Alerts, Notices, and Case Reports

The Sulfone Syndrome in a Patient Receiving Dapsone Prophylaxis for *Pneumocystis carinii* Pneumonia

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DAPSONE IS A DIAMINOPHENYL sulfone indicated for the treatment of leprosy, to prevent malaria in travelers to endemic regions, and to treat several dermatologic conditions, including dermatitis herpetiformis. Dapsone interferes with the production of folate from para-aminobenzoic acid (PABA). Because PABA is the main substrate for folate synthesis by *Pneumocystis carinii*, dapsone is used in the treatment of and prophylaxis against *P carinii* pneumonia in patients infected with the human immunodeficiency virus type 1.[1-4]

Common side effects of dapsone therapy include the development of abnormal serum aminotransferase levels and hemolysis in patients deficient in glucose-6-phosphate dehydrogenase (G6PD).[5] A severe dapsone hypersensitivity syndrome, also known as the sulfone syndrome, has been reported sporadically in the literature. This is characterized by fever, rash, hemolytic anemia, atypical lymphocytosis, and acute (rarely fulminant) hepatic injury.[6] We report a case of the sulfone syndrome in a patient with the acquired immunodeficiency syndrome (AIDS) who was receiving dapsone as primary prophylaxis against *P carinii* pneumonia.

Report of a Case

The patient, a 35-year-old homosexual man with AIDS, was admitted to Stanford University Hospital with nausea, vomiting, and jaundice. He had been diagnosed with Kaposi's sarcoma eight weeks before admission based on the results of a biopsy of violaceous lesions on his legs. The patient was being treated with trimethoprim-sulfamethoxazole as prophylaxis against *P carinii* pneumonia. In retrospect, the patient had noted a coated tongue, fevers, night sweats, and the skin lesions on his legs for a year. Six weeks before admission, he was randomly assigned to the dapsone treatment arm of a *P carinii* pneumonia prophylaxis protocol, and trimethoprim-sulfamethoxazole was discontinued. He received 50 mg of dapsone orally twice a day and 200 mg of zidovudine orally five times per day. At the time of study entry, his laboratory tests revealed a hemoglobin level of 140 grams per liter (14 grams per dl), a hematocrit of 0.40 (40%), normal serum liver function test values, a G6PD activity of 45 minutes (normal 0 to 60 minutes), and a total T-helper lymphocyte count of 0.168×10^9 per liter (168 per μl).

He continued to have night sweats and occasional low-grade fevers after dapsone therapy was begun. Two weeks before admission his hemoglobin level was 103 grams per liter (10.3 grams per dl) and his hematocrit was 0.302 (30.2%). One week before admission, chills and fever to 40°C (104°F), anorexia, headache, nausea, dark urine, and diarrhea developed. Three days before admission he had a hematocrit of 0.24 (24%), a leukocyte count of 5.5×10^9 per liter (5,500 per μl), a bilirubin level of 63.27 μmol per liter (3.7 mg per dl), alkaline phosphatase 229 units per liter, aspartate aminotransferase 772 units per liter, alanine aminotransferase 650 units per liter, and lactate dehydrogenase 4,896 units per liter. The administration of dapsone and zidovudine was discontinued. Two days before admission his leukocyte count was 5.5×10^9 per liter, with 0.32 polymorphonuclear leukocytes, 0.04 band forms, 0.46 lymphocytes, and 0.10 reactive lymphocytes. He continued to have chills, sweats, and high fevers and in addition had dizziness with standing and shortness of breath with minimal exertion. He was admitted to Stanford University Medical Center for further evaluation.

The patient's history was notable for a positive hepatitis B surface antigen test. He had no history of blood transfusions, intravenous drug abuse, or alcoholism and no known drug allergies. He was taking no medications other than zidovudine and dapsone during the six weeks before being admitted to hospital.

On physical examination, he was jaundiced and appeared toxic. His temperature was 38.6°C (101.5°F), blood pressure 120/80 mm of mercury, pulse 80 per minute, and respirations 20 per minute. There were no orthostatic changes in blood pressure or pulse. Skin lesions consistent with Kaposi's sarcoma were noted on the lower extremities, the right groin, the soft palate, and the left side of the face. Scleral icterus was present. A funduscopic examination revealed cotton-wool spots bilaterally. The tongue was coated white, and there were small, mobile, tender anterior cervical and left axillary lymph nodes. The results of respiratory and cardiovascular examinations were normal. The abdomen was soft with normal bowel sounds; the right upper quadrant was tender to palpation. His liver measured 15 cm by percussion and was palpable 3 cm below the right costal margin. His spleen was palpable 2 cm below the left costal margin. Results of the genital, rectal, and neurologic examinations were normal.

Laboratory data on admission were significant for 2+ bilirubinuria. Testing resulted in a hemoglobin level of 79 grams per liter (7.9 grams per dl), a hematocrit of 0.238 (23.8%), a mean corpuscular volume of 122 fl, and a reticulocyte count of 37×10^{-3} (3.7%). The leukocyte count was 8.5×10^9 per liter (8,500 per μl), with 0.26 polymorphonu-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
G6PD = glucose-6-phosphate dehydrogenase
PABA = para-aminobenzoic acid

clear leukocytes, 0.11 band forms, 0.44 lymphocytes, and 0.19 reactive lymphocytes. A peripheral smear showed numerous atypical lymphocytes, spherocytes, schistocytes, and macrocytes. Results of direct and indirect Coombs' tests were unremarkable. Haptoglobin measurement and a Heinz body preparation were not done. Levels of serum electrolytes, blood urea nitrogen, and creatinine were within normal limits. The total bilirubin level was 104.3 μmol per liter (6.1 mg per dl), with a direct-reacting bilirubin of 87.2 μmol per liter (5.1 mg per dl). Other laboratory values were alkaline phosphatase, 329 units per liter; alanine aminotransferase, 1,159 units per liter; aspartate aminotransferase, 1,099 units per liter; and lactate dehydrogenase, 4,961 units per liter. The serum albumin level was 37 grams per liter and the prothrombin time was 14.0 seconds.

A chest radiograph showed a normal cardiomediastinal silhouette and no parenchymal infiltrates. An abdominal ultrasonogram revealed a homogeneous liver without focal masses or biliary tract abnormalities but with splenomegaly. Assays revealed no antibodies to hepatitis A and D but did detect hepatitis B surface antigen and hepatitis B e antigen.

The patient was treated with intravenous ampicillin, gentamicin sulfate, and clindamycin; these were discontinued when blood cultures showed no growth after 48 hours. He received intravenous fluids and transfusions of packed erythrocytes. He did not receive corticosteroid treatment. He continued to have a high fever, and the aminotransferase abnormalities progressed over the first five hospital days. He developed a maculopapular rash on the trunk and extremities on the fourth hospital day, which was thought to be a reaction to treatment with intravenous ampicillin.

