Agranulocytosis and aplastic anemia possibly due to ibuprofen

To the editor: We wish to report a case of agranulocytosis and aplastic anemia possibly due to ibuprofen (Motrin, Upjohn), which we recently encountered. Except for "sporadic abnormalities of white blood count",[1] no hematologic complications appear to have been reported with the use of this drug.

An 82-year-old woman had been a resident of a home for the aged for almost 4 years, requiring general nursing care because of severely disabling joint disease.

Her joint complaints had started about age 50 and she had since been treated primarily with salicylates. Knees and shoulders had been most severely affected and she had received at least one intra-articular injection of dexamethasone in the shoulder; earlier that year, 1971, she had received a 1-week course of phenylbutazone without any apparent undesirable side effects.

The clinical and radiographic appearance of her joints strongly suggested rheumatoid arthritis. Her arthralgia had never had the typical features of acute gout. Degenerative changes were evident radiographically in the cervical and lumbar spine but did not appear to be producing symptoms.

A summary of selected laboratory data and therapy is shown in Fig. 1. The erythrocyte sedimentation rate had been moderately elevated between 1971 and 1974 (33 to 89 mm/h) but the latex fixation test had repeatedly been negative. Total serum protein value and electrophoresis findings were normal, and search for LE cells was negative at least twice. Serum uric acid values varied widely (3.0 to 8.7 mg/dl), probably the combined result of varying doses of salicylates and progressive renal insufficiency (serum urea nitrogen values, 22 to 32 mg/dl).

Abdominal distress had been a recurring complaint for at least the last 4 years and salicylates had been suspected as the cause. A variety of antacids had been used to control this, and on Feb. 25, 1975 acetaminophen had been substituted for salicylates to avoid further gastric irritation. This provided less effective analgesia, and 1 week later ibuprofen therapy was introduced, at 600 mg/d, but it was apparently of no benefit.

Mild sideropenic anemia had been evident since at least 1971. Because of associated mild intermittent rectal bleeding sigmoidoscopy and radiography of the upper and lower intestine were performed; only diverticulosis coli and hiatus hernia with reflux were revealed. The bleeding was attributed to obvious hemorrhoids, and iron therapy was initiated with a series of injections of iron sorbitex (Jectofer) and continued with ferrous succinate, then ferrous sulfate and ferrous gluconate. No iron was given after Mar. 25, 1974. No appreciable improvement in hemoglobin concentration or hematocrit occurred except for a mild increase between April and September 1974 (Hb values, 10.7 to 12.0 g/dl; Hct., 35 to 37%); values then subsided to their previous range (Hb, 9.4 to 11.3 g/dl; Hct., 29 to 35%). Hematologic studies were repeated at approximately monthly intervals throughout this time, and between July 2 and Sept. 3, 1975 an abrupt decrease in leukocyte count was noted (from 4.5 to 2.6 x $10^9/l$). Previous leukocyte counts had ranged from 3.3 to 7.5 x $10^9/l$ (average, 4.96 x $10^9/l$), and since May 6, 1975 there had been a definite downward trend. Ibuprofen therapy was discontinued Sept. 9, 1975.

About Sept. 16, 1975 malaise, anorexia and a mild sore throat developed. One week later her oral temperature was noted to be elevated (38.6°C) and it remained so; she was therefore admitted to hospital. Leukopenia worsened during the final 24 hours of life and granulocytes virtually disappeared; the number of lymphocytes was noted to be 0.8 x $10^9/l$ from a buffy coat count. Abnormal physical findings at this time were minimal and nonspecific. She was restless and stuporous, with tachypnea and tachycardia but normal blood pressure. The tongue was dry but otherwise normal, and the pharynx was moderately red, with a mucoid, nonpurulent postnasal discharge. Indefinite inspiratory crepitations were heard at both lung bases, and a long-standing apical systolic murmur was unchanged. Because of obesity and reflex guarding, results of abdominal palpation were not definitive; there did not appear to be hepatomegaly but the spleen was palpable to some observers. Lymph nodes were not enlarged and there was no purpura.

Routine laboratory tests revealed hyponatremia (serum sodium value, 127 mmol/*l*) and hypochloremia (serum chloride value, 89 mmol/*l*), with normal serum potassium value (4.6 mmol/*l*) and CO_2 content (25 mmol/*l*). Mild azotemia (serum urea nitrogen value, 31 mg/dl) was noted; values were unchanged from those observed over the previous 2½ years. Urinalysis disclosed moderate proteinuria but only occasional leukocytes, and urine culture was sterile. Cultures of blood yielded only *Staphylococcus epidermidis*, indicating contamination from the skin. No abnormal opacifications were seen on lung radiographs.

The severe leukopenia was thought to be evidence of a drug reaction, and all medications but digoxin were discontinued on Sept. 23. Digoxin had been used continuously since June 1972 for heart failure, the consequence of an acute myocardial infarction. Other agents withdrawn included furosemide (initiated in June 1972) and potassium chloride.

