Pleurisy and pericarditis occurring in rheumatoid arthritis are generally held to have non-specific histological characteristics, except where rheumatoid nodules are demonstrated. This view was emphasized in the Symposium on "The Rheumatoid Lung" at the 1966 Annual General Meeting of the Heberden Society in London (Leading Article, Brit. med. J., 1967):

"The experts at the meeting were, however, at pains to point out that there is nothing specific about the histology of the pleura in rheumatoid pleurisy; usually nothing more than a simple fibrous thickening with chronic inflammatory changes can be found".

However, Gruenwald (1948) in a case report of considerable interest stated that:

"There are indications that a type of growth similar to that of the nodules may also occur in a continuous layer spread out over large areas of serous surfaces. In that event the various layers of the granuloma are arranged roughly parallel to the surface of the organ rather than concentrically".

Sporadic reports of similar pathology of pleura and pericardium have appeared in the literature, but have received little attention in review articles (Bevans, Nadell, Demartini, and Ragan, 1954; Heller, Kellow, and Chomet, 1956; Horler and Thompson, 1959; Schools and Mikkelson, 1962; Lassiter and Tassy, 1965; Portner and Gracie, 1966; Sutton, 1967).

Three further cases with serous membrane involvement, as described by Gruenwald, are presented below. The appearance may be likened to that of a rheumatoid nodule opened out, exposing the fibrinoid zone to the serous cavity, a feature which is seen not uncommonly in rheumatoid synovitis (Sokoloff, 1961, 1966). The analogy between the pleurisy and synovitis may be carried further by consideration of biochemical and cytological studies on the effusions from these and other cases reported in the literature.

**Case 1.** A fitter aged 60 years was admitted to hospital in January, 1956, with a history of breathlessness of 3 to 4 weeks’ duration. In the same period he developed polyarthritis involving the cervical spine, knees, shoulders, elbows, and hands.

**Examination.**—Signs of a pleural effusion were detected at the right base. There was active arthritis of the right knee with effusion, restriction of cervical and elbow movement, and right olecranon bursitis.

**Laboratory Investigations.**—3 l. fluid were aspirated from the right pleural space. Specific gravity was 1020, and protein 4.7 g. per cent. The fluid was sterile, and contained no visible carcinoma cells on cytological examination.

Haemoglobin 15 g. per cent.; white cell count 8,800/cu. mm.; ESR 7 mm. in one hour; no LE-cells.

Repeated x-rays revealed no abnormality in the chest apart from the right pleural effusion. Needle biopsy of the pleura provided an inadequate specimen. Sputum was negative for acid-fast bacilli.

**Progress.**—The arthritis increased in severity, requiring cortisone 200 mg./day for symptomatic relief. The dyspnoea worsened, and the patient was noted to have atrial fibrillation and congestive cardiac failure. Hypertension and mental confusion followed a few days later. An electrocardiograph showed flattening of T waves relative to previous tracings. Repeated pleural aspirations assisted the dyspnoea but he remained confused. Deterioration was progressive and was associated with fever, anaemia, and impaired renal function.

**Termination.**—Death ensued in April, 1956, 14 weeks after the onset of symptoms.
Autopsy.—The pleural cavities contained a small quantity of blood-stained fluid, and were partly obliterated by fibrinous and fibrous adhesions. The left lung showed evidence of septic inhalational pneumonia. The pericardial cavity contained a small quantity of blood-stained fluid, and was also partly obliterated by fibrinous adhesions. The right ventricle was slightly dilated. The endocardium was a little thickened, and adhesions were noted between two of the aortic valve cusps near the commissure. Widespread atherosclerosis and congestive changes were observed. The splenic capsule appeared thickened and inflamed.

Microscopic Examination

Lung.—The pleura (Fig. 1) was markedly thickened. On the surface was a zone of fibrinoid in which necrotic nuclear debris could be seen. A palisaded zone of histiocytes separated this from a deeper zone of inflammatory granulation tissue in which occasional giant cells were present. This pathological change was widespread throughout the pleura.

A similar appearance was noted in the pericardium (Fig. 2) where, however, the surface fibrin was particularly thick.

