language medical literature. Our findings, though, are similar to the ultrastructural observations of Roth\(^6\) in a cervical lesion and Mahoney\(^5\) in an extrauterine lesion.

Ultrastructural examination of this tumor has confirmed many of Clement and Scully’s original impressions concerning uterine adenosarcoma.\(^3\) The epithelium was clearly benign and proliferative, while the stroma had malignant features characteristic of endometrial stromal sarcoma\(^4\) and the mesenchymal component of uterine mixed müllerian tumor.\(^2\,7\) This stromal similarity to the mixed müllerian tumor supports the müllerian nature of this tumor, as does the variety of glandular epithelia present. These features allow its inclusion in the general category of mixed müllerian tumor, although the epithelial benignity clearly separates the adenosarcoma from the latter.

**ADDENDUM**

Since this manuscript was submitted for publication, Katzenstein and associates have reported results of ultrastructural studies of four uterine adenosarcomas. Their findings agree with ours. (Katzenstein AA, Askin FB, Feldman PS: Müllerian adenosarcoma of the uterus: An ultrastructural study of four cases. Cancer 40: 2233–2242, 1977.)

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**Bone Marrow Granulomas in Q Fever**

**DAVID B. OKUN, M.D., NORA C. J. SUN, M.D., AND KOUICHI R. TANAKA, M.D.**

Okun, David B., Sun, Nora C. J., and Tanaka, Kouichi R.: Bone marrow granulomas in Q fever. Am J Clin Pathol 71: 117–121, 1979. This report describes the case of a patient who had a fever of unknown origin and granulomatous hepatitis. Numerous granulomas were present in sections from a bone-marrow biopsy and bone-marrow clot obtained as a part of the diagnostic evaluation. Subsequent serologic studies proved the patient had Q fever. The authors re-emphasize that a distinctive form of granuloma occurs in the bone marrow with Q fever and that Q fever should always be a consideration in the differential diagnosis of bone-marrow granulomas. (Key words: Q fever; Bone marrow; Granulomas.)

Q FEVER is an acute infectious disease of man and animals that ranges in clinical severity from inapparent to fatal. Respiratory manifestations usually predominate, but may be absent in some cases of patients who have primary hepatic involvement.\(^1\,5\,9\) The typical histologic reaction is focal hepatocellular necrosis with infiltration of mononuclear cells and eosinophils.\(^10\,20\) Some cases with widespread severe liver-cell necrosis with granulomas\(^5\,9\,18\,19\) have been described. Ende and Gelpi\(^8\) have described a vasculitis within the...
bone marrow of a patient with Q fever. In guinea pigs with experimental Q-fever, Lilie\textsuperscript{13} observed small granulomas of the bone marrow. However, in two discussions of granulomatous lesions in human bone marrow,\textsuperscript{6,16} Q fever is not considered in the differential diagnosis.

This report describes a case of Q fever manifesting as a fever of unknown origin with granulomatous hepatitis, in which small granulomas seen in sections of bone-marrow biopsy and clot were felt to be characteristic of this disease.

Report of a Case

A 41-year-old Caucasian Mexican-American man came to Harbor General Hospital on May 2, 1977, with a history of fever, chills, malaise, and severe headaches beginning abruptly six days prior to admission. Oral administration of ampicillin had been started by his local physician, but, while the headaches gradually abated, the fever persisted. On admission there was no history of weight loss, rash, petechiae, cough, chest pain, stiff neck, abdominal pain, or dysuria. Both the patient’s wife and his daughter had symptoms of pharyngitis with nonproductive cough over the preceding two-week period. There was no history of travel outside southern California. The patient had had conversion of his tuberculin skin test documented in 1969, but did not take any prophylactic medication. There was a positive occupational history of raising goats for sale of milk and meat. The patient had recently stuck a needle with a needle used to administer antibiotics to a pregnant goat with severe conjunctivitis.

Physical Examination

Physical examination on admission revealed that the patient was well developed and well nourished, and in no acute distress. Temperature was 40°C orally; pulse rate was 100/min and regular; blood pressure was 120/70 mm Hg. There was no rash or petechiae. There was no lymphadenopathy. The lungs were clear; the liver was palpable 1 cm below the right costal margin, and a spleen tip was felt. Neurologic examination disclosed no abnormality except the absence of ankle jerks bilaterally.