Her condition deteriorated rapidly, with declining level of consciousness and increasing dyspnea, and she died Sept. 24, about 48 hours after admission to hospital, no specific therapy having been instituted. No autopsy was done.

This case has been reported to the drug adverse reaction program of the health protection branch of Health and Welfare Canada.

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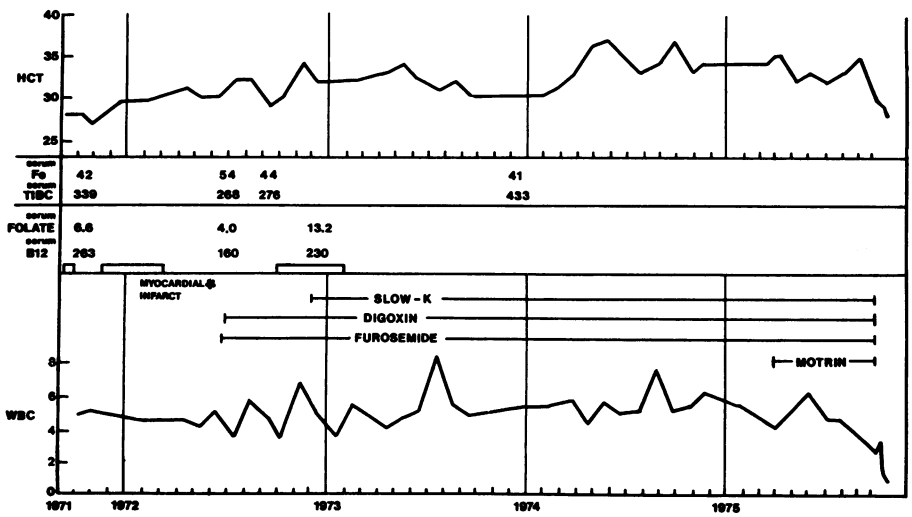

FIG. 1—Selected laboratory data and therapy over 4-year period in elderly woman with severely disabling joint disease. Values are given in the following units: hematocrit, %; serum iron, μg/dl; serum total iron-binding capacity, μg/dl; serum folate, ng/ml; serum B_{12}, pg/ml; leukocyte count, x $10^9/l$.

Reference

1. Motrin, in *Compendium of Pharmaceuticals and Specialties*, 10th ed, ROTENBERG GN, HUGHES FN (eds), Toronto, Can Pharm Assoc, 1975, pp 451-52

Constrictive pericarditis and pericardial calcification with positive histoplasmin skin test

To the editor: Histoplasma capsulatum was first reported as the etiologic agent of an acute, disseminated, fatal disease in 1906 by Darling.[1] In 1955 Billings and Couch[2] described two patients with pericardial calcification and histoplasmin sensitivity and suggested that *H. capsulatum* might be the cause of the pericardial disease.

Constrictive pericarditis is an uncom-

mon disease: in a 10-year period only 79 cases were evaluated at the Mayo Clinic.[3] We have recently studied two patients from the Ottawa area who were admitted to the cardiology service of Ottawa Civic Hospital in May 1974 with constrictive pericarditis and pericardial calcification.

Patient 1

A 51-year-old man was admitted to hospital with a 2-year history of shortness of breath on exertion and palpitation, and a 2-week history of swelling of both legs and abdominal discomfort. He had had no chest pain.

Blood pressure was 100/65 mm Hg; radial pulse rate was 100 beats/min and the rhythm, irregular. Jugular venous pressure was estimated at 6 cm H_2O; no a waves were noted in the pulse, the y descent was sharp and Kussmaul's sign was observed. No clubbing or cyanosis was noted. Pitting edema was detected in both legs. The first heart sound was loud, the second was split and a pericardial knock was heard at the apex. Coarse crepitations were heard at both lung bases. The liver was tender and palpable 4 cm below the right costal margin. Moderate ascites was noted.

Laboratory investigations yielded the following abnormal values: erythrocyte sedimentation rate (ESR), 55 mm/h; serum alkaline phosphatase, 190 IU/*l*; serum albumin, 2.8 g/dl; and total serum bilirubin, 2.4 mg/dl. A trace of albumin was detected in the urine. The electrocardiogram (ECG) showed atrial fibrillation, a ventricular rate of 86 beats/min and nonspecific ST-segment and T-wave changes. Apex cardiogram showed retraction of the apex during ventricular systole, with a large, early-diastolic outward motion. Chest radiographs in several views showed linear pericardial calcification and perihilar calcified spots. Tuberculin skin test with 5 TU of purified protein derivative (PPD) was negative but histoplasmin skin test with 0.1 ml of histoplasmin was strongly positive (14 mm of induration). Sputum cultures were negative. The titre of complement-fixing serum antibodies to *H. capsulatum* was 1:4.

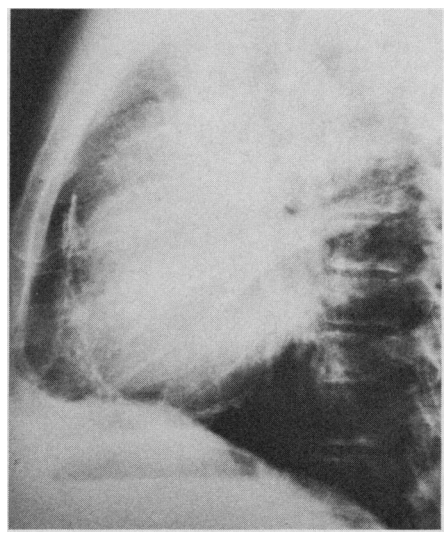

FIG. 1—Linear pericardial calcification in patient 2 preoperatively.

Patient 2

A 55-year-old man was admitted to hospital with a 2-month history of shortness of breath on exertion and a 1-month history of swelling of both legs and pain in the right hypochondrium. He had had no chest pain.

Blood pressure was 120/80 mm Hg; radial pulse rate was 120 beats/min and the rhythm, regular. Jugular venous pressure was estimated at 4 cm H_2O; the y descent was sharp and Kussmaul's sign was present. Pitting edema was noted in both legs. The apex beat was ill-defined. The first heart sound was normal but the second was split and a pericardial knock was heard at the apex. Coarse crepitations were detected at both lung bases. The liver was palpable 2 cm below the right costal margin and there was evidence of minimal ascites.

Laboratory investigations yielded the following abnormal values: ESR, 30 mm/h; serum alkaline phosphatase, 105 IU/*l*; serum albumin, 3.2 g/dl; and total serum bilirubin, 1.2 mg/dl. A trace of protein was detected in the urine. ECG showed atrial flutter (240 beats/min) with a 2:1 ventricular response, nonspecific ST-segment and T-wave changes and borderline low voltage. Chest radiography and fluoroscopy revealed pericardial calcification (Fig. 1). Tuberculin skin test with 5 TU of PPD was negative but histoplasmin skin test with 0.1 ml of histoplasmin was strongly positive (12 mm of induration). The titre of complement-fixing serum antibodies to *H. capsulatum* was 1:2.

Special investigations

Characteristic findings from cardiac catheterization in both patients were elevated mean right atrial pressure, M pattern of the right atrial pressure pulse and early diastolic dip, and elevated end-diastolic pressure in both ventricles. Pulmonary wedge, pulmonary artery, right ventricular end-diastolic, mean right atrial and superior vena caval pressures were identical in the two patients. Cardiac outputs were within normal limits. Coronary artery angiograms were normal.

Treatment

The two patients underwent pericardiectomy. Both required digoxin and diuretics during the immediate postoperative period. Much symptomatic improvement was observed in both patients during 6 months of postoperative follow-up. Histopathologic study and culture of pericardial tissue failed to demonstrate fungal growth.

The cause of calcification of the pericardium is obscure in many instances. In most cases, by the time bacteriologic and pathologic studies can be undertaken, evidence of specific infection or injury is not demonstrable. Pericardial calcification is seen in approximately half the patients with constrictive pericarditis. Chronic constrictive

pericarditis is thought to result from the healing of acute fibrinous or serofibrinous pericarditis;[4] most cases are due to tuberculosis, but some are due to staphylococcal or pneumococcal infection.

It is unlikely that pericardial calcification due to histoplasmosis is a new entity, but it has probably often been overlooked. It is frequently difficult to differentiate from other types of calcification without histoplasmin skin testing.[5] Brodsky and colleagues[6] reported that skin tests were positive in 70 to 79% of residents in Delaware County, Ohio during an outbreak of histoplasmosis. The Ottawa Valley has been reported to be an area of high prevalence of skin-test sensitivity (A.G. Jessamine, Provincial Chest Clinic, Ottawa: personal communication, 1974) and positive titres of complement-fixing antibodies to *H. capsulatum* (S.E. Johnson, community health protection branch, Ontario Ministry of Health: personal communication, 1974). Complement-fixing antibodies appear in the blood about the 3rd week after pulmonary infection with this fungus. There is some evidence that the antibody titre in histoplasmosis is proportional to the severity of the infection; with recovery the antibodies gradually disappear from the blood.

A definitive diagnosis of histoplasmosis can be made only by isolating the fungus,[7] and in our patients special stains failed to demonstrate any fungi in the pericardial tissue sections. However, in an area of high incidence of histoplasmosis, strongly positive histoplasmin skin tests suggest the diagnosis. Histoplasmin skin tests and complement-fixing antibody tests are valuable in recognizing acute pericarditis due to *H. capsulatum* and in determining the cause of pericardial calcification with constrictive pericarditis.

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