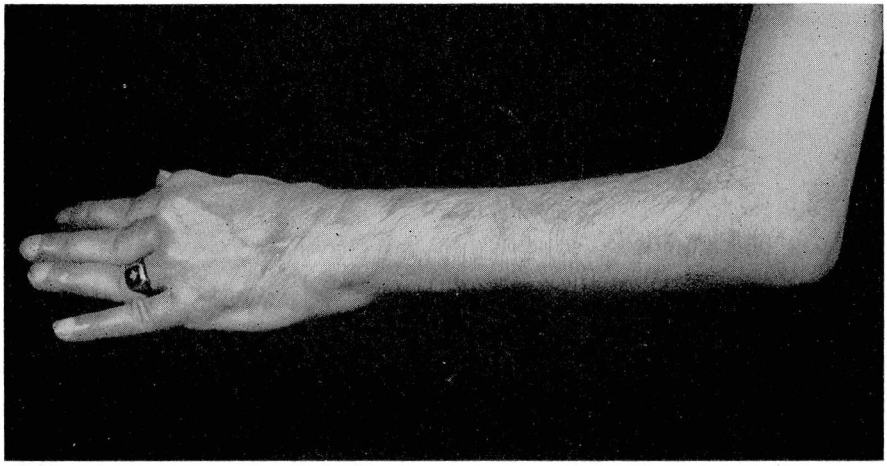


Fig. 2. Advanced arthritic changes and multiple nodules in the hand and wrist, 1955.

both elbows, and nodules were present on the extensor surfaces of both elbows and wrists. There was pronounced synovial thickening of both knees with bilateral effusion and severe atrophy of both quadriceps muscles. Both ankles were tender to light pressure, and moderate periarticular swelling was noted. There was tenderness, moderate synovial thickening, and subluxation of the metatarsal phalangeal joints. The dorsolumbar spine was almost completely ankylosed, and nodules were present over the sacrum.

A roentgenogram of the chest on January 5, 1955, revealed rounded nodular densities scattered throughout both lung fields; the densities were in the same distribution as they had been in 1949, although they appeared slightly smaller and contained areas of calcification (Fig. 3). There was some increase in size of the density in the lateral part of the base of the left lung. The density at the right costophrenic angle was unchanged. Roentgenograms of both knees showed pronounced narrowing of the joint spaces with evidence of demineralization, as well as localized erosion and cystic changes, adjacent to the articular cortex (Fig. 4). The wrists were markedly demineralized and there was nearly

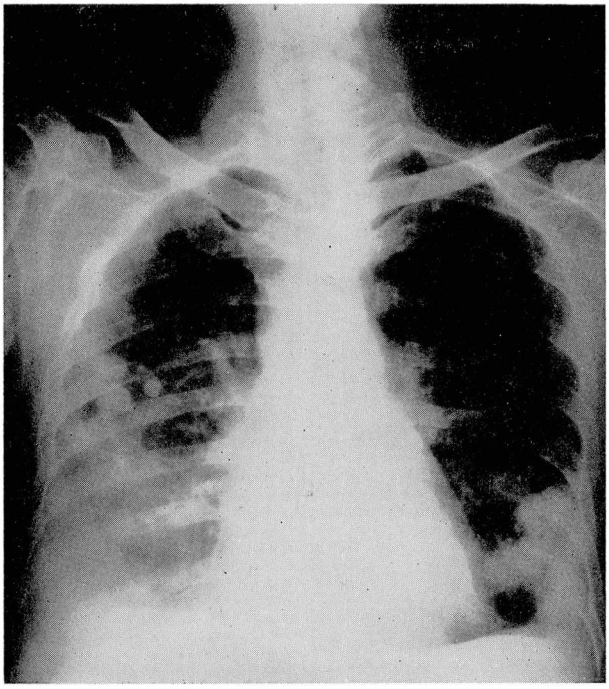


Fig. 3. Roentgenogram of chest in 1955.

complete obliteration of both joint spaces with localized erosion of the articular surfaces of each radius. Extreme flexion deformity of the hands with partial subluxation between the metacarpal and phalangeal bones was present (Fig. 5). A roentgenogram of the lumbar spine revealed hypertrophic changes of the lumbar bodies with partial collapse of L-2, which had not progressed since 1949. There were narrowing and sclerosis of the left hip joint and cystic changes in the femoral head, which had increased considerably since 1949.