Laboratory Studies

Leukocyte count was 5,600, with a normal differential. Hemoglobin was 13.2 g/dl (2.05 mmol/l); hematocrit, 39.3%. Examination of a peripheral blood smear revealed normocytic, normochromic erythrocytes; the segmented neutrophils showed slight toxic granulation, and a few contained Döhle bodies. Platelets appeared adequate. Renal function was normal. Bilirubin was 0.7 mg/dl (12.0 µmol/l); serum glutamic oxaloacetic transaminase (SGOT) 97 IU/ml; serum glutamic pyruvic transaminase (SGPT) 166 IU/ml; lactate dehydrogenase (LDH) 484 IU/ml; alkaline phosphatase 75 IU/ml; S\textsuperscript{+} nucleotidase 13.8 mU/ml. The following tests had normal or negative results: serum protein electrophoresis and quantitative immunoglobulin determinations, cold agglutinins, hepatitis-associated antigen, antistreptolysin O, Venereal Disease Research Laboratory (VDRL), anticardiolipin antibody, Monospot\textsuperscript{a} test, and serum complement. Cultures of blood, urine, sputum, material from the throat, cerebrospinal fluid, and stool were negative for bacteria, mycobacteria, and fungi. Serologic tests for typhoid fever and brucella were negative. Chest roentgenogram and scout film of the abdomen were normal.

Hospital Course

The patient had remittent fever, with temperatures as high as to 40.33°C, during the first 12 days of hospitalization. Intravenous pyelogram revealed slightly enlarged kidneys bilaterally, with normal function. A \textsuperscript{99}Ga scan was negative. A \textsuperscript{99m}Te liver–spleen scan revealed hepatosplenomegaly and mild portal hypertension. Skin testing revealed a positive STU (tuberculin unit) purified protein derivative (PPD) test. Results of liver function tests gradually returned to normal.

On May 12, 1977, both bone-marrow and liver biopsies were performed. The bone-marrow smear was not diagnostic. The marrow was cellular. Erythropoiesis was focally active and megaloblastoid. Myelopoiesis was very active, with increases in promyelocytes. Toxic granules were present in the granulocytes. Megakaryocytes were plentiful, and thrombopoiesis was normal. Only very few foamy histiocytes could be found. These cells contained hemosiderin, eosinophilic granules, and other cellular or nuclear debris. No microorganism could be identified by Gram, methenamine silver, periodic acid–Schiff (PAS), or Ziel–Neelsen stains.

Sections of the bone biopsy and bone-marrow clot revealed a normal bony architecture. The marrow was normocellular. Several discrete nodules, which probably represented a spectrum of granulomas, were found (Fig. 1). Focal fibrinoid necrosis intermixed with polymorphonuclear leukocytes and lymphocytes was seen. This was best demonstrated by Masson’s trichrome stain, and it was also quite distinctive on slides stained by PAS or Gram’s methods. Several “doughnut type” granulomas, which were thought to be characteristic of Q fever, were present. These granulomas often had an empty space in the center (probably representing dissolved lipid), encircled by a mixture of polymorphonuclear leukocytes, mononuclear cells, and concentric lamination of fibrinoid material. Serial sections revealed a close relationship of these granulomas and the vasculature, as they frequently appeared at the perivascular region. However, the blood vessels are frequently uninvoluted, and elastic stain (Verheoef’s method) failed to demonstrate the presence of elastic fibers in any of these granulomas.

The needle biopsy of the liver also revealed punched-out lesions, which were identical to and more numerous than those seen in the bone marrow. They were mostly located in the sinusoïds, with no predilection for the central or peripheral zonal demarcations. The sinusoïds were markedly dilated and congested, and several of them appeared to coalesce, filled with eosinophilic fibrinoid material. Multinucleated giant cells with peripherally arranged nuclei were frequently seen. ‘‘Doughnut type’’ granulomas were numerous.

By May 18, 1977, the patient had become consistently afebrile. He was treated with isoniazid, 300 mg, q.d., ethambutol, 1,000 mg, q.d., and tetracycline, 500 mg, q.i.d., because of the possibility of tuberculosis, brucellosis, or Q fever. On May 20, 1977, isoniazid was discontinued because of an urticarial reaction, and rifampin, 600 mg, q.d., was substituted. The patient was discharged on May 20, 1977, in good health.

Serologic tests for brucellosis, leptospirosis, and tularemia were reported as negative on May 31, 1977. Specimens for complement-fixation tests for influenza A, influenza B, parotitis, adenovirus, mycoplasma, Q fever, and cytomegalovirus drawn on May 18, 1977 and May 27, 1977, were reported as anticomplementary.

