CASE REPORT

Systemic Granulomatous Reaction to Salicylazosulfapyridine (Azulfidine) in a Patient with Crohn's Disease

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Recently several authors have noted the occurrence of noncaseating granuloma in nondigestive system tissue with regional enteritis (RE). This association has been used to uphold the systemic nature of RE (1) as well as to support speculation on a common etiology for the pathologically similar diseases, sarcoidosis and RE (2). The following case suggests a third alternative.

CASE REPORT

A 35-year-old black woman entered Rush-Presbyterian-St. Luke's Hospital in November 1972 for evaluation of crampy, periumbilical pain of nine months' duration and weight loss of ten pounds over the four months before admission. Physical examination was unremarkable. Workup showed an iron-deficiency anemia and a small-bowel x-ray compatible with regional enteritis involving the terminal ileum. On December 3, 1972, she was started on treatment with Azulfidine (salicylazosulfapyridine), 500 mg, p.o., q.i.d., and ferrous sulfate, 300 mg, p.o., t.i.d., and was discharged from the hospital.

On December 22, nineteen days later, the patient experienced shaking chills with a fever to 105 F, headache, dizziness, and a sore tongue. Four days later she lost her taste for cigarettes, and her urine became dark. On December 31, several raised, pruritic, circumscribed lesions developed on her legs, and one day later, a diffuse, maculopapular rash developed over her entire body. At the time of her first visit to her physician on January 3, 1973, she was noted to be icteric. When severe myalgias developed in both thighs the next day, the salicylazosulfapyridine (SASP) and ferrous sulfate were discontinued, and she was readmitted for evaluation.

Physical examination revealed a toxic-appearing patient with a temperature of 103 F and a pulse of 136. A diffuse, maculopapular rash covered her body, and marked periorbital edema, scleral icterus, and conjunctivitis were evident. The buccal mucosa was erythematous with several hemorrhagic areas, and the corners of the mouth were fissured. The lips, tongue, and gums were exquisitely tender. Diffuse, tender lymphadenopathy was present. Examination of the abdomen revealed RUQ tenderness and a liver of 12 cm total span. She was lethargic, but manifested no localizing neurologic findings.

Table 1 summarizes the pertinent laboratory data. The second strength PPD was negative, and cultures of sputum, urine, liver biopsy, and lymph node biopsy were negative for AFB and fungus. Serum complement fixation titers for blastomycosis, histoplasmosis, and coccidiomycosis were nondiagnostic. Viral titers for adenovirus, influenza A and B, respiratory syncytial, and cytomegalovirus were less than 1:8, and Epstein–Barr virus less than 1:32. Also negative were urine for cytomegalovirus, monospot test, toxoplasmosis fluorescent antibody, and an amoeba slide agglutination test. Serum complement components were all normal, but the prekallikrein was elevated to 758 (normal 100 ± 20). Lupus cell prep, antideoxynucleoprotein, and Coomb's test were negative. Electrolytes, blood urea nitrogen, creatinine, chest x-ray, and urinalysis were normal. Analysis of cerebrospinal fluid revealed a white blood cell count of 98/mm^3 (all lymphocytes), a protein of 95 mg/100 ml, and a glucose of 53 mg/100 ml. The bone marrow was active with many lymphocytes but no blasts, and a liver scan showed enlargement of the liver when compared to one done one month previously. A percutaneous liver biopsy (Figures 1 and 2) revealed noncaseating granulomata, and an epitrochlear lymph node biopsy (Figure 3) showed sinus eosinophilia with noncaseating granulomata. An analysis for glucose-6-phosphate dehydrogenase done prior to initiation of SASP was normal.

All medications were discontinued, and within 24 hours the patient was afebrile. Her laboratory tests also returned toward normal over the course of the hospitalization (Table 1). Fever and urticaria recurred once and appeared related to the administration of Peri-colace. However, the laboratory tests remained unchanged during its administration, and the fever disappeared when it was discontinued. The patient had never received Peri-colace prior to this hospital admission.