An electrocardiogram was interpreted as showing myocardial changes. There were sinus rhythm and depression of RS-T in standard leads 2 and 3, aVF, V5, and V6. T waves were inverted in standard leads 2 and 3, aVF, and V6; diphasic in V4 and V5; and upright in aVR.

Laboratory findings were as follows: blood hemoglobin content 13.4 gm. per hundred milliliters; red cell count 4,900,000 and white cell count 4,500 per cu. mm., with 64 per cent neutrophils, 32 per cent lymphocytes, and 4 per cent eosinophils. A sedimentation rate was 1.3 mm. per minute (Rourke-Ernstene method). Urine specific gravity was 1.008, and tests for sugar and albumin were negative. Cholesterol crystals were not found microscopically in the urine. Blood urea content was 33, serum calcium 10.4, serum phosphorus 3.1, and serum cholesterol 130 mg. per hundred milliliters. Serum alkaline phosphatase was 3.5 Bodansky units, thymol turbidity was 4.5, and zinc sulfate turbidity was 6.8 units. Total serum bilirubin was 0.59 mg. per hundred milliliters. Cephalin cholesterol flocculation was negative at 48 hours. Prothrombin time was 14 seconds, or 100 per cent, and serum polysaccharides were 180 (normal 160) mg. per

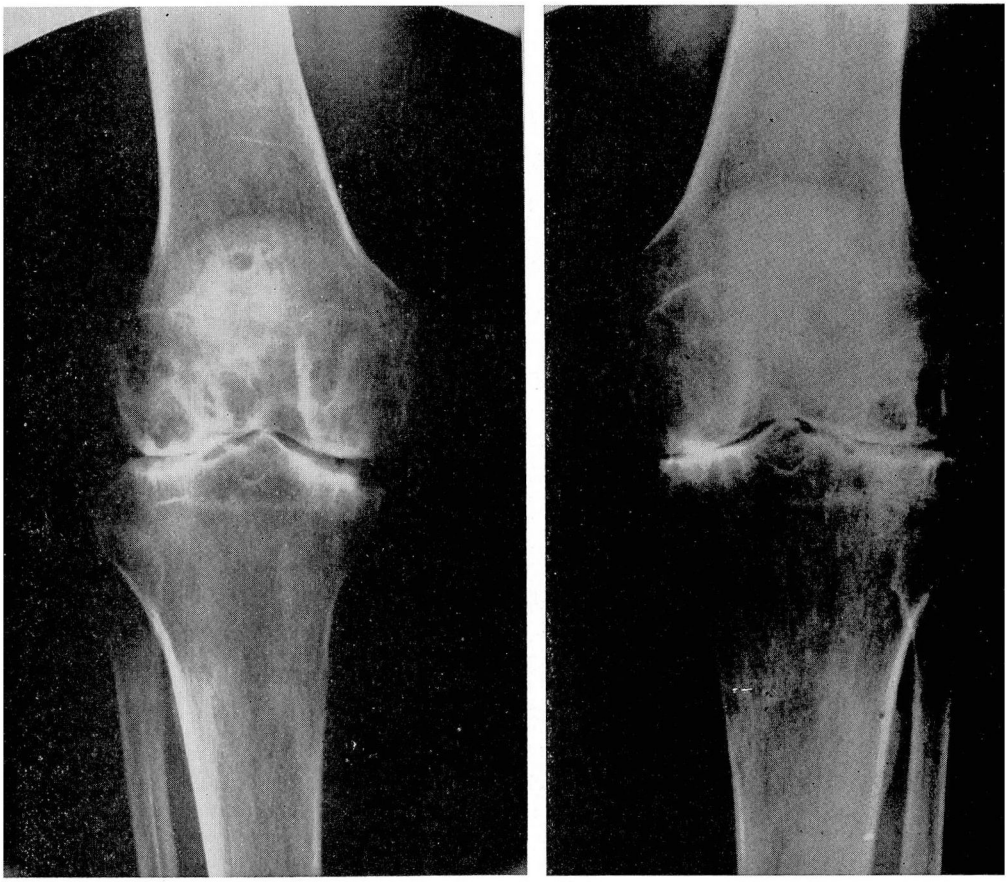


Fig. 4. Roentgenograms of knees in 1955.

hundred milliliters of blood (Shetlar method[6]). A plasma test for lupus erythematosus was negative.

On January 7, three days after the patient had been admitted, the total plasma protein content was 6.40 gm. per hundred milliliters by the biuret method. Electrophoretic analysis showed that the albumin was 3.28 (51.3 per cent of total proteins), alpha globulin 0.80 (12.5 per cent of total proteins), beta globulin 1.03 (16.1 per cent of total proteins), gamma globulin 0.84 (13.1 per cent of total proteins), and fibrinogen 0.43 gm. per hundred milliliters (7 per cent of total proteins).

Four hundred milliliters of turbid yellow fluid with masses of yellow flocculant precipitate was aspirated from the right knee. The fluid had a cholesterol level of 400 mg. per hundred milliliters with cholesterol esters of 211 mg. per hundred milliliters, and numerous cholesterol crystals were present.

A Vim-Silverman needle biopsy of the liver revealed old, slight cirrhosis that was compatible with the postnecrotic type. Histologically there was a slight-to-moderate

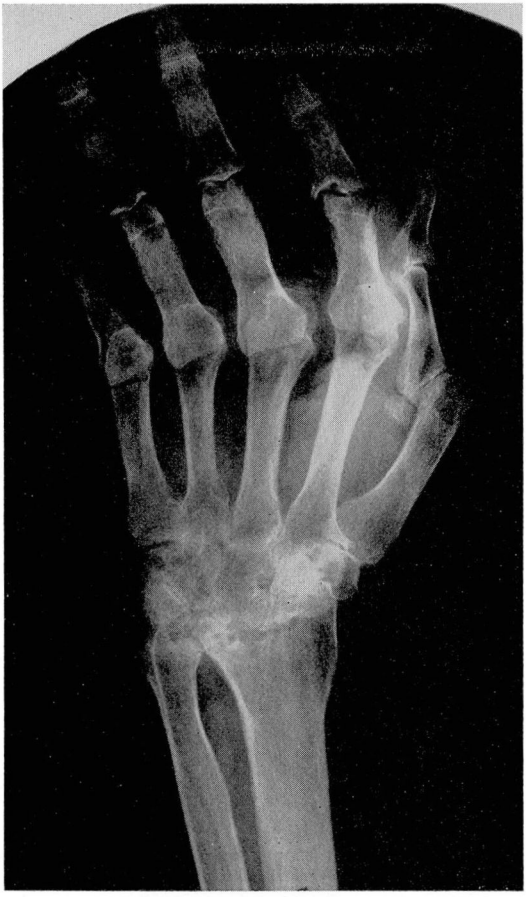
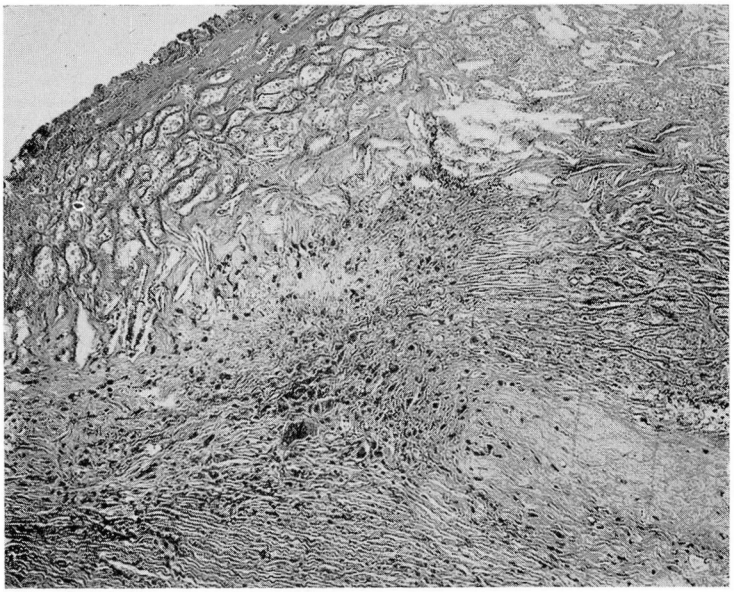


