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Quindine-induced hepatitis has received more attention only recently whereas quinidine-induced thrombocytopenia is well recognized. Over the past two years the authors saw four patients with quinidine-hepatitis accompanied by malaise, anorexia, fever in two patients and marked elevation of liver enzymes in all. Two patients had associated quinidine-induced thrombocytopenia of 81,000 and 6,600 platelets / cu mm, respectively. Liver biopsy in two patients revealed small foci of hepatocellular necrosis, Kupffer cell hyperplasia and Kupffer cells containing lipochrome. In one patient noncaseous granulomatous lesions were seen. Symptoms subsided and laboratory tests returned to normal rapidly on withdrawal of quinidine. In one patient, drug challenge reproduced symptoms and abnormal liver function test results. Quinidine-induced hepatitis is probably more frequent than recognized heretofore and may be associated with quinidine-induced thrombocytopenia.

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HEPATITIS or abnormal liver function test results have been reported with a number of drugs.[1] Only recently has quinidine hepatotoxicity been reported.[2-8]. According to a recent report,[8] there was a 2% incidence of quinidine-induced hepatitis and a 6.5% incidence of hypersensitivity reactions to quinidine which included skin rash, fever, diarrhea, liver involvement, hemolytic anemia and thrombocytopenia. We present four patients with quinidine-induced hepatitis, two of whom also had quinidine-induced thrombocytopenia. This combination has not been previously noted in case reports of quinidine hepatitis.

Case 1

A 73-year-old black housewife had been under observation for arteriosclerotic heart disease, old anterior myocardial infarction and angina pectoris. On April 22, 1975, she was hospitalized for pulmonary embolus. Multifocal ventricular premature contractions (VPC) were noted and quinidine gluconate, 330 mg, orally every 12 hours, was administered. Prior to initiating quinidine therapy, liver enzymes were normal (Table 1). VPCs were suppressed and the patient was discharged.

On May 23, 1975, she was readmitted with a two-day history of marked anorexia, malaise, nausea without vomiting and loose bowel movements. She denied fever, chills, abdominal pain, change in color of stool or urine. There was no history of blood transfusion, ethanol abuse or gall bladder disease. Medications at the time of admission included quinidine gluconate, warfarin, digoxin, furosemide, potassium chloride and nitroglycerin.

When examined, she was afebrile and had questionable scleral icterus. There was slight car-

iomegaly. The abdomen was soft without any tenderness, hepatosplenomegaly or lymphadenopathy. Other findings of the physical examination were also within normal limits.

Laboratory studies revealed a normal white blood cell and differential count. There was no eosinophilia. Serum electrolytes, blood urea nitrogen, serum creatinine, hemoglobin, hematocrit, platelet count, serum protein electrophoresis and urine analysis were all within normal limits. Hepatitis B antigen and antibody, purified protein derivative skin test for acid fast bacilli were negative. Liver function tests are summarized in Table 1.

Quinidine and all other medications were discontinued on May 23, 1975. The patient became asymptomatic in the next three days and liver enzymes gradually became normal. Since the patient was on five other medications at the time of her liver dysfunction, it was decided, after informed consent was obtained, to challenge her with a single dose of quinidine sulfate, 200 mg on August 3, 1975. Prior to quinidine challenge, she was taken off all medications for three weeks. The liver enzymes were normal just before quinidine challenge. Thirty-six hours after the oral dose of quinidine sulfate, the liver enzymes all became abnormally elevated (Figure 1), confirming the clinical diagnosis of quinidine-induced hepatitis. After the quinidine challenge she felt slight malaise but was afebrile. A lymphocyte transformation test performed with quinidine on August 4 was negative.

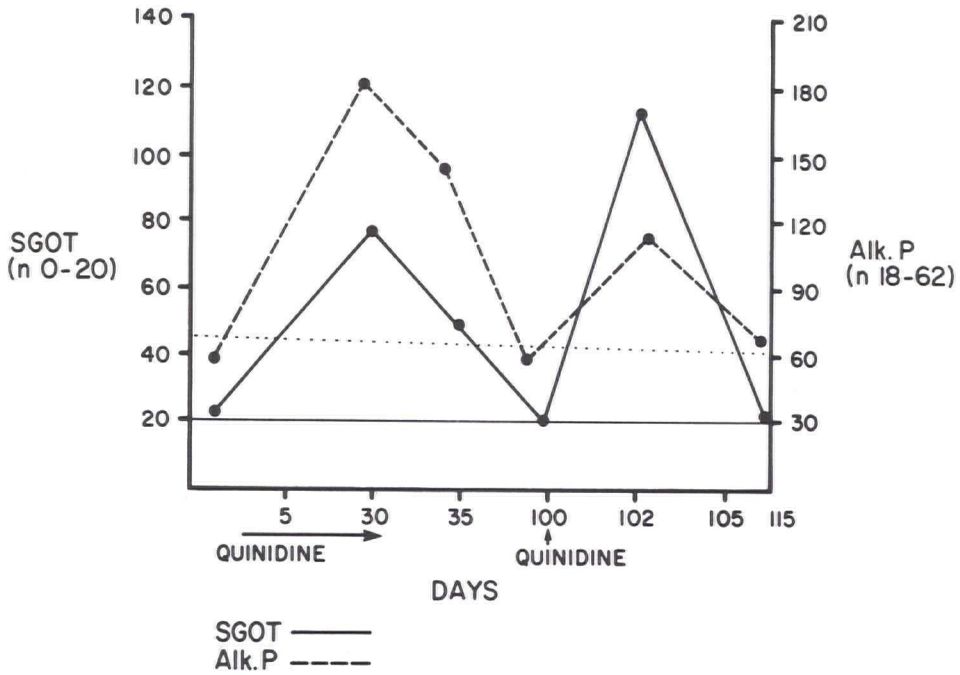

Figure 1
Elevation of both SGOT (serum glutamic oxalactic transaminase) and Alk. Phos. (alkaline phosphatase) after a single dose of quinidine sulfate.

Case 2

A 57-year-old white male was hospitalized in January, 1975, with acute myocardial infarction. In early February, 1975, he was put on a regimen of quinidine sulfate, 300 mg (Quinidex), orally every eight hours for frequent premature ventricular contractions.

Three weeks later, the patient developed fever of 104°F (40°C) along with chills. The fever and chills persisted all through March and early April. He was admitted to the hospital on April 11, 1975, for evaluation of fever of undetermined origin. He denied any history of blood transfusions, ethanol abuse or gastrointestinal symptoms. There was no evidence of heart failure. Medications prior to admission included quinidine sulfate and pentaerythritol tetranitrate.

Physical examination revealed a questionable scleral icterus. The temperature was 38°C. Cardiovascular examination was completely normal. The abdomen was soft, without any tenderness, hepatomegaly or lymphadenopathy. The patient developed a macular skin rash on both legs on the second hospital day. The rest of the physical examination was within normal limits.

Laboratory studies showed a normal white blood count and differential count. Hemoglobin was slightly low at 11.9 grams. Hematocrit was 36.0. Platelets were reduced on blood smear and the platelet count was low at 81,000. The patients had negative blood cultures, hepatitis B antigen and antibody, lupus erythematosis cell phenomenon, negative antinuclear factor and alpha fetoprotein. Urine analysis, serum electrolytes, serum creatinine, blood sugar, serum protein electrophoresis, immunoelectrophoresis, prothrombin time, were all within normal limits. Chest x-ray and oral cholecystogram were negative. Lymphocyte transformation test with quinidine was negative. Liver biopsy, done on April 23,* showed hepatitis which was characterized by presence of numerous small foci of hepatocellular necrosis and Kupffer cell hyperplasia. In the necrotic areas, hepatocytes were pyknotic or degenerative with lipid vacuoles. There were variable numbers of leukocytes which included lymphocytes, plasma cells, neutrophils and a few eosinophils. A round, phagocytized, "eosinophilic" body was also seen. The necrotic process was gradually replaced by Kupffer cell hyperplasia. The Kupffer cell lesions often contained lipofuscin pigment, and looked granulomatous (Figure 2) without caseation necrosis or Langhans' giant cells.

The patient became afebrile three days after discontinuation of quinidine. The skin rash subsided and the platelet count became normal. Liver enzymes returned to high normal level (Table I).

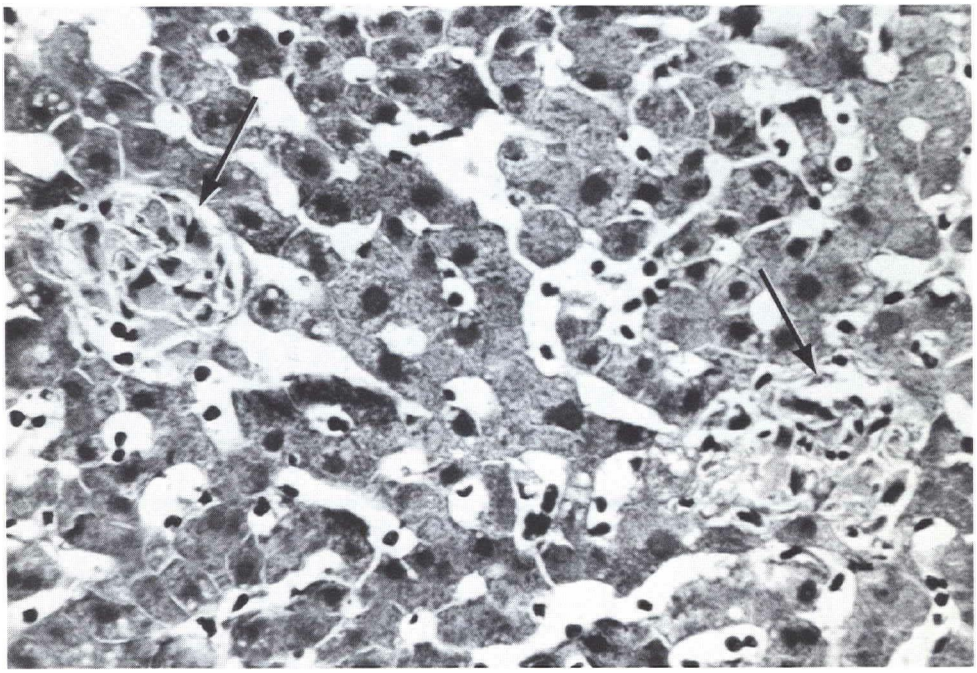

Figure 2

The liver biopsy of second patient showing granulomatous lesions(arrows) without caseation necrosis or Langhans' giant cells.

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TABLE I

Liver Function Test Results and Platelet Counts (Peak Values) Before, During and After Quinidine Therapy

Case No.	SGOT (nl. 0-21)			SGPT (nl. 0-20)			Alkaline Phosphatase (nl. 18-62)			S. Bilirubin (nl. 0.2-1.0)			Platelet Count (nl. 200,000-400,000)	
	Before	During	After	Before	During	After	Before	During	After	Before	During	After	During	After
(1)	23	112	24	—	73	27	—	181	78	—	2.9	0.6	Normal	Normal
(2)	—	88	36	—	161	38	—	492	75	—	2.4	0.8	81,000	302,000
(3)	—	420	15	—	580	49	—	—	—	—	—	—	6,600	315,000
(4)	16	88	15	9	67	—	54	798	58	0.4	1.1	—	Normal	Normal

SGOT (serum glutamic oxalacetic transaminase)
SGPT (serum glutamic pyruvic transaminase)

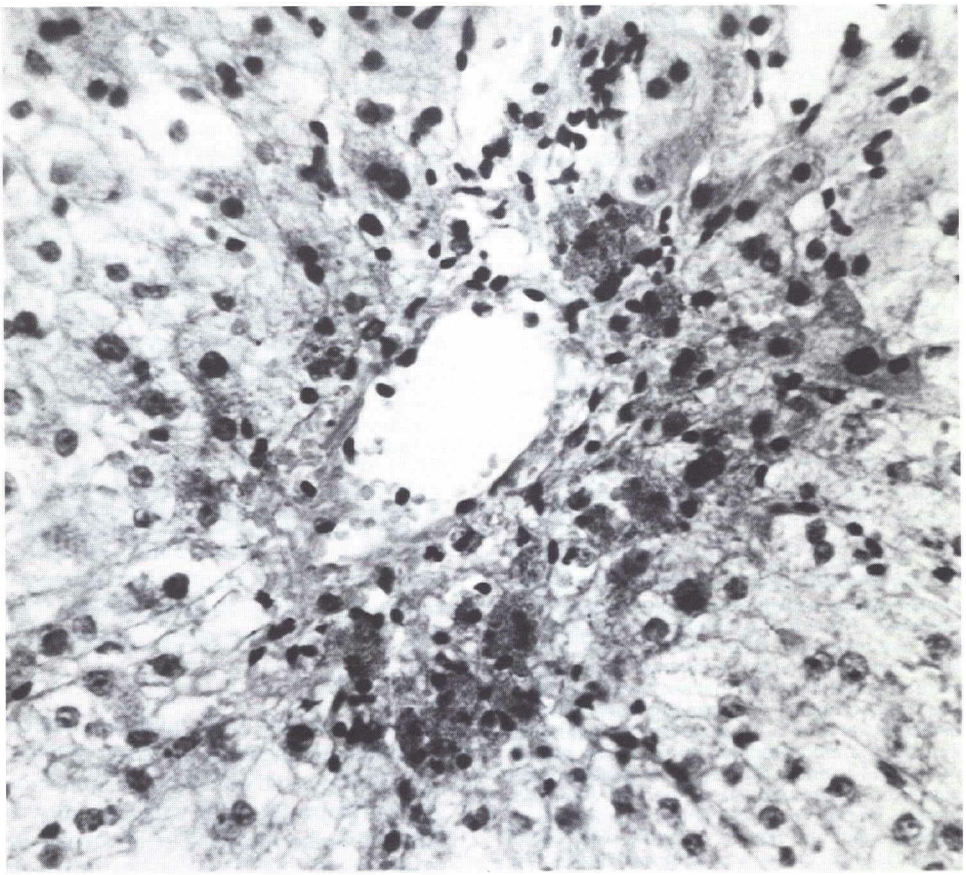

Figure 3
The liver biopsy of the fourth patient showing periportal collection of inflammatory cells. There was Kupffer cell hyperplasia, many cells containing lipofuscin pigments.

Case 3

A 64-year-old white housewife was admitted on 3/22/76 with a history of acute lower back pain which radiated down her right leg to her right foot. The onset of pain had been six days prior to admission with constant progression in the severity and intensity of the pain. The patient had been treated in the past for angina pectoris and had had an initial episode of paroxysmal atrial fibrillation, causing syncope in September of 1975. At that time, isosorbide dinitrate and nitroglycerin were prescribed. She did well until February, 1976, when she had a recurrent syncopal episode, secondary to paroxysmal atrial fibrillation. She was given quinidine gluconate, 330 mg every 12 hours to control her arrhythmia. Since that time, her rhythm had remained sinus. She had rectal polyps removed four weeks prior to admission without hemorrhage. Two weeks prior to admission, the patient noted weakness, fatigue and poor appetite with intermittent vomiting. She noted that her urine became darker at that time. At the time of admission her physical examination revealed no icterus. There were no ecchymoses or petechiae. There was no hepatosplenomegaly. An initial laboratory study revealed abnormal liver function tests (Table 1). The hemoglobin was 11.9, hematocrit of 39.8, WBC of 5,100 with 23 bands, 9 monocytes, 18 lymphocytes, 50 neutrophils. Platelets were reported as "adequate." Quinidine-induced liver disease was suspected. In preparation for a liver biopsy, routine clotting studies were ordered and her platelet count was found to be 6,600/cu mm. The quinidine gluconate had been discontinued on 3/25/76. A quinidine clot retraction test was positive. In this test, fresh whole blood of a normal person of compatible blood group was added to a test tube containing the patient's serum plus a solution of quinidine (10) and this inhibited platelet dependent clot retraction. Direct and indirect Coombs test, Australian antigen and antinuclear factor were negative. It was felt that her lower back pain could be secondary to expanding subarachnoid hematoma at level L_2-L_3, secondary to quinidine-induced thrombocytopenic purpura. The patient was given 10 units of platelet concentrate and was placed on prednisone, 80 mg per day. After this therapy, improvements in clinical state as well as platelet count and hepatic enzymes were noted (Table 1). A liver biopsy was performed on 4/5/76 (Figure 3) and the most striking feature was that of Kupffer cell hyperplasia, with numerous Kupffer cells containing a golden yellow-brown pigment which represented lipofuscin. Small accumulations of lymphocytes with occasional neutrophils were also present within hepatic lobules. No evidence of granulomas was seen. Bone marrow aspiration revealed normal thrombocytogenesis.

Case 4

A 61-year-old white physician had an acute transmural myocardial infarction on 12/10/75. His post-infarct course was uneventful.

He was seen on 12/29/75 because of multifocal premature ventricular contractions and was placed on quinidine sulphate (Quinidex), 300 mg, four times daily.

He was admitted on 3/16/76, with a two-week history of fever, chills, night sweats, malaise and lethargy. He denied any history of abdominal, joint or muscle pain, pruritis, jaundice, change in urine or stool color.

The patient drank ethanol on rare occasions and did not have a history of gall bladder disease or exposure to known hepatotoxic agents. He was taking no other medication besides quinidine sulfate.

Physical examination revealed a temperature of 37.7°C. There was no jaundice or lymphadenopathy. The liver edge was felt 2 cm below the right costal margin with a total span of 14 cm. There was no splenomegaly and the rest of the physical examination was within normal limits. Laboratory studies revealed a white blood cell count of 3,600/cu mm with a normal differential count. Hemoglobin, platelet counts, prothrombin time, urinalysis were all within normal limits. Antinuclear factor, lupus erythematosis preparations, direct and indirect Coombs test, blood urine cultures and chest x-ray were all negative. Echogram of the liver revealed a normal liver and gall bladder. The liver function tests are summarized in Table 1.

Quinidine sulfate was discontinued on 3/15/76. The patient became afebrile within the next 36 hours and had an uneventful recovery.

Discussion

Fifteen patients with quinidine-induced hepatitis have been reported so far. We have presented four additional cases of quinidine-induced hepatitis along with quinidine-induced thrombocytopenia in the second and third patients. Malaise, nausea, anorexia, and/or fever, chills and abdominal pain were the presenting features in all of these four patients. These symptoms were consistent with the clinical diagnosis of quinidine-induced hepatitis or liver disease. In all the patients, the symptoms and hepatic enzymes elevation occurred after the patients had been using quinidine for three to eight weeks. All the patients improved clinically and the liver function normalized soon after quinidine was discontinued. This suggested quinidine as the causative drug.

The first patient was on five other medications besides quinidine when she first had liver dysfunction. However, her typical response to drug challenge confirmed quinidine as the drug responsible for hepatic damage. In all patients, history and laboratory studies ruled out liver disease due to other causative agents. All our patients, like the 15 reported cases, had reversible liver damage. The patient of Handler et al[7] ingested quinidine for 16 months and still the liver damage was reversible when quinidine was discontinued.

Two of our patients had concomitant thrombocytopenia besides quinidine induced liver disease. Thrombocytopenia and hepatitis were probably due to hypersensitivity to quinidine where the drug combined with a serum factor and acted like a haptene-forming antibody which caused platelet agglutination and liver cell destruction.

It is reported that quinidine caused platelet destruction by agglutination rather than serum complement induced platelet lysis.[9, 10] To our knowledge, there are no previous reports of concomitant thrombocytopenia and hepatitis due to quinidine in the literature. Histopathologic findings of the liver biopsies in our two patients were similar to those described by Handler et al[7] and by Chajek et al[5, 6, 8] where one patient had a nonspecific hepatitis and the other had a granulomatous hepatitis. The presence of granulomatous hepatitis which has been attributed to immune mechanism[11] and reported with hypersensitivity hepatitis due to many other drugs like allopurinol[12] phenyl butazone[13] and hydralazine[14] would seem to support the hypersensitivity theory for quinidine hepatitis.

There was no evidence of cholestasis in liver biopsy of our two patients or any patients described in the literature. The lymphocyte transformation test with quinidine was negative in two of our patients. Lymphocyte transformation test, when positive, is now accepted as a good in vitro test for drug hypersensitivity.[15] A negative test on the other hand does not rule out drug sensitivity.

In conclusion, quinidine hepatitis, though rare, should be considered in any patient with fever of undetermined origin or with vague gastrointestinal symptoms while taking quinidine. The combination of hepatitis and thrombocytopenia due to quinidine hypersensitivity can occur.

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