Fig. 1.—Case 1. Rheumatoid pleurisy with superficial fibrinoid and necrotic nuclear debris, subjacent palisade layer, and thick zone of granulation tissue with lymphocytes, plasma cells, and occasional giant cells. Haematoxylin and eosin. × 125.

Fig. 2.—Case 1. Rheumatoid pericarditis with surface fibrin, a continuous layer of large cells with histiocytic characteristics, and underlying oedema and inflammatory cell infiltration. Haematoxylin and eosin. × 125.
Patchy myocardial fibrosis and infective and congestive pulmonary changes were seen.

Knee.—Synovitis consistent with rheumatoid arthritis was observed in a section taken from the right knee.

Elbow.—A subcutaneous rheumatoid nodule was found adjacent to the right elbow, and necrotizing arteritis was noted in the adjacent connective tissue.

Gut.—Necrotizing arteritis was seen in the subserosal region.

In summary, the arthritis, subcutaneous nodule, arteritis, pleurisy, and pericarditis were all considered to be manifestations of rheumatoid disease.

Case 2. A 42-year-old housewife first came to the outpatient department in February, 1965, with a 2-year history of mild rheumatoid arthritis. There were no subcutaneous nodules. Chest x ray showed ill-defined opacities in the right mid-zone—a small round lesion and a ring shadow (Fig. 3). Tomography demonstrated these to be situated in the pleura.

A policy of observation was indicated, and she was treated with aspirin.

In September, 1965, a right pleural effusion developed (Fig. 4), coincident with an exacerbation of arthritis, and admission to hospital was advised.

Laboratory Investigations.—Waaler-Rose test positive (1:1028); ESR 57 mm. in one hour; haemoglobin concentration and white cell count normal; no LE-cells. Mantoux test was negative. Aspiration of the right pleural space produced 180 ml. of turbid green-grey fluid, in which the protein was 5·4 g. per cent., glucose 35 mg. per cent., and the lactic acid dehydrogenase 3,900 I.U./l. (serum 165 I.U./l.). The fluid was sterile and negative for acid-fast bacilli. No malignant cells were seen on cytological examination.

At this stage the possibility of rheumatoid pleurisy was considered. The arthritis settled with rest and aspirin.

Progress.—18 months later (February, 1967) a diagnostic right thoracotomy was advised because of the recurrent nature of the effusion, and because cytological examination of the fluid at this stage revealed abnormal cells which raised the possibility of carcinoma. The pleural lesions previously seen in the right mid-zone were no longer apparent.

Thoracotomy.—The visceral and parietal pleura were white, glistening, and thickened. In the right upper lobe there was an area 1·5 cm. in diameter which macroscopically resembled an abscess. This lesion was removed and total pleurectomy performed. Post-operatively the arthritis has been inactive, there have been no complications and the chest x ray is clear.

Microscopic Examination.—The visceral and parietal pleura (Figs 5 and 6, overleaf) showed marked fibrous thickening deep to a surface layer of cells, sometimes in palisade formation, which were presumably of the serosa. The fibrous tissue was hyaline and relatively acellular superficially, but nearer to the underlying lung there were large collections of lymphocytes and macrophages. In
one section a typical rheumatoid nodule was seen. The edge of what was thought, at operation, to be an abscess showed central fibrinoid necrosis with a wall formed by the relatively acellular fibrous tissue which was part of the thickened pleura. In the subpleural zone of the lung in this region there was quite extensive fibrous thickening of interalveolar septa, and marked lymphocytic and plasma cell infiltration. Neighbouring blood vessels showed intimal thickening and cellular infiltration of their walls.

Case 3. A 55-year-old storeman developed polyarthritis in June, 1966, which involved the small joints of the hands and feet, the wrists, knees, elbows, and shoulders. His general practitioner prescribed prednisone 15 mg. per day to minimize the loss of working hours.

In January, 1967, he was recalled from a routine yearly chest x-ray because of a right-sided pleural effusion and referred to hospital for investigation. Respiratory symptoms were specifically denied, and there was no fever. The arthritis was quiescent despite the recent withdrawal of prednisone.
Examination.—Metacarpophalangeal and proximal interphalangeal joint swelling and stiffness, and a subcutaneous nodule and bursitis in relation to the left elbow, enabled a clinical diagnosis of rheumatoid arthritis to be made. Signs of a pleural effusion were evident at the right base.