Fig. 5. Roentgenogram of the hand and wrist showing the advanced arthritic changes in 1955.

increase in connective tissue, principally in portal areas, and at least in one instance adjoining a central area. The involved portal zones were of irregular configuration but mostly were sharply demarcated from adjoining hepatic parenchyma. One focus of fibrosis showed slight extension of the fibrous tissue between hepatic cell cords. There was slight and somewhat focal infiltration of lymphocytes in areas of fibrosis. The hepatic cells were well preserved, and had a slightly pale, granular appearance that indicated normal glycogenation. No lipophages were evident.

Synovial biopsy specimens of the right knee and of the right wrist were obtained. Histologic sections (Fig. 6) revealed that portions of synovial membrane were formed externally by dense hyaline connective tissue with occasional foci of inflammatory cells, principally lymphocytes, but with some plasma cells and occasionally with histiocytes and a few neutrophils. The narrower, inner zone was comprised of less dense, at times finely fibrillar connective tissue and areas of degenerating and necrotic connective tissue, which was evident as ill-defined, granular, pink- or bluish-staining material containing



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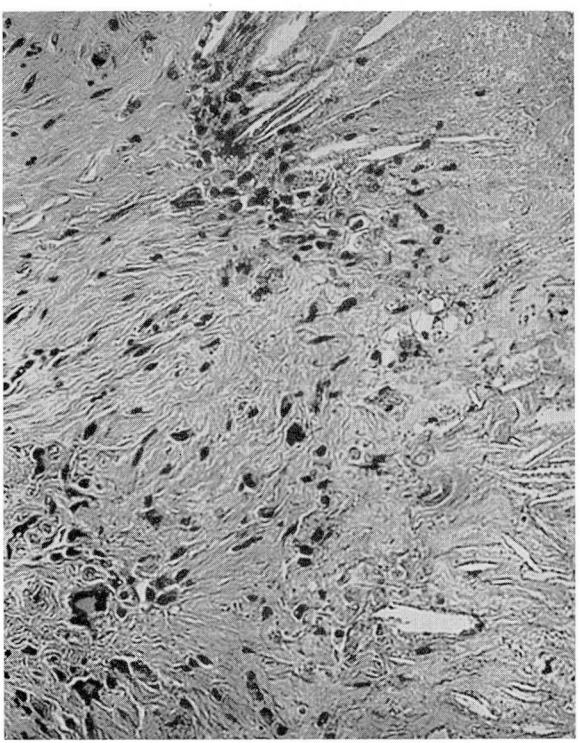