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Table 1

	Normal	First hospitalization Nov 18, 1972	Second hospitalization	
			Jan 6, 1973	Jan 27, 1973
Hemoglobin	12.0–16.0 g	10.0	10.8	8.1
White blood count	4,000–10,000	6,300	21,000*	12,000
Total EOS	<400/mm^3	96	144	–
SGOT	5–45 units	12	33	20
SGPT	5–40 units	7	17	17
Alkaline phosphatase	<2.5 units (Bessey–Lowry)	5.6	16.0	5.0
SLAP†	<184 units	228	354	–
Bilirubin				
total	<1.2 mg/100 ml	0.3	1.8	0.5
direct	<0.5 mg/100 ml	0.1	1.3	0.1

* Differential included 38% lymphs (few atypical) and 6% plasma cells.
† Serum leucine amino peptidase.

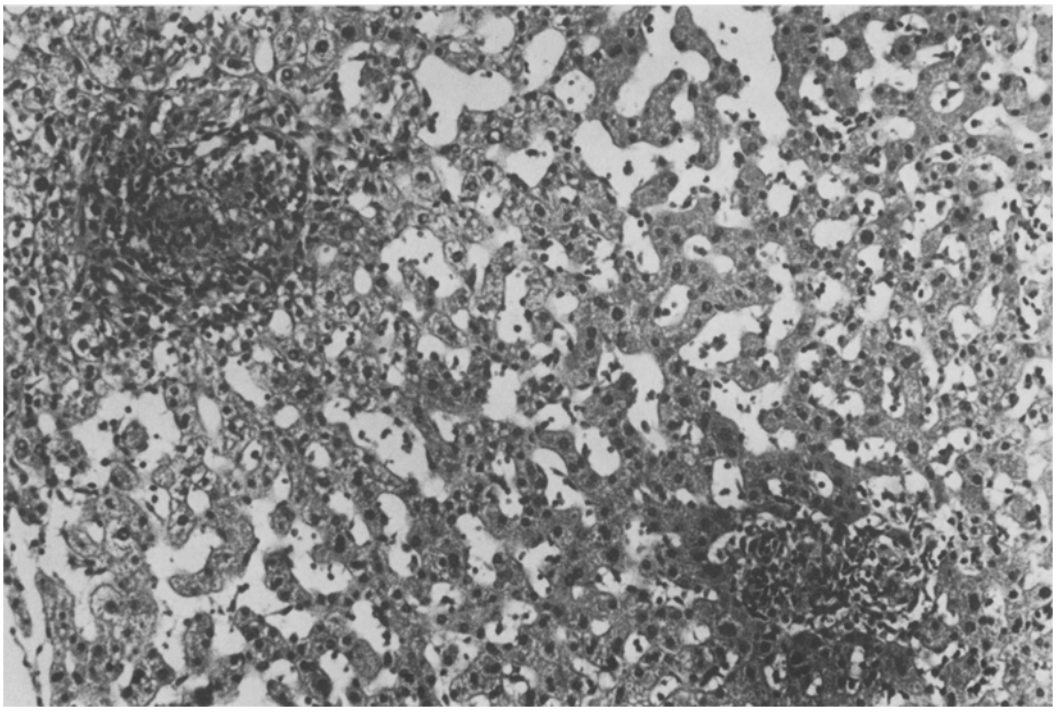

Fig 1. Percutaneous liver biopsy demonstrating two noncaseating granuloma. (H&E, × 108)