Laboratory Investigations.—The Mantoux test was positive. Sputum was negative for acid-fast bacilli on direct examination and culture on two occasions. Chest x-ray revealed no abnormality other than the effusion. Haemoglobin 12·2 g. per cent., white cell count 8,500/cu. mm.; ESR 65 mm. in one hour (Westergren); no L.E.-cells. The RA latex test was positive and the Waaler-Rose titre 1:64. Total serum protein was 7·8 g. per cent., albumin 4·5 g. per cent.; globulin 3·3 g. per cent. Electrophoretic pattern showed a slight rise in a2 and γ globulins. Joint x rays were consistent with early rheumatoid arthritis, erosions being present only in the hands.

1,500 ml. of turbid yellow fluid was aspirated from the right pleural space. The fluid contained red cells, polymorphs, and lymphocytes, was sterile, negative for acid-fast bacilli on direct examination and culture, and contained no visible malignant cells on cytological examination. The RA latex test was positive, and the Waaler-Rose titre 1:4. The total protein was 7·8 g. per cent., identical with the serum, but the distribution of the proteins was markedly dissimilar, the albumin being 3·4 g. per cent. and the total globulin 4·4 g. per cent. Electrophoretic analysis of these proteins revealed a high concentration of γ globulin (approximately 3·9 g. per cent. compared with 1·3 g. per cent. in the serum, bearing in mind the considerable inaccuracies of quantitation by these means).

Needle biopsy failed to provide sufficient pleura for diagnosis. Bronchoscopy, normal.

Pleural Biopsy.—The visceral pleura was thickened and was studded with multiple pleural and subpleural nodules, some approaching 1 cm. in diameter, particularly over the right upper lobe.

Progress.—The postoperative course was complicated by empyema, and also by pericarditis which may have been of rheumatoid aetiology. The patient was discharged from hospital in July, 1967, the arthritis being adequately controlled by aspirin and phenylbutazone.

Microscopic Examination.—Sections of the nodular lesions showed the three zones characteristic of rheumatoid nodules (Fig. 7). Ziehl-Neelsen stain revealed no acid-fast bacilli. The remainder of the sections of pleura were all of similar appearance (Figs 8, 9, and 10, overleaf). On the surface was a thin layer of fibrin which had been separated in some sections.

Deep to this was a continuous layer of palisaded cells with their long axes orientated perpendicularly to the surface. These cells were indistinguishable by light microscopy from the palisaded histiocytes of the pleural nodules. Between the palisaded layer

Fig. 7.—Case 3. Section of rheumatoid nodule situated in pleura. Haematoxylin and eosin. × 100.
and the normal underlying lung was a broad zone of relatively vascular fibrous tissue, infiltrated by plasma cells and lymphocytes, in which occasional giant cells and lymphoid follicles were also seen.

**Discussion**

The discrete nodules situated in the pleura in Cases 2 and 3 were sufficiently characteristic to enable a diagnosis of rheumatoid pleurisy to be made. The remainder of the sectioned pleura in these two cases, and the pleura and pericardium of Case 1 had a similar histological picture, in which three layers or zones were readily discerned. On the surface was a layer either of fibrin or of fibrinoid necrosis with necrotic nuclear debris, of varying thickness, which in some sections had been partly shed during preparation. The subjacent cells were arranged in a palisaded fashion with their long axes perpendicular to the surface. Between the palisaded layer and the underlying lung (and myocardium in Case 1) was a thick layer of vascular fibrous tissue (granulation), infiltrated by lymphocytes and plasma cells, in which giant cells and lymphoid follicles were also seen.

The surface fibrinoid necrosis may be compared with the central zone of a rheumatoid nodule. The palisaded cells, which may be derived, at least in part, from the pleural mesothelium, are indistinguishable by light microscopy from the elongated connective tissue cells arranged radially around the central zone of the subcutaneous nodules. The underlying granulation tissue on the pleura is also akin to the equivalent zone of the nodule. This resemblance is even more striking when one compares the pleural reaction with the wall of a nodule which, as not uncommonly happens, had undergone central softening and developed a bursa-like cavity.