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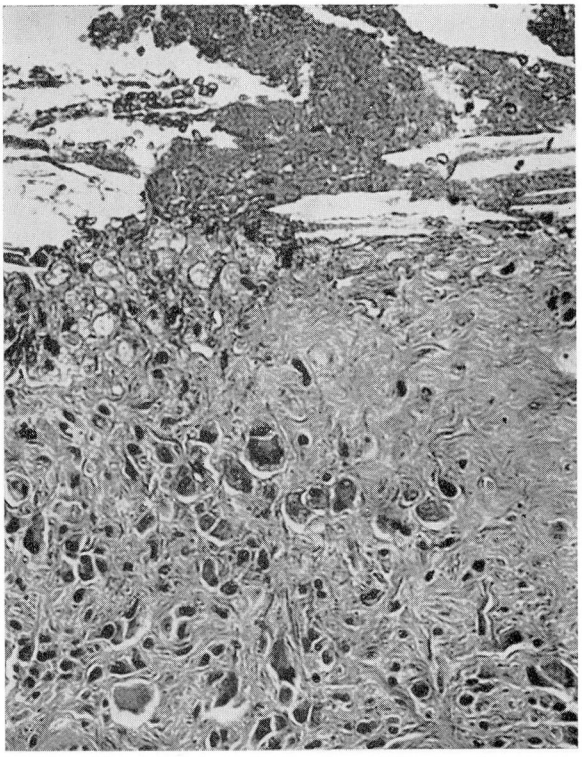
Fig. 6. Joint membrane. (**a**) Clefts (cholesterol) in zone bordering lining surface; X90. (**b**) Degenerating collagen, clefts (cholesterol), and hypercellular area with histiocytes and giant cells; X200. (**c**) Lining membrane covered with unorganized material containing clefts (cholesterol) and infiltrated by histiocytes, lipophages, and giant cells; X270.



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scattered cleftlike clear spaces (cholesterol). Histiocytes, vacuolated macrophages (lipophages), and giant cells, occasionally of Touton type, were present singly or in small groups adjoining some of the areas with the cleftlike spaces. The acellular, degenerated areas were in part imperfectly marginated by an ill-defined zone of fibroblasts and histiocytes, which at times were more distinct than others, but without true palisading. The lining surface was formed in patches by a fibrinoid layer of irregular thickness, focally containing small, cleftlike spaces. Synovial epithelial cells were not evident in any section.

A nodule was removed from the dorsum of the right hand. Histologically (Fig. 7) this was formed centrally by necrotic collagenous connective tissue in which the hazy outlines of collagen bundles were in part evident and also areas in which the precedent structure could not be identified since there was only a granular pink-staining material present. Areas in the central necrotic portion contained cleftlike spaces (cholesterol). The phosphotungstic acid—hematoxylin stain revealed dense patches of dark purple-staining fibrin-like material. The outer portion of the nodule was formed by dense collagenous and hyaline connective tissue, with hypercellular zones of fibrocytes, histiocytes, and lipophages, most apparent immediately adjoining the zone of central degeneration, producing a somewhat palisaded appearance. There was no evidence of old hemorrhage. In one area at the junction zone there was a microscopic focus of liquefaction necrosis, marginated by fibrinoid and bluish-staining material. Blood vessels in the loose areolar tissue immediately adjoining the nodule showed a pronounced but focal adventitial infiltration by lymphocytes and a few neutrophils.

