GRANULOMATOUS HEPATITIS IN A PATIENT RECEIVING ALLOPURINOL

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An alcoholic patient with normal liver function received 100 mg of allopurinol three times a day for 1 month. Fever, eosinophilia, and abnormal liver function were noted after 3 weeks and liver biopsy showed focal necrosis, fatty change, and noncaseating granulomas. One month following allopurinol withdrawal the patient was clinically well and had normal liver function. Liver biopsy showed no granulomas.

Since its introduction in 1962 and subsequent widespread use allopurinol (4-hydroxyprazolo-(3, 4-d) pyrimidine) has caused several adverse effects. Alopecia and ichthyosis, gastrointestinal distress and diarrhea, pruritus, macular rash leukopenia, and alterations in liver function with and without jaundice have been reported.1-6 All these abnormalities have subsided promptly after withdrawal of the drug. However, more serious adverse effects are being reported with increasing frequency. Reports of xanthine stones,7 bilateral ureteral obstruction,8 and fatal cases of toxic epidermal necrolysis9 and acute vasculitis10 are now in the literature.

This report documents the onset and resolution of granulomatous hepatitis in an alcoholic patient receiving allopurinol for acute renal failure secondary to rhabdomyolysis and myoglobinuria.

Case Report

A 50-year-old white male entered Wadsworth General Hospital on April 22, 1970 with a 1-week history of progressive weakness and swelling of upper and lower extremities associated with heavy drinking. Three days prior to admission he had noticed “almost black urine” and received an unknown amount of penicillin from a physician at another hospital.

He was hospitalized in 1968 for acute rhabdomyolysis and myoglobinuria secondary to alcoholism. Oliguria was present but responded to mannitol. Liver biopsy showed moderate focal fatty change. No granulomas were detected. Recovery was uneventful and although he continued to drink he had remained well.

Physical examination revealed an afebrile, dehydrated man with a blood pressure of 160/120 and a regular pulse of 100. The liver was enlarged to 20 cm by percussion. Upper and lower extremities were tender and slightly swollen with marked pain and weakness on active motion. Deep tendon reflexes were symmetrical throughout and cranial nerves were intact. Pertinent laboratory data obtained shortly on admission are shown in table 1 (April 23). The urine was positive for hemoglobin and myoglobin on spectrophotometry.

Electromyography showed findings consistent with an acute myopathy. After rehydration, an acute renal failure regimen consisting of fluid restriction, a diet low in sodium, potassium, and protein and 15 g of Kayexalate was instituted. Compazine and aluminum hydroxide gel were given for nausea. Three days after admission the serum uric acid was 12 mg per 100 ml and 100 mg of allopurinol, three times a day was started. Despite the gradual onset of a low grade fever, weight loss, and complaints of anorexia and night sweats, pro-
gressive improvement in renal and hepatic function was noted. Pertinent biochemical findings at this time are shown in table 1 (May 11).

Three weeks after admission, eosinophilia and a deterioration in liver function were observed (table 1, May 19). The uric acid was 4.1 mg per 100 ml. One month after admission allopurinol was discontinued and a liver biopsy was performed revealing multiple, non-caseating epithelioid granulomas chiefly in or adjacent to portal triads, focal necrosis, and a mild, fatty metamorphosis (fig 1). Special stains for acid-fast bacteria and fungi were negative. The biopsy was not cultured. However, serological tests for salmonella, syphilis, typhus fever, mononucleosis, coccidiomycosis, brucellosis, and viral hepatitis and intradermal tests for histoplasmosis, coccidiomycosis, blastomycosis, and tuberculosis were negative. An X-ray film of the chest was normal. Other medications received were chloral hydrate, multivitamins, milk of magnesia, and mineral oil. No history of allergy to penicillin or exposure to other drugs or toxins could be elicited.

Shortly after allopurinol was discontinued the patient became afebrile and noted a marked increase in appetite. Fourteen days after discontinuing allopurinol liver function was entirely normal although eosinophilia persisted (table 1).

One month after stopping allopurinol liver biopsy was repeated. A 2-cm specimen showed complete absence of granulomas with occasional areas of focal necrosis, mild fatty change, and portal fibrosis. Culture of the biopsy was negative. Liver function was normal but eosinophilia persisted (table 1, June 17). An oral cholecystogram revealed a normally functioning gallbladder.

Four months following allopurinol withdrawal the patient was again hospitalized with acute rhabdomyolysis secondary to alcoholism. Liver biopsy showed only mild fatty change. An absolute eosinophil count was 425.

### Discussion

There is convincing clinical and laboratory evidence that this alcoholic patient experienced his second episode of rhabdomyolysis and renal failure. The syndrome of painful muscles, elevated enzymes, abnormal electromyography with myoglobinuria, and renal failure closely parallels that described by Perkoff et al.\(^1\) and others.\(^2\)

Because rechallenge with allopurinol was not possible in this case there is no direct proof that allopurinol caused a granulomatous hepatitis. However, there is substantial indirect evidence in that physical examination, skin testing, bac-
FIG. 1. Liver biopsy following allopurinol showed fatty change, focal necrosis, and an epithelioid granuloma containing a giant cell (hematoxylin and eosin, × 400).

The possibility that granulomatous disease predated the institution of allopurinol must be considered. Liver biopsy obtained 2 years previously showed no granulomas and the patient had remained clinically well in the interval. Extensive clinical, radiographic, and serological tests revealed none of the common causes of granulomatous disease as listed by Guckian and Perry. Furthermore, it seems extremely unlikely that a long-standing, histologically active granulomatous hepatitis would coincidentally resolve in 1 month.

Although the hepatomegaly and elevated bilirubin and alkaline phosphatase noted on admission were consistent with alcoholic hepatitis, the hyperenzymemia may well have been due to the rhabdomyolysis. It is noteworthy that prior to the onset of malaise, fever, and eosinophilia the liver function had returned to normal. Unfortunately, decrease in the hepatomegaly was not documented.

The abnormal liver function seen after 4 weeks of allopurinol (table 1) is not consistent with alcoholic hepatitis. Furthermore, alcoholic hepatitis is excluded by lack of appropriate histological changes in the biopsy obtained at that time.

Lipogranulomas associated with fatty liver have been described. Typically, lipogranulomas are located in the parenchyma often close to central veins and on serial sectioning can be shown to contain fat vacuoles. Serial sectioning was not performed in this case but none of the numerous epithelioid granulomas seen contained fat vacuoles and the majority were in portal tracts. Liver biopsies obtained 2 years before and 4 months following this hospitalization showed fatty change but no evidence of lipogranuloma formation. As
abstinence from alcohol and improvement in hepatic function was documented prior to the biopsy showing multiple epithelioid granulomas, it is felt that alcohol was not an important factor in their production.

There is no satisfactory explanation for the slow resolution of the eosinophilia. The patient was lost to follow-up for 3 months following discharge. On readmission with another episode of rhabdomyolysis secondary to alcoholism the absolute eosinophil count was 425.

While some of the features of this case resemble those of the 5 cases of granulomatous hepatitis accompanying a self-limited febrile disease reported by Eliakim et al.,15 there are several important differences. The absence of respiratory symptoms, splenomegaly, and lymphocytosis as well as the presence of a markedly elevated alkaline phosphatase and definite giant cells in the granuloma suggest strongly that our patient should not be included in this group.

Granulomatous hepatitis has been reported with other drugs16-18 and in the case of granulomatous hepatitis associated with sulfadimethoxine it is noteworthy that granulomatous deposits resolved completely in 16 days.

In summary, evidence consistent with drug-induced hepatitis (malaise, fever, eosinophilia, and abnormal liver function) and histological evidence of granulomatous hepatitis followed by prompt resolution of symptoms, biochemical, and pathological findings following allopurinol withdrawal suggest that allopurinol caused a granulomatous hepatitis.

REFERENCES