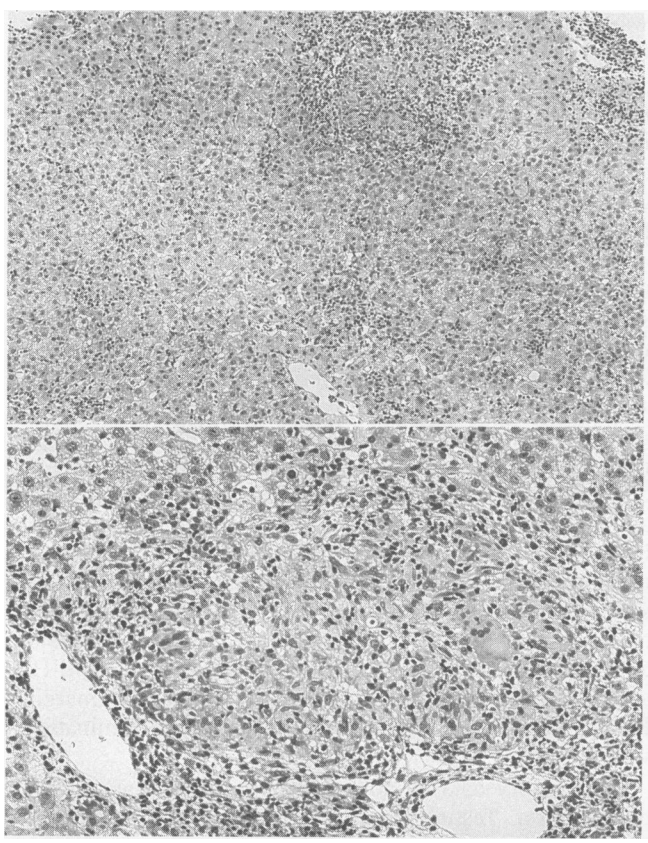

Figure 1.—Liver biopsy findings included **Top,** panlobular mixed mononuclear and polymorphonuclear infiltrate (hematoxylin and eosin stain; original magnification x 100) and **Bottom,** a well-formed portal granuloma with a giant cell (hematoxylin and eosin stain; original magnification x 200).

A liver biopsy done on the third hospital day revealed lobular and portal infiltrates with mononuclear and polymorphonuclear (predominantly eosinophilic) granulocytes; granulomas and eosinophilic bodies were present throughout the lobule (Figure 1). There was normal lobular architecture with no fibrosis or lobular collapse. No intranuclear or cytoplasmic inclusion bodies were identified.

The presence of infectious agents known to cause acute granulomatous hepatitis was ruled out by the following tests: serologic assays were negative for immunoglobulin M antibodies to cytomegalovirus; shell vial cultures were negative for cytomegalovirus; cultures of the liver biopsy specimen for bacterial, mycobacterial, fungal, and viral agents showed no growth; and peripheral blood cultures did not grow *Mycobacterium avium-intracellulare* or other pathogens.

The patient's fever, systemic symptoms, rash, and serum aminotransferase abnormalities resolved over 10 days (Figure 2), and the patient was discharged from the hospital. Two weeks after discharge his serum aminotransferase levels were nearly normal. Zidovudine was reinstituted at the previous dosage, and pentamidine 300 mg was given monthly by aerosolization. The patient has had no recurrence of hepatitis or anemia. He remains positive for hepatitis B surface antigen and hepatitis B e antigen.

Discussion

This case illustrates that treatment with relatively low doses of dapsone can result in hemolytic anemia and the sulfone syndrome, even in patients with normal G6PD activity. Dapsone is metabolized to *N*-hydroxyl, diaminodiphenyl sulfone (NOH-DDS); this compound has a mild oxidant activity, and mild methemoglobinemia and hemolysis occur in most persons treated with dapsone. The hemolysis is accentuated, resulting in anemia in patients who are G6PD deficient and in those treated with high doses for prolonged periods.[5] Hemolysis has been reported independent of as

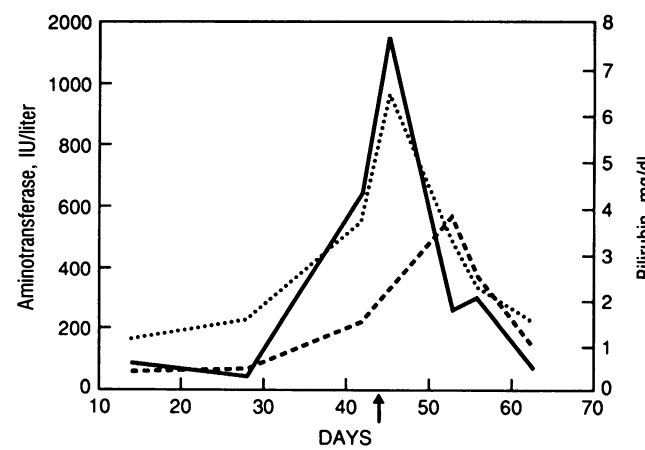

Figure 2.—The graph shows the time course of abnormal liver tests in the patient. ↑ = time of liver biopsy, —= ALT = alanine aminotransferase (normal 7 to 56 IU/liter), - - = alkaline phosphatase (normal 43 to 122 IU/liter), ···= total bilirubin (normal 0.2 to 1.0 mg/dl).