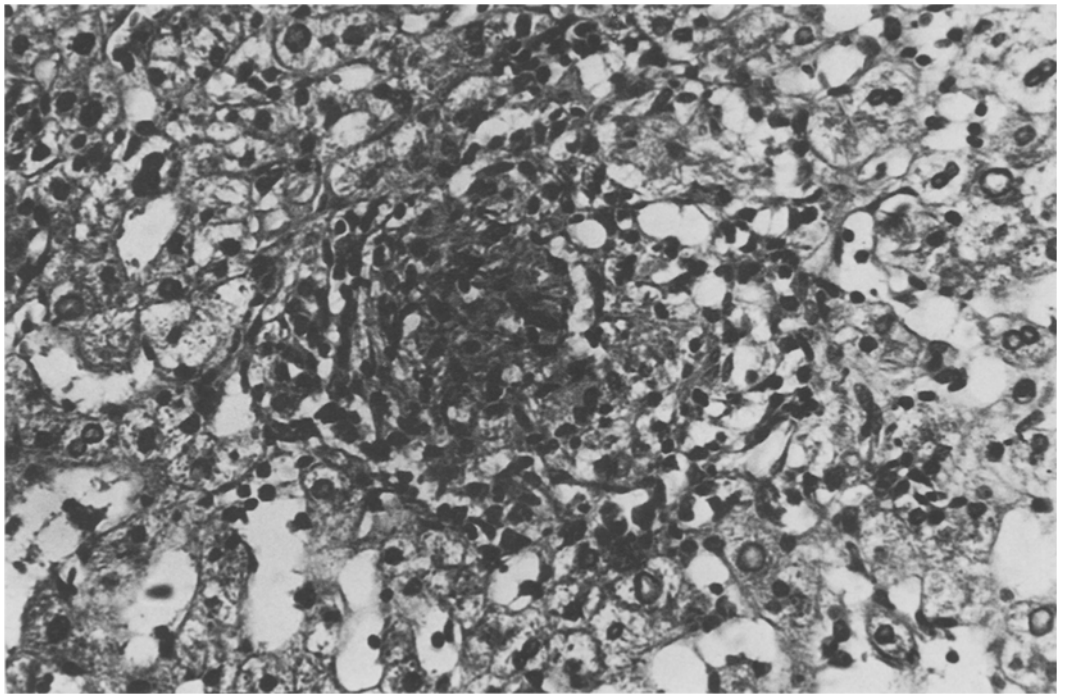

Fig 2. Percutaneous liver biopsy demonstrating structure and epithelioid cells in the smaller of the two granuloma seen in Figure 1. (H&E, × 215)

DISCUSSION

Noncaseating granulomata in the liver, and less commonly in peripheral lymph nodes, are known to be associated with drug hypersensitivity (3, 4). Sulfonamides, particularly, have been linked with this type of reaction. Soon after their introduction, the sulfa drugs were linked with postmortem findings of multisystem vasculitis and granuloma formation (5–7). The Stevens–Johnson syndrome, a clinical picture of mucous membrane lesions and multisystem disease, has been particularly associated with the long-acting sulfonamides (8). In this patient, the clinical picture of skin and mucous membrane lesions with multiple visceral abnormalities involving the central nervous system and reticuloendothelial system is consistent with the diagnosis of the Stevens–Johnson syndrome, and circumstantial evidence points strongly to therapy with SASP as the etiologic agent.

The onset of symptoms 19 days after the initiation of therapy is consistent with previous reports of sulfa hypersensitivity (8) and is identical to the 19-day period noted in the previous case of Stevens–Johnson syndrome secondary to SASP therapy (9). The precedent for this type of reaction to sulfa drugs in general (5–7) and sulfapyridine specifically (10) is well documented. The recent demonstration that sulfapyridine is the major metabolite of SASP (11) makes a significant relationship even more plausible. The clinical response to discontinuing the SASP was dramatic, with defervescence and return of a feeling of well-being and appetite within 48 hours. There was an associated resolution of the recent lymphadenopathy over a 7- to 10-day period.