On June 17, 1977, the patient remained well, and tetracycline was discontinued. Repeated serologic tests on June 29, 1977, revealed a
complement-fixation titer for Q fever positive at 1:2,048. Convalescent follow-up titer obtained on September 30, 1977, was 1:1,024.

Discussion

Granuloma may be a macroscopic or microscopic term. It is usually characterized by a fairly well circumscribed firm area, as compared with the uninvolved adjacent tissue, or may be characterized by the accumulation of varying numbers of large mononuclear phagocytes (macrophages) derived from proliferating reticuloendothelial cells. The finding of granulomas in the bone marrow represents an inflammatory response by the host to a diverse variety of stimuli, including neoplasms (lymphomas and Hodgkin’s disease); bacteria (brucellosis); fungi (histoplasmosis); mycobacteria (tuberculosis); viruses (infectious mononucleosis); and unknown causes (sarcoidosis). In Pease’s study $^{48}$ granulomas for which no etiologic agent or process could be identified were also found. Lipid granulomas are not uncommonly found in sections of bone-marrow biopsy or bone-marrow clot, $^{23}$ and their etiology is unknown.

On the basis of histologic examination alone, the characteristic features of a granuloma may allow the clinician to narrow considerably the differential diagnosis. A proliferative or epithelioid granuloma with or without giant cells is relatively nonspecific, and may be seen in patients with tuberculosis, sarcoidosis, infectious mononucleosis, leprosy, kala-azar, or sometimes even malignant lymphoma. A necrotizing granuloma is seen in tuberculosis (caseous necrosis), syphilis (gumma), some fungal infections (such as histoplasmosis or coccidioidomycosis), and Hodgkin’s disease. A supplicative granuloma is frequently seen in association with bacterial or viral infections such as tularemia, lymphogranuloma venereum, cat-scratch disease, melioidosis, and brucellosis. A definitive diagnosis, nevertheless, has to rely on the demonstration of microorganisms...
in the tissue section by appropriate special stains, serologic tests, or bacterial cultures from the tissue or fluids.

In the evaluation of the patient with fever of unknown origin, the use of bone-marrow biopsy is achieving increasing utility. In Petersdorf and Beeson’s original series, bone-marrow biopsy was performed in only four of 100 cases and was diagnostic in two. Subsequent reports have shown the efficacy of bone-marrow examinations in military tuberculosis, where the procedure is diagnostic in 15-40% of cases. In fact, bone-marrow examination performed as part of the evaluation of fever of unknown origin has established the diagnosis of tuberculosis in occasional early cases in which roentgenograms of the chest showed no abnormality. Similarly, bone-marrow examination with appropriate stains of granulomas may provide rapid diagnosis of disseminated histoplasmosis. Granulomas have also been seen frequently in cases of brucellosis, and positive bone-marrow cultures may be found when blood cultures are negative. In our patient were not unlike “lipid granuloma.” In case of any doubt, serial sections may be helpful. The clinical manifestations, the serologic findings, and the response to tetracycline all differentiate lipid granuloma from Q fever.

The pathologic changes of Q fever are less well known, although some feel that a distinctive type of eosinophilic necrosis occurs in the walls of the sinusoids in the liver. The bone marrow has not been studied as carefully in this entity. Perrin reported a fatal case of Q fever in which the marrow was described as showing an increase in fat and a depression of the myeloid elements. Lillie and associates described bone-marrow granulomas in experimental animals but normal marrow in a human case. Ende and Gelpi described a case in a man in whom they found changes in the bone marrow consistent with an angiitis. Bernstein and colleagues, in their description of the hepatic lesion of Q fever, mentioned its similarity to the bone-marrow lesion of Endc and Gelpi, while Dupont and co-workers did not identify a similar histologic pattern in their cases of patients with Q fever hepatitis. The diversified appearances of these granulomas seen in histologic sections in cases of Q fever have ranged from a proliferative lesion (characterized by an accumulation of foamy histiocytes) to a necrotizing lesion (characterized by fibrinoid necrosis with subsequent polymorphonuclear leukocyte infiltration), and a specific “doughnut granuloma” (characterized by an empty space in the center of the lesion, rimmed by polymorphonuclear leukocytes and epithelioid cells, surrounded by eosinophilic fibrinoid material and/or eosinophils). Schleicher illustrated a “doughnut-type” granuloma from a patient with acute typhoid fever that was similar, but not identical, to the lesions in our patient. However, neither a description of the lesion nor detailed clinical information was available. It is therefore difficult to be absolutely certain that the “doughnut granulomas” seen in these two entities are the same. We believe the histologic findings in our case are similar to those described by Ende and Gelpi, although they regarded this lesion as representing a form of vasculitis. Nevertheless, several intact blood vessels were seen in the sections of the bone marrow in our patient. Furthermore, elastic stain by Verhoeff’s method and periodic acid-Schiff reaction failed to demonstrate elastic or basement-membrane components in the granulomas. It was shown from serial sections of our case that the lesions might be related to the vasculature, as they frequently appeared in the vicinity of the blood vessels. It is therefore probably more appropriate to consider this a perivasculitis. Some “punched-out” lesions in our patient were not unlike “lipid granuloma.” In case of any doubt, serial sections may be helpful. The clinical manifestations, the serologic findings, and the response to tetracycline all differentiate lipid granuloma from Q fever.