well as coincident with the sulfone syndrome.[6] In the present case, there was a mild reduction of the hematocrit within the first two weeks of therapy. In the third week a dramatic hemolysis was seen coincident with the cholestatic hepatitis and fever, which resolved after treatment with dapsone was discontinued. The methemoglobin level was not measured.

A dapsone hypersensitivity syndrome was first alluded to by Lowe and Smith in 1949 when they noted a 2% incidence of exfoliative dermatitis among patients treated with dapsone for leprosy.[7] In the subsequent decade, the sulfone syndrome was described as a mononucleosis-like syndrome characterized by exfoliative dermatitis, hepatomegaly, jaundice, splenomegaly, lymphadenopathy, and a predominance of peripheral mononuclear cells in ten patients treated for less than two months with dapsone for leprosy[8,9] and in three malnourished patients who were treated for six weeks with dapsone for tuberculosis.[10] Liver biopsies in the patients with tuberculosis revealed extensive liver necrosis in one and focal necrosis in the other two.

Since the original description, there have been similar reports in patients who were treated with dapsone for leprosy[11] and for many dermatologic disorders.[6,12-16] The dosage of dapsone in these cases ranged between 50 and 300 mg per day. Four were receiving 100 mg or less of dapsone per day. With relatively low doses of oral dapsone in most of the cases, the serum concentrations achieved would likely be lower than those associated with hepatotoxicity. In addition, the findings of a peripheral blood mononuclear cell predominance—an exfoliative dermatitis and granuloma formation with eosinophilia—suggest a delayed hypersensitivity reaction. Therefore, the sulfone syndrome is most likely a hypersensitivity reaction rather than a toxic reaction.

TABLE 1.—*Summary of Published Cases of the Sulfone Syndrome*

Source	*Underlying Disease*	*Age and Sex of Cases*	*Dose of Dapsone, mg/day*	*Time to Onset After Dapsone Begun, wk*	*Clinical Features*	*Liver Abnormalities*	*Leukocyte Abnormalities*
Allday and Barnes, 1951[8]	Leprosy	7 cases: age and sex not available	100×2 wk, 200 thereafter	8	Fever, rash, hepatomegaly, lymphadenopathy	Not available	Increased lymphocytes or monocytes
Jelliffe, 1951[10]	Tuberculosis, malnutrition	3 cases: 2 men Girl, 7 y	100×1 wk, 200×1 wk, 300 thereafter	6	Fever, rash	Liver biopsy: necrosis	Not available
Leiker, 1956[9]	Leprosy	Woman, 25 y	100 twice/wk, increase by 100 each week	5	Fever, rash, splenomegaly, lymphadenopathy		All had increased lymphocytes or monocytes
		Man, 25 y		4	Fever, rash	Jaundice	
		Woman, 26 y		7	Fever, rash, splenomegaly, lymphadenopathy		
Potter et al, 1967[14]	Erythema elevatum diutinum	Man, 68 y	200	3-4	Rash, lymphadenopathy	Jaundice, hemolytic anemia	Increased lymphocytes or monocytes, atypical lymphocytosis
Millikan and Harrell, 1970[6]	Dermatitis herpetiformis	Man, 21 y	200	3	Fever	Abnormal liver function tests, hemolytic anemia	Both had increased lymphocytes or monocytes
		Man, 50 y	200	3	Fever	Jaundice, abnormal liver function tests, hemolytic anemia	
Frey et al, 1981[11]	Leprosy	Boy, 17 y	100	3	Fever, rash, hepatomegaly, splenomegaly, lymphadenopathy	Abnormal liver function tests, hemolytic anemia, jaundice	Increased lymphocytes or monocytes, atypical lymphocytosis
Tomecki and Catalano, 1981[15]	Acne vulgaris	Girl, 16 y	50	2	Fever, hepatomegaly, splenomegaly, lymphadenopathy	Abnormal liver function tests, jaundice, hemolytic anemia	Atypical lymphocytosis
Kromann et al, 1982[13]	Psoriasis	Woman, 33 y	100	2-3	Fever, rash, hepatomegaly, lymphadenopathy	Abnormal liver function tests, liver biopsy	Increased lymphocytes or monocytes, atypical lymphocytosis
Johnson et al, 1986[12]	Leukocytoclastic vasculitis	Woman, 49 y	50	2	Fever, rash, hepatomegaly	Abnormal liver function tests, hemolytic anemia	None
Lawrence et al, 1987[17]	Dermatitis herpetiformis	Woman, 19 y	50 increased to 150	3-4	--	Hemolytic anemia, jaundice, abnormal liver function tests	Not available
Wille and Morrow, 1988[16]	Brown recluse spider bite	Man, 55 y	100	3	Fever	Abnormal liver function tests	Increased lymphocytes or monocytes, atypical lymphocytosis