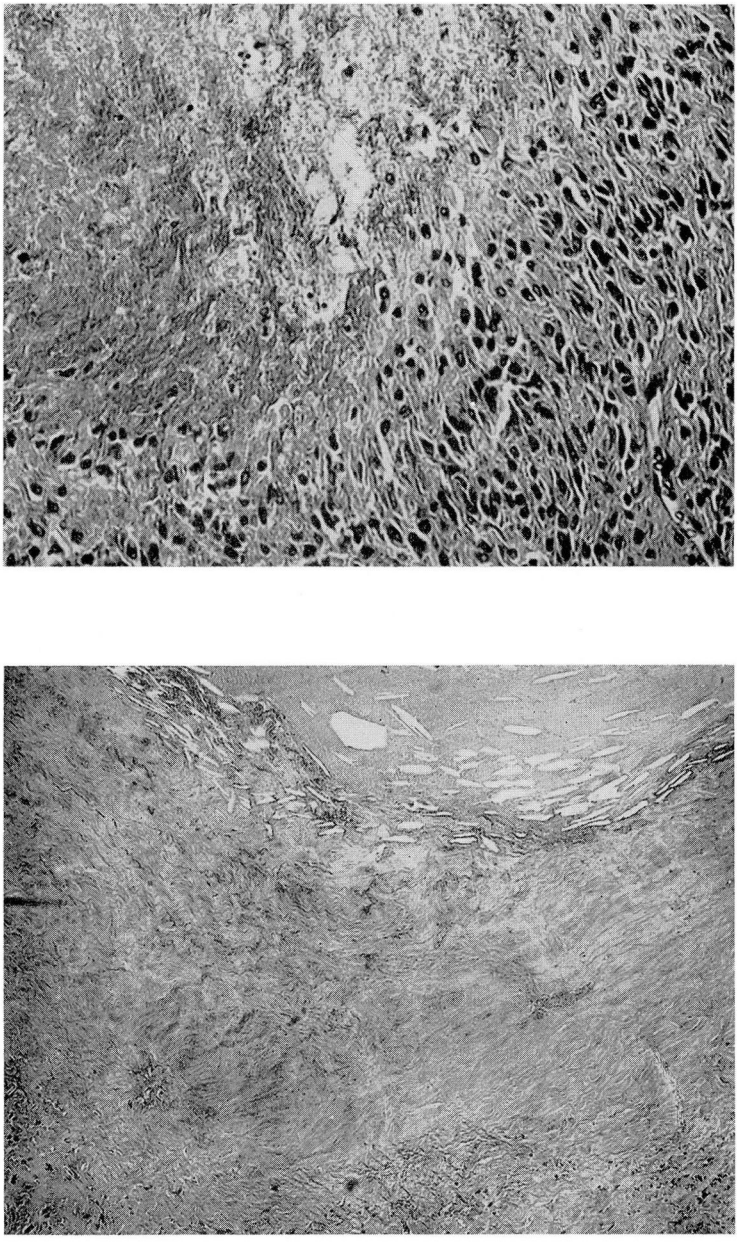

Fig. 7. Nodule from dorsum of hand. (a) Acellular zone with central area of necrosis, clefts (cholesterol), and peripheral collagen; X80. (b) Another area showing degenerating collagen and hypercellular periphery; X270.

Eleven months later, in December 1955, the patient was re-examined. The joint involvement was unchanged and a mild effusion of the right knee persisted. The serum cholesterol content was 126 mg. per hundred milliliters of blood. A roentgenogram of the chest revealed the same atypical parenchymal and pleural changes with no significant difference from previous films.

Discussion

It is well recognized that under certain conditions excess accumulation of cholesterol may occur in various body cavities while the serum cholesterol remains normal. Cholesterol-containing pericardial effusion may accompany myxedema or may occur as a result of tuberculous pericarditis or hemopericardium.[7] Cholesterol-containing pleural effusion has been reported to be associated with tuberculosis, diabetes, syphilis, and metastatic adenocarcinoma of the lung and pleura.[8-11] Neither pericardial nor pleural cholesterosis has been reported in association with deforming polyarthropathy.

Although the etiology of the pulmonary lesions has not been determined, it is reasonable to assume that the pleural effusion is directly associated with the pulmonary lesions. The pulmonary nodular lesions probably are not malignant, inasmuch as no appreciable change could be identified roentgenographically during the past six years. Tuberculosis was considered an etiologic possibility, although numerous sputum examinations and cultures of gastric washings have been negative for tubercle bacilli. The roentgen appearance of the pulmonary lesions and the positive skin test (Purified Protein Derivative # 1) contraindicated sarcoidosis. Pulmonary xanthomatosis also was considered because it can occur as granulomatous nodular infiltration or as solitary xanthomas.[12-15] However, while bone and tendon lesions may occur, advanced deforming polyarthritis has not been reported in xanthomatosis; it would be most unusual for the pathologic changes in the joints and the lungs to be unrelated while both are characterized by excess accumulation of cholesterol.