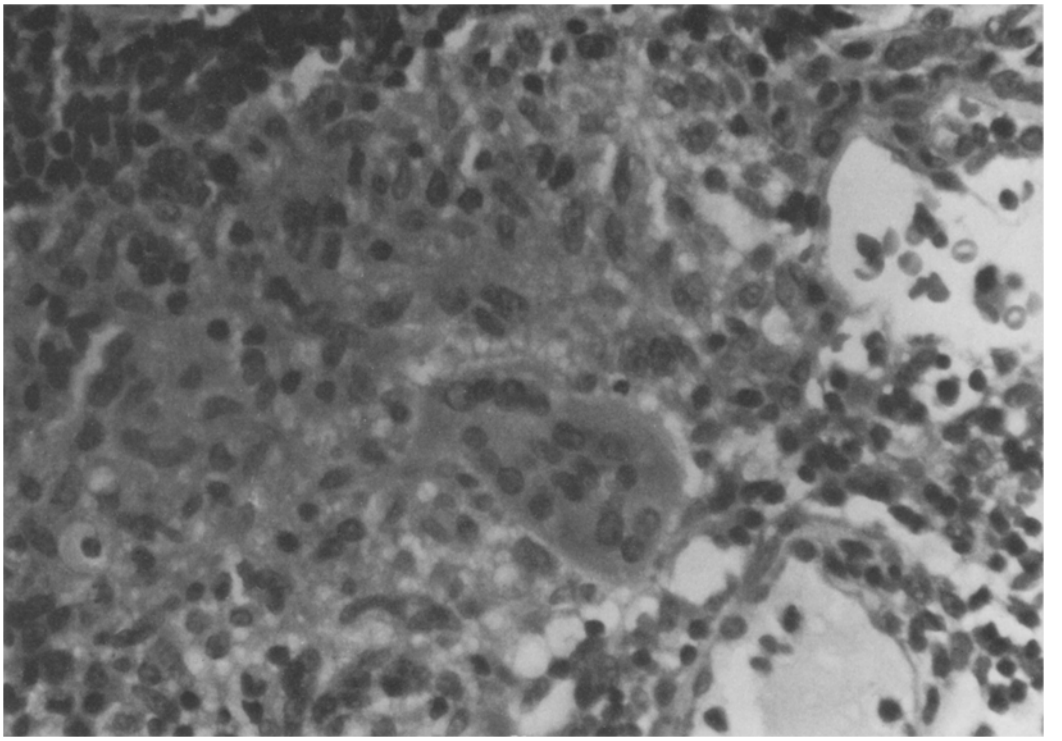

Fig 3. Epitrochlear lymph node biopsy demonstrating sinus eosinophilia and a noncaseating granuloma with a foreign body giant cell. (H&E, × 275)

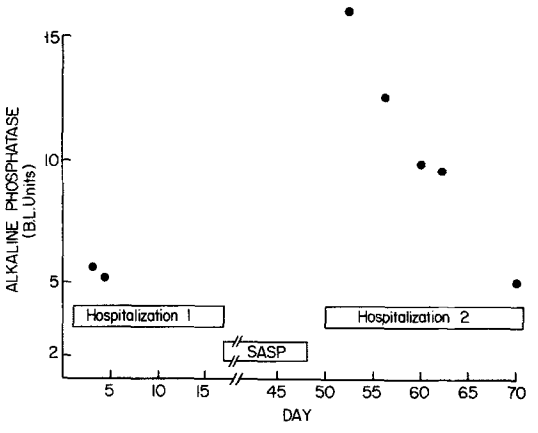

Fig 4. Relationship of alkaline phosphatase (Bessey-Lowry units) and treatment with salicylazosulfapyridine (SASP) 2 g/day. Day 1 is the beginning of the first hospitalization (November 18, 1972).

Other causes of noncaseating granulomata including untreated tuberculosis, Q fever, and fungal infections, as well as sarcoidosis, would rarely clear this quickly. Regional enteritis itself has been associated with noncaseating granulomata in the liver in approximately a dozen published cases (12), but this is usually an incidental pathologic finding with no distinctive clinical picture. Although the initial elevation of the alkaline phosphatase to 5.0 suggests underlying parenchymal liver disease, this test is abnormal in 12% of patients with documented regional enteritis and has been seen in patients with normal liver biopsies in this disease (12). However, the subsequent elevation to 10.0 is unusual as most cases, including those with granuloma, have had elevations less than two and one-half times normal (12). The rapid fall in this parameter correlating with the clinical

course and discontinuance of SASP again supports the impression of resolving drug toxicity, presumably allergic granulomatous hepatitis.

A recent paper (13) correlating adverse reaction to SASP with elevated serum levels of sulfapyridine raises the question of a direct toxic rather than allergic etiology. Unfortunately, the serum sulfapyridine levels were not measured in this patient, and the possibility of a toxic reaction in a slow acetylator cannot be excluded.

A review of previous reports of systemic granuloma with regional enteritis (1, 2, 14) reveals that medical therapy with SASP is mentioned only once (1), and then the temporal sequence of therapy is not given. Demonstration that SASP, available since the early 1940's and now commonly used in the management of regional enteritis, might give this type of reaction makes it imperative that future reports specifically note use of this drug.

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