By reviewing the 21 reported cases,[6,8-17] we can make several generalizations concerning the sulfone syndrome:

- all cases occurred within two months of the patients' starting dapsone treatment;
- all patients had fever; and
- all but three patients had a rash and evidence of hepatic injury (hepatomegaly, jaundice, or hyperbilirubinemia).

There were 15 cases with lymphadenopathy and 6 cases with splenomegaly. A predominance of lymphocytes was reported in 15, and atypical lymphocytosis was noted in 4 cases. Hemolytic anemia was reported in 6 patients. Table 1 summarizes these case reports.

Our patient has the following features in common with other patients reported with the sulfone syndrome: onset of illness within two months of initiating treatment, fever, jaundice, hepatomegaly, lymphadenopathy, atypical lymphocytosis, hemolytic anemia, elevated aminotransferase levels, and a liver biopsy revealing granulomas with a panlobular eosinophilic infiltrate. Although the histologic differential diagnosis of granulomatous hepatitis is extensive,[18] our patient's clinical course was characteristic of an acute toxic injury, and the presence of a large number of eosinophils supports the histologic diagnosis of an allergic granulomatous reaction.[19] The presence of infectious agents known to cause acute granulomatous hepatitis was ruled out, no drug or toxic exposure was reported by the patient other than the use of zidovudine and dapsone, and subsequent challenge with zidovudine has not resulted in a recurrence of his hepatitis.

We think that this is the first report of the sulfone syndrome occurring in a patient with AIDS in whom *Pneumocystis carinii* pneumonia prophylaxis was the indication for dapsone use. The dose of dapsone used was relatively high, in accordance with the AIDS Cooperative Treatment Group 081 protocol, but the evidence suggests a hypersensitivity reaction rather than a dose-related adverse effect. Given the probable widespread use of dapsone for treating AIDS patients in the future, physicians should be alert for other cases of the sulfone syndrome.

REFERENCES

1. Safrin S, Sattler FR, Lee BL, et al: Dapsone as a single agent is suboptimal therapy for *Pneumocystis carinii* pneumonia. J Acquir Immune Defic Syndr 1991; 4:244-249
2. Kemper CA, Tucker RM, Lang OS, et al: Low-dose dapsone prophylaxis of *Pneumocystis carinii* pneumonia in AIDS and AIDS-related complex. AIDS 1990; 4:1145-1148
3. Montgomery AB: Prophylaxis of *Pneumocystis carinii* pneumonia in patients infected with the human immunodeficiency virus type 1. Semin Respir Infect 1989; 4:311-317
4. Medina I, Mills J, Leoung G, et al: Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome—A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. N Engl J Med 1990; 323:776-782
5. Degowin RL, Eppes RB, Powell RD, Carson PE: The haemolytic effects of diaphenylsulfone (DDS) in normal subjects and in those with glucose-6-phosphate-dehydrogenase deficiency. Bull WHO 1966; 35:165-179
6. Millikan LE, Harrell ER: Drug reactions to the sulfones. Arch Dermatol 1970; 102:220-224
7. Lowe J, Smith M: The chemotherapy of leprosy in Nigeria, with an appendix on glandular fever and exfoliative dermatitis precipitated by sulfones. Int J Lepr 1949; 17:181-195
8. Allday E, Barnes J: Toxic effects of diaminophenylsulfone in treatment of leprosy. Lancet 1951; 2:205-206
9. Leiker D: The mononucleosis syndrome in leprosy patients treated with sulfones. Int J Lepr 1956; 24:402-405
10. Jelliffe D: Toxic hepatitis caused by diaminodiphenylsulfone. Lancet 1951; 1:1343-1344
11. Frey HM, Gershon AA, Borkowsky W, Bullock WE: Fatal reaction to dapsone during treatment of leprosy. Ann Intern Med 1981; 94:777-779
12. Johnson DA, Cattau EJ, Kuritsky JN, Zimmerman HJ: Liver involvement in the sulfone syndrome. Arch Intern Med 1986; 146:875-877
13. Kromann NP, Vilhelmsen R, Stahl D: The dapsone syndrome. Arch Dermatol 1982; 118:531-532
14. Potter B, Szymanski F, Fretzin D: Erythema elevatum diutinum and sulfone hypersensitivity—Society transactions. Arch Dermatol 1967; 95:436-440
15. Tomecki KJ, Catalano CJ: Dapsone hypersensitivity—The sulfone syndrome revisited. Arch Dermatol 1981; 117:38-39
16. Wille RC, Morrow JD: Case report: Dapsone hypersensitivity syndrome associated with treatment of the bite of a brown recluse spider. Am J Med Sci 1988; 296:270-271
17. Lawrence WA, Olsen HW, Nickles DJ: Dapsone hepatitis [Letter]. Arch Intern Med 1987; 147:175
18. Schaffner F: The liver in HIV infection. Prog Liver Dis 1990; 9:505-522
19. Ishak KG, Zimmerman HJ: Drug-induced and toxic granulomatous hepatitis. Baillieres Clin Gastroenterol 1988; 2:463-480

Odontoid Osteomyelitis

An Unusual Presentation of an Uncommon Disease

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OSTEOMYELITIS of the upper cervical vertebrae is rare. There have been few published reports, and these have stressed the difficulties inherent in making the diagnosis.[1-5] Virtually all patients have had some underlying chronic disorder, such as long-standing diabetes mellitus[2-4] or intravenous drug abuse.[5] We therefore report a case of odontoid osteomyelitis that occurred in a previously healthy person. The diagnosis in this patient was promptly made using magnetic resonance imaging (MRI). Although experience with this imaging technique in evaluating cases of suspected osteomyelitis is gradually expanding,[6-8] this is the first instance, to our knowledge, in which MRI has been applied in the diagnosis of cervical osteomyelitis.

Report of a Case

The patient, a 57-year-old man, was seen because he had had persistent neck pain, tactile fever, and sore throat for three weeks. The neck pain was not alleviated by local heat compresses or by taking ibuprofen. He was not given antibiotics. He had no history of surgical procedures or trauma of the neck and no evidence of underlying disease. Although he occasionally drank large amounts of alcohol, this had not caused medical problems, nor had it interfered with his work for 25 years as an aircraft assembler.

On physical examination, he was well developed and in no acute distress. His temperature was 37.9°C. The pharynx was swollen and edematous, and lateral movement of the neck was notably impaired. There were no other abnormal physical findings.

(Ruskin J, Shapiro S, McCombs M, Greenberg H, Helmer E: Odontoid osteomyelitis—An unusual presentation of an uncommon disease. West J Med 1992 Apr; 156:306-308)

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