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CASE REPORTS

Immunoblastic Sarcoma Following Waldenström’s Macroglobulinemia

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Choi, Young, Yeh, George, Reiner, Leopold, and Spielvogel, Arthur: Immunoblastic sarcoma following Waldenström’s macroglobulinemia. Am J Clin Pathol 71:121-124, 1979. Immunoblastic sarcoma has been observed in association with, or subsequent to, chronic immune stimulation, connective tissue disorders, and immunoblastic lymphadenopathy. A case of Waldenström’s macroglobulinemia progressing after a few years into immunoblastic sarcoma is reported. Splenectomy led to disappearance of hemolytic anemia and of pulmonary infiltrates, as well as to marked reduction of macroglobulins. Although immunoblastic sarcoma usually terminates fatally within two or three months, complete remission was induced by combination chemotherapy. It is speculated that Waldenström’s macroglobulinemia, immunoblastic lymphadenopathy, and immunoblastic sarcoma are related disorders reflecting a clonal nature of immunoblastic lymphoma cells and the plasmacytic cells. (Key words: Immunoblastic sarcoma; Waldenström’s macroglobulinemia; Splenectomy.)

IN 1974, LUKES AND COLLINS described a malignant lymphoma that they designated immunoblastic sarcoma. The disease is characterized by a monomorphous proliferation of immunoblasts, i.e., large cells with plasmacytoid features. Immunoblastic sarcoma has been observed in association with, or subsequent to, connective tissue disorders, chronic immune stimulation, and immunoblastic lymphadenopathy. We report the case of a patient whose disease originally had the classic features of Waldenström’s macroglobulinemia, evolving into immunoblastic sarcoma some years later.

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Report of a Case

A 38-year-old woman, when first seen in September 1972, had a two months’ history of weakness, pallor, and progressive blurring of vision. Physical examination revealed cervical lymphadenopathy, splenomegaly, and sausage-shaped retinal vessels with hemorrhages and bilateral blindness. The hematocrit was 18.5% and the leukocyte count 5,700/cu mm, of which 55% were polymorphonuclear leukocytes and 38% were lymphocytes. Platelets were 232,000/cu mm. Marked rouleaux formation was seen on smear. Serum protein electrophoresis showed an M-spike consisting of 7,000 mg/dl of IgM of k type. A biopsy and smear of the bone marrow revealed aggregates of plasmacytoid lymphocytes. A diagnosis of Waldenström’s macroglobulinemia was made. Microscopic examination of an enlarged cervical lymph node was considered compatible with that diagnosis. The patient immediately underwent several courses of plasmapheresis by IBM-NCI cell separator, which reduced serum viscosity from 12.0 to 3.2. Her general condition improved following treatment with chlorambucil, and remained relatively stable on a maintenance dose (4 mg daily). The hematocrit stayed around 30% and IgM around 2,000 mg/dl. Additional plasmapheresis was necessary twice because of recurrence of symptoms and increases of IgM. During this period the patient had persistently high reticulocyte counts of 5-10% and low haptoglobin levels (10 mg/dl), both suggesting hemolysis. Coombs’ test and cold agglutinin tests were negative, however.

In January 1975, the patient was readmitted because of severe pain in the left upper quadrant, dry cough, and anemia. Hematocrit was 15% and leukocyte count 5,200/cu mm. Platelet count was 160,000/cu mm. IgM was 2,900 mg/dl. Lymphadenopathy was not seen. Chest x-ray showed diffuse reticulonodular infiltrates. A scan of the spleen revealed great enlargement as well as an infarct. The spleen was removed uneventfully and, after several weeks, chlorambucil was increased to 8 mg/day for six weeks. The patient’s condition im-