We have observed a very close similarity of this pleural pathology to the very early lesions of rheumatoid synovitis as described by Kulka, Bocking, Ropes, and Bauer (1955). In this study, biopsies were taken from the knee joint within weeks or months of the onset of disease in that joint. A
generalized proliferative synovitis was the dominant feature. In this reaction stratification of the synoviocytes was frequent, the more superficial cells often becoming arranged in a palisade formation, so resembling the proliferative zone of rheumatoid nodules. Summarizing, they state that the relatively early and active articular lesions differed from the classic descriptions of the permanently-deforming stage of rheumatoid arthritis in showing a closer resemblance to the type of tissue reaction characterizing the subcutaneous nodules and other systemic lesions of the disease. It is apparent that the early changes of rheumatoid pleurisy and pericarditis may simulate the earliest lesions in the synovium, and that it is in the later stages of the disease, as exemplified by Case 2, that the appearances are more fibrotic and less distinctive.

In more recent reviews of the pathology of rheumatoid arthritis, Sokoloff (1961, 1966), commenting on the occasional similarity of the synovitis to the rheumatoid nodule reaction, suggested that the necrotic material, unlike that in the subcutaneous nodule which is circumscribed by firm cicatrix, tends to be cast off into the joint space, leaving a superficial palisade of elongated connective tissue cells. Grimley and Sokoloff (1966) suggested that in this situation the synovial lining layers might be conceived as an advancing front of granulation tissue, with macrophage-like cells selectively migrating to, or proliferating at, the surface. Kulka (1966), however, from studies of the microcirculatory derangement in rheumatoid arthritis, attributed this appearance to terminal vascular thrombosis and ischaemia in the synovial villi, with selective survival of synoviocytes. The latter may satisfy their metabolic requirements by interchange with the synovial fluid.

Although early rheumatoid synovitis is not usually diagnostic microscopically, pleurisy and pericarditis with the histological features of these

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Fig. 9.—Case 3. Rheumatoid pleurisy with some of surface fibrin infiltrated with chronic inflammatory cells. A focal collection of lymphocytes can be seen. Haematoxylin and eosin. × 130.
three cases may be specific or at least strongly suggestive of rheumatoid disease. We have been unable to find similar histological changes in pleurisy and pericarditis due to other diseases either in the literature or in pathological material from this hospital. However, it is appreciated that pleural mesothelium is capable, in the presence of certain irritants, of undergoing metaplasia and assuming the characteristics of columnar epithelium.

A review of the literature of rheumatoid arthritis with involvement of serous membranes has revealed several examples of the same pathological process, the references having been listed in the introductory paragraphs. Gruenwald’s case was of particular interest in that not only were the pleura and pericardium involved but also the splenic capsule. Furthermore, typical rheumatoid nodules were also found on the serous membranes. The authors of the more recent reports have given no indication of awareness of the previous similar findings.

Linear or band-like fibrinoid necrosis and cellular infiltration, of the same type as found in the nodule, have also been described in mitral and aortic valves and adjacent endocardium (Bevans and others, 1954; Waaler, 1967).

Needle biopsy of the parietal pleura has not, in the past, been a fruitful source of material of diagnostic value. But more recent reports of needle biopsy material showing typical rheumatoid nodules (Schools and Mikkelsen, 1962; Berger and Seckler, 1966), and the pathology described above (Schools and Mikkelsen, 1962; Portner and Gracie, 1966) indicate the possible usefulness of this procedure.

If indeed the pathology of the pleurisy and pericarditis is analogous to the synovitis, then one would anticipate similar findings in their respective effusions. Recent reports of investigations in rheumatoid pleural and pericardial effusions tend to support this concept. Low glucose concentration, positive tests for rheumatoid factor, poly-
morphs with inclusions containing rheumatoid factor—IgG complexes, very high lactic acid dehydrogenase levels, high lipid concentrations, and cholesterol crystals, all of which may be seen in synovial effusions have been found in rheumatoid pleural and pericardial effusions (Ball and Whitfield, 1966; Berger and Seckler, 1966; Carmichael and Golding, 1967; Dodson and Hollingsworth, 1966; Lassiter and Tassy, 1965; Schools and Mikkelsen, 1962; Stengel, Watson, and Darling, 1966; Walker and Wright, 1967). Further studies are required to assess the diagnostic significance of all these findings. It is not known whether such a series of investigations can differentiate rheumatoid pleural effusions from effusions of other aetiology occurring in rheumatoid patients.

The investigations on the pleural fluid in the cases presented were incomplete, serving mainly to exclude tuberculosis, pyogenic infection and malignancy. The high pleural fluid concentration of γ-globulin in Case 3 is interesting in view of the commonly-held concept that the γ-globulin concentration of exudative pleural effusions remains less than in the serum (Zinneman, Johnson, and Lyon, 1957). Although the literature includes one or two instances in which the γ-globulin concentration appears to be high (Lassiter and Tassy, 1965), the possible value of this investigation has not been studied.

The three cases illustrate several of the well-known clinical features of rheumatoid pleurisy which have recently been reviewed by Walker and Wright (1967). Cases 1 and 3 were males in the sixth decade with rheumatoid subcutaneous nodules, who developed pleurisy at or shortly after the onset of the disease. This is the most characteristic story. The woman (Case 2) was younger and did not have subcutaneous nodules. The relationship of the pleurisy with age, and with the duration and nature of the rheumatoid arthritis, is more variable in women.

Coexistent with the pleurisy in Case 1 was pericarditis; in Case 2 pleuropulmonary nodules and localized interstitial fibrosis: and in Case 3 pleural nodules, and pericarditis which may also be of rheumatoid origin. When rheumatoid pleurisy is suspected, a careful search for pleuropulmonary nodules and early interstitial pneumonia or fibrosis on chest x ray, and for pericarditis, may assist the diagnosis. Review of the literature indicates that such coexistence of manifestations is more frequent than is generally appreciated. Of the patients with rheumatoid pleural effusions reported by Walker and Wright (1967), three of the eleven men also developed pericarditis.

Summary

Three cases of rheumatoid pleurisy, one also with pericarditis, are presented, in which the pathology was of distinctive appearance, resembling a rheumatoid nodule but with the various layers of the granuloma arranged parallel with the surface of the organ rather than concentrically. The second and third cases also had typical rheumatoid nodules in the pleura.

Similar histopathology has been reported in several other cases, not only in the pleura and pericardium, but also involving the splenic capsule, but there is no general awareness of this change, and of the assistance it may render in the interpretation of pleural needle biopsy findings. The resemblance to rheumatoid synovitis, particularly in the early stages, is emphasized.

The third case is of further interest in that a high concentration of γ-globulin was present in the pleural fluid.

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REFERENCES


**Pleurésie et péricardite rhumatoïdes**

On rapporte sur trois cas de pleurésie rhumatoïde, y compris une péricardite chez un malade. L'aspect anatomopathologique y était distinctif, revêtant la forme de nodules rhumatoïdes, mais les différentes couches du granulome étaient alignées parallèlement à la surface de l'organe et non pas d'une manière centripète. Le deuxième et le troisième cas avaient aussi des nodules rhumatoïdes typiques dans la plèvre.

Une image histopathologique similaire avait été rapportée dans plusieurs autres cas, non seulement dans la plèvre et le péricarde, mais aussi dans la capsule de la rate; toutefois ces altérations et leur valeur pour l'interprétation des résultats de la biopsie pleurale ne sont pas généralement connues. On souligne la ressemblance à la synovite rhumatoïde, particulièrement à la période de début.

Le troisième cas présente un intérêt additionnel du fait qu'on y a trouvé une forte concentration de gammaglobuline dans le liquide pleural.

**Pleuresía y pericarditis reumatoide**

Se relatan tres casos de pleuresía reumatoide, comprendiendo uno de pericarditis asociada. El aspecto anatomopatológico fue distintivo en forma de nódulos reumatoídes, pero las diferentes capas del granuloma se alineaban paralelamente a la superficie del órgano y no de la manera centrónica. El segundo y el tercer-caso tuvieron también nódulos reumatoídes típicos en la pleura.

Un cuadro histopatológico similar había sido relatado en varios otros casos, no sólo en la pleura y en el pericardio, sino también en la cápsula esplénica, sin embargo estas alteraciones y su valor para la interpretación de los resultados de biopsia de la pleura no se conocen extensamente. Se subraya la similaridad a la sinovitis reumatoide, en particular en el periodo inicial.

El interés adicional del tercer caso reside en el hallazgo de una fuerte concentración de gammaglobulina en el líquido pleural.