According to Horwitz,[4] rheumatoid nodules when stained with scarlet red, histologically show a high incidence of lipid and a variety of lipid changes have been described. He has attempted to simplify the problem by postulating that the primary change is the deposition of a small amount of cholesterol or other lipid in the central necrotic area, and that the subsequent appearance of a nodule probably depends to a great extent on the site of deposition, the amount of lipid that is deposited, and the reaction of the surrounding tissues to the presence of the lipid. This postulation would explain the presence of cholesterol crystals or other lipid material in varying amounts extracellularly, and the presence of foam cells containing lipids in variable amounts intracellularly, resulting in various histopathologic appearances. The presence of lipid is not limited to rheumatoid arthritis but may occur in gouty arthritis. Kersley, Gibson, and Desmarais[2] have noted the presence of cholesterol crystals and foam cells in tophi of gouty patients.

Horwitz[4] suggested that the subcutaneous nodules of rheumatoid arthritis

with lipid deposition that have been described are not distinct entities but merely are different histopathologic end results of a process with a common pathogenesis, that is, the deposition of lipid in the necrotic foci in the nodules. This may be the case, still, the manner in which lipid is deposited in the necrotic areas remains unknown.

Fletcher[1] described a case of rheumatoid arthritis in a 42-year-old man who had widespread necrosis of numerous subcutaneous nodules, cellular proliferation, round-cell infiltration, and vascular lesions in these nodules. The presence of cholesterol was demonstrated in the areas of necrosis surrounded by foam cells; the serum cholesterol remained normal. Layani reported a case, reviewed by Horwitz,[4] which was similar to ours except that the patient was a 46-year-old woman with deforming arthritis of 15 years' duration. She developed xanthoma planum et tuberosum, angina, jaundice, hepatomegaly, and hypercholesteremia. Autopsy was not performed, but Thannhauser[12] believes that this patient's condition probably was a coincidental combination of rheumatoid arthritis with generalized primary xanthoma and xanthomatous biliary cirrhosis.

The hepatomegaly and the histopathologic findings on liver biopsy in our patient are interesting and not easily or readily explained. Possibly hepatitis without jaundice had occurred previously, although the history failed to confirm this suspicion. Or it is possible that the disease, because of its generalized and widespread distribution, also involved the liver, which later healed with residual fibrosis and scarring.

Accumulation of lipid, such as cholesterol, in certain serous cavities apparently is a nonspecific reaction, since it is not limited to single sites or to specific diseases. Thus, cholesterol deposition in some cases may be minimal and localized to a single solitary inflamed bursa, and in others may be increased in amount and distribution so as to involve the pleural or the pericardial sac or both, and, as in the present case, nodules, joints, pleurae, and conjunctivae.

It is unlikely that the cholesterol accumulations in the case reported here are attributable to transport of excess lipid to the affected areas, since the serum cholesterol concentration always has been normal or low. Rather, since fibrous tissues, such as in the aorta, are capable of cholesterol synthesis,[16] it may be that this synthetic mechanism can be locally accelerated or that the mechanisms of destruction or transport of cholesterol can be locally suppressed. Again, it may be that local factors act in such a way as to promote deposition of free cholesterol from cholesterol that was transported to the joint or formed locally at normal rates. Any of these circumstances, to the extent that they would result in formation of crystalline cholesterol, would remove the cholesterol from effective contact with mechanisms that normally transport or destroy cholesterol so that the accumulation, after it had started, would tend to increase with time. In an attempt to analyze which of these various mechanisms may be at fault in this case, studies of local cholesterol metabolism are planned.

Summary

An unusual case is reported in which deforming polyarthropathy is associated with extensive cholesterosis involving nodules, pleural and synovial membranes, conjunctivae, and probably the lungs.

Mesenchymal cholesterosis appears to be nonspecific and not limited to a single disease.

The mechanism of accumulation of free cholesterol is not known.

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