Resistance to Trimethoprim-Sulfamethoxazole in the Treatment of Pneumocystis carinii Pneumonia*

Implication of Folic Acid

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Pneumocystis carinii pneumonia is a well-known complication of immunosuppression in renal transplant recipients. Treatment is generally with trimethoprim-sulfamethoxazole (TMP-SMZ). A case of Pneumocystis pneumonia failed to respond to TMP-SMZ until concomitant administration of folic acid was stopped. Physicians should be alerted to the possibility that folic acid may impair the efficacy of TMP-SMZ in Pneumocystis carinii infection.

First line treatment of Pneumocystis carinii pneumonia (PCP) is generally accepted to be with high dose intravenous or oral trimethoprim-sulfamethoxazole (TMP-SMZ). But TMP-SMZ can cause megaloblastosis in man, and immunosuppressed patients are at risk from bone marrow depression either from their underlying disease or from their immunosuppressive treatment, so the administration of folic acid, together with TMP-SMZ has been advocated. The combination is given routinely as prophylaxis in some centers. It has been known since 1948 that folic acid can inhibit diaminopyrimidines such as trimethoprim (TMP) in vitro, but it has been assumed that the microbial inability to absorb it prevented widespread resistance to TMP-SMZ due to folic acid. The theoretical possibility of such resistance to TMP-SMZ was considered by Winston et al., but they found no such cases in their review of 80 cases of confirmed PCP. We report a case of PCP in a renal transplant recipient which failed to respond to adequate dosage of TMP-SMZ until the concomitant administration of folic acid was stopped following which he recovered completely.

Case Report

A 54-year-old Asian man who had received a cadaveric renal transplant for hypertensive renal failure 24 months previously, presented with a dry cough, dyspnea on exertion, and pyrexia. He was taking azathioprine, 100 mg, and prednisolone, 15 mg, together with atenolol, 100 mg, and bendroflumethiazide, 10 mg daily. On examination, he was pyrexic (37.5°C), but his chest was clear. A chest roentgenogram, however, showed extensive consolidation of the right lung field with smaller fluffy opacities on the left (Fig 1a). Microscopic examination of sputum was negative for acid-fast bacilli, mycobacterial organisms, fungi, and P carinii, and sputum culture was also negative. Bronchoscopic washings revealed only mucus plugs with a mixed growth of bacteria. Treatment was started with amoxicillin, 250 mg three times daily, but this had no effect on the pyrexia (Fig 1b). Open lung biopsy specimen revealed large numbers of P carinii organisms, trophozoites, and cysts. Trimethoprin (30 mg/kg/day) and sulfamethoxazole (100 mg/kg/day) was started intravenously with the temperature falling to normal in 36 hours when oral therapy was substituted. A roentgenographic response was also seen (Fig 1c). On days 5 and 8 of therapy, serum levels of TMP were 5.4 and 9.5 µg/ml, and of SMZ, 159 and 230 µg/ml. (Therapeutic range 1/16 hours past dose is >5 µg/ml TMP and >100 µg/ml SMZ.) Pyrexia returned on day 10 of treatment, at which time the white cell count had fallen from 7,100/cu mm, with 70 percent neutrophils on admission to 1,600/cu mm, with 80 percent neutrophils, some of which were hypersegmented. Megaloblastic changes were seen on bone marrow biopsy specimen. Azathioprine was stopped and intravenous administration of cefotaxime and amikacin was begun. Folic acid, 15 mg every six hrs., was also started at this time. The pyrexia continued, and by day 13 confluent shadowing was seen again in the right upper zone (Fig 1c), from where transbronchial biopsy specimens revealed persistence of Pneumocystis trophozoites. Cytomegalovirus, Legionella and Mycoplasma titers were all negative at this time, and no other organism was isolated. By day 21, the white cell count had improved slightly to 2,300/cu mm, with 69 percent neutrophils. The hypersegmented forms had disappeared. Pentamidine was considered as an alternative treatment, but in view of its side effects and the theoretical possibility that folic acid was inhibiting the action of TMP-SMZ, it was decided to embark on a short therapeutic trial of withdrawing folic acid. The pyrexia resolved within 30 hours. The TMP-SMZ was continued for a further three weeks. Subsequent challenge with folic acid for two weeks did not cause pyrexia. Renal function remained normal throughout the illness.

Discussion

Although TMP-SMZ has been the preferred treatment for PCP since the comparison of TMP-SMZ and pentamidine isethionate by Hughes et al., its mechanism of action on P carinii is unknown, and therefore, must be inferred from its action on other microorganisms. The efficacy of TMP-SMZ depends upon its selective toxicity for microbial cells. Mammalian cells are relatively unaffected by it because they can absorb folates from plasma. Most microorganisms, on the other hand, cannot, and they must synthesize them from precursors which include para- amino benzoic acid (p-ABA). Sulfamethoxazole competitively inhibits the formation of dihydrofolate from p-ABA. Farther down the same metabolic pathway, dihydrofolate reductase (DHFR) catalyzes the conversion of folinic acid & amikacin.

![Diagram](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21422/)

**Figure 1.** Temperature and treatment chart. Day 0 represents the start of treatment with TMP-SMZ. Diagrams (a-d) of chest x-ray films on admission and days 6 and 13, and three months after start of treatment are set out below.

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version of dihydrofolate to tetra-hydrofolate or folinic acid, which is a necessary compound for 1-carbon transfer reactions involved in purine synthesis. Trimethoprim competitively inhibits microbial DHFR. The effectiveness of TMP thus depends on the ability of the organism to absorb folinic acid from the plasma.

However, failure, to respond to TMP-SMZ occurs in approximately 30 percent of cases of PCP, despite adequate antibiotic serum levels. Initial failure to respond to TMP-SMZ therapy may be reversed by increasing the dose, and this may have been effective in our patient, although retrospectively, drug levels appear adequate by the criteria of Winston et al. However, it would be very unusual for PCP organisms still to be present at day 19 after starting treatment, unless the TMP-SMZ had not been effective. The subsequent dramatic clinical and roentgenographic improvement (Fig 1d) was achieved purely as a response to the withdrawal of folinic acid. Physicians should, therefore, be alerted to the possibility that concomitant use of folinic acid and TMP-SMZ in the treatment of PCP may result in the failure to effect a cure.

Since this report was written, a further case of relapse of PCP has occurred in this hospital in a renal transplant recipient treated with TMP-SMZ and folinic acid: a successful outcome was seen with TMP-SMZ alone.

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REFERENCES
9 McKenna F, Davison AM, Giles GR. Response of Pneumocystis carinii pneumonia only after high dose cotrimoxazole. Lancet 1982; 1:174

Esophageal Cyst as a Cause of Chronic Cough*

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The previously unreported association of chronic persistent cough due to a duplication esophageal cyst is presented. The presence of a long history of atopy, bronchitis, and asthma resulted in a delay in diagnosis. When vigorous bronchodilator therapy was unsuccessful, close observation of the patