Cytodiagnosis of rheumatoid pleural effusion[1]

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The characteristic cytologic features of rheumatoid pleuritis are described in a patient with rheumatoid arthritis and pleural effusion.

Index terms: Arthritis, rheumatoid • Pleural effusion

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Although the main purpose of cytodiagnosis is the detection of malignant cells, other disease patterns are often noted in specimens submitted for cytologic evaluation. Occasionally, a specific nonmalignant disease can be diagnosed. Usually this involves the detection of characteristic causative organisms such as acid-fast bacilli, fungi, viral inclusions, or various protozoans or helminths. Inflammatory exudates, though frequently seen, are almost always nonspecific. One exception is the unique cytologic presentation of rheumatoid pleural effusion first described by Nosanchuk and Naylor[1] and subsequently reported by others.[2,3]

We present a case in which this distinct cytologic picture was sufficiently recognizable to suggest the diagnosis of rheumatoid pleuritis without prior knowledge that the patient had a history of rheumatoid arthritis. The cytologic and histologic features are also compared.

Case report

A 49-year-old white man was admitted for evaluation of right-sided pleural effusion. One month earlier there had been a gradual onset of right pleuritic pain, low grade fever, chills, night sweats, and a partly intentional 15-pound weight loss. The patient had a 5-year history of progressive rheumatoid arthritis with arthralgia and swelling of the joints. He denied recent exposure to tuberculosis or productive cough. Physical examination revealed dullness to percussion and decreased breath sounds at the right base of the chest. Additionally, the metacarpal and proximal interphalangeal joints of both hands, both knees, and both ankles were swollen, but with no evidence of nodularity over the joints or extensor surfaces. A chest roentgenogram showed a right pleural effusion. Significant laboratory studies included a Westergren sedimentation rate of 123 mm/hr, rheumatoid factor of 355 RLS (negative, less than 10), and an antinuclear factor titer of 1:320. Hemoglobin was 12.6 g/dl (normal, 15.5 ± 2) and hematocrit 38.7% (normal, 46% ± 6), with normal red blood cell indices.

A right thoracentesis was performed with removal of 650 cc of yellow-green cloudy fluid. Laboratory findings for the fluid included a specific gravity of 1.040, glucose of 1 mg/dl (normal serum, 65–110), and lactic acid dehydrogenase (LDH) of 1915 U/L (normal serum, 100–225). Cultures were negative for bacteria, fungi, and acid-fast bacilli.

Materials and methods

A cytocentrifuged preparation was made from a 0.5 cc aliquot of the pleural fluid on the Shandon Cytospin. This and smears of sediment from the remaining fluid were fixed immediately in modified Carnoy's fixative (95% ethanol with 3% glacial acetic acid) and stained by the Papanicolaou method.

Results

Slides of the effusion sediment showed a prominent background of necrotic granular debris containing abundant leukocytes in varying stages of degeneration (*Fig. 1, A*). Rare giant multinucleated cells had both peripheral and central nuclei. Delicate spindle cells with long tapered cytoplasm (*Fig. 1, B*) were much more frequent, occurring singly or in small clumps. Occasionally, multinucleated cells also demonstrated some degree of tapering (*Fig. 1, C*). There were no malignant cells, organisms, or intracellular polarizable material.

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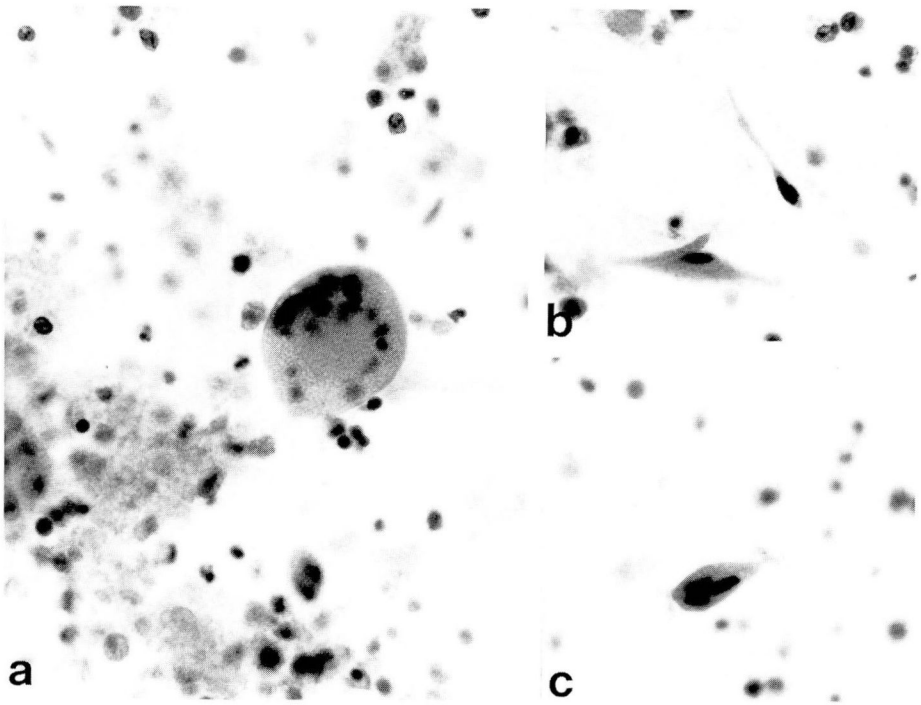

Fig. 1. Pleural fluid sediment. **A.** Giant multinucleated histiocyte in a background of granular debris and degenerated leukocytes.
B. Spindle cell.
C. Tapered multinucleated cell (all portions at Papanicolaou stain, ×600).

Discussion

The unique cytologic features of rheumatoid pleural effusion reflect the histopathologic features of the rheumatoid nodule. In the well-formed nodule a central area of necrosis is rimmed by a corona of palisading fibroblasts and/or epithelioid histiocytes which, in turn, is surrounded by fibrous tissue with perivascular collections of chronic inflammatory cells. In the pleura the necrotic centers usually abut the surface, thereby promoting exfoliation of the acellular necrotic debris and surrounding histiocytes and spindle cells (*Figs. 2–4*).

Nodular development is thought to be mediated through small arterioles and the terminal vascular bed. These small vessels proliferate as do fibroblasts and, possibly, resident histiocytes. In addition, there is an influx of monocytes and lymphocytes. Nodular tissue in an organ culture produces large quantities of collagenases and proteinases. If these are released by the palisaded layer of cells, the surrounding collagen matrix is destroyed, leading to their death and a centrifugally expanding central necrosis.[4]

The granular necrotic debris of the effusion sediment corresponds to the central necrosis of the rheumatoid nodule. The spindle cells and multinucleated giant cells originate from the palisaded lining of fibroblasts and epithelioid histiocytes. This combination of debris, spindle cells, and multinucleated cells in fluid is considered pathognomonic for rheumatoid pleuritis.[1–3,5,6] According to one report, tapered giant multinucleated cells are thought to occur in no other entity.[2] Although a similar picture of necrotic debris with multinucleated and other epithelioid histiocytes might be expected in a pleuritis containing infectious necrotizing granulomas (e.g., tuberculosis or fungal infections), such is not the case. These granulomas are small, well circumscribed, and localized compared to rheumatoid nodules and thus less likely to shed their cells in an effusion.[1]

Boddington et al[2] have shown positive reactions of the extracellular necrotic debris with fluorescent anti-γ globulin antisera. Although these reactions were considered nonspecific, they contrasted with the negative reaction given by fibrin, the only similar material in sediments of serous fluids.

Rheumatoid effusions also have a characteristic biochemical and serologic profile in addition to the characteristic cytologic findings. Protein and lactic acid dehydrogenase (LDH) values are elevated; glucose content is low; and rheumatoid

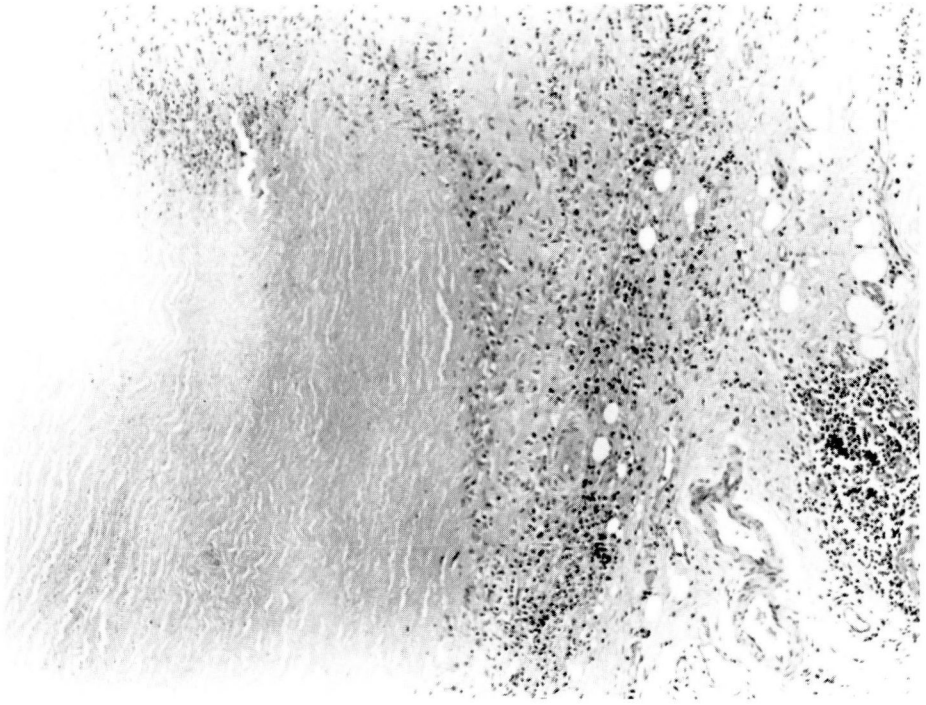

Fig. 2. Histopathologic features of pleural rheumatoid nodule. Acellular necrosis at the surface (*left*) is outlined by histiocytes and chronic inflammatory cells. Note fibrous tissue infiltrated by chronic inflammatory cells at the periphery (hematoxylin and eosin, ×100).

factor activity is present, usually greater than the serum level.[7]

All rheumatoid arthritis patients with pleural effusion do not have the characteristic cytologic findings since these are present only in patients whose pleurae contain rheumatoid nodules.[2,5] Other causes for pleural effusions in rheumatoid patients include infection, non-specific pleuritis,[8]

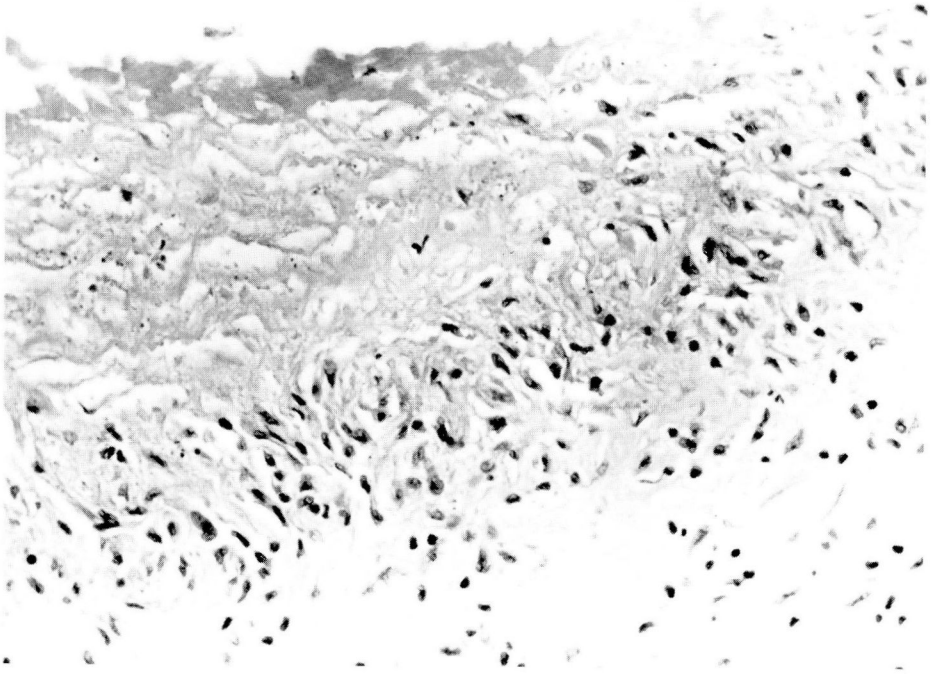

Fig. 3. Pleural rheumatoid nodule at higher magnification. Palisaded spindle cells lie between necrotic debris at the surface and fibrous tissue below (hematoxylin and eosin, ×300).

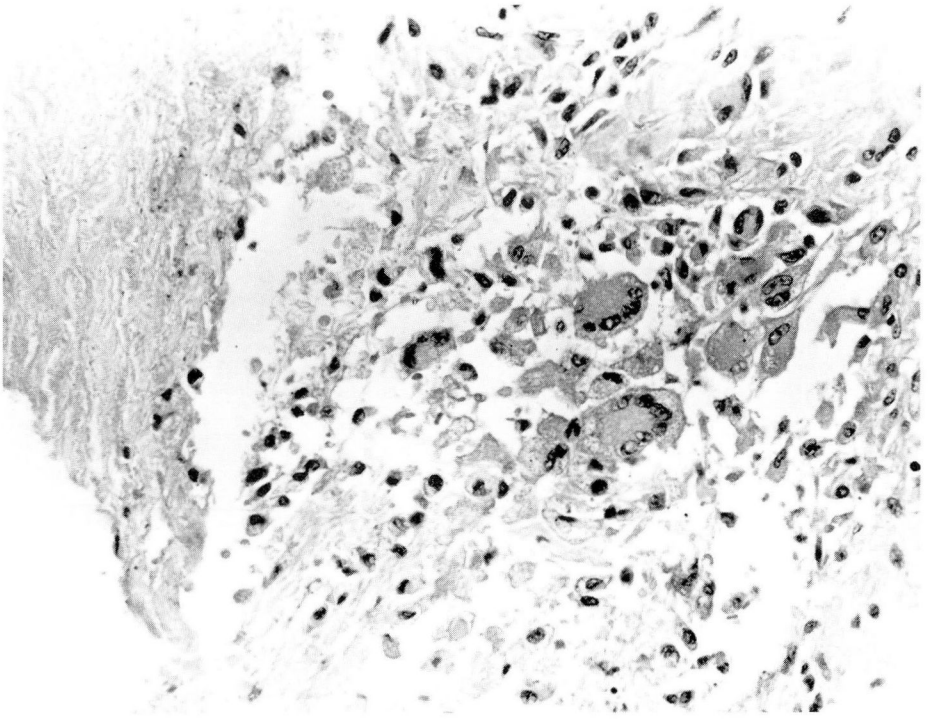

Fig. 4. Another area of pleural rheumatoid nodule with several multinucleated giant cells (hematoxylin and eosin, ×300).

chronic pneumonitis with interstitial fibrosis,[8,9] and malignancy.[8,10] The latter would also be amenable to cytodiagnosis by the detection of malignant cells.

Rheumatoid disease patients with pleural effusion usually, but not invariably, have an established history of arthritis.[1,9] Thus the cytologic features will rarely provide the primary diagnosis for the disease. Also, these features do not correlate with the duration of rheumatoid arthritis, chest symptoms or signs, duration of the effusion, or quantity of fluid obtained at thoracentesis.[1] Patients with rheumatoid nodules of the lung and pleura are especially likely also to have subcutaneous nodules[8] and almost invariably have elevated serum rheumatoid factor.[4] Males have a disproportionate predilection for pulmonary involvement.[1,2,8] The nodules, wherever they occur, usually regress spontaneously.[8]

Rheumatoid nodules occur at other sites where they may give rise to the characteristic cytologic findings which have already been reported in a rheumatoid pericardial effusion.[2] They may possibly appear in peritoneal effusions, joint effusions, and cerebrospinal fluid since rheumatoid nodules have been reported in the peritoneum, synovium, and meninges. Also, ruptured cavitary pulmonary rheumatoid nodules may result in these features being present in sputa and bronchial brushings and washings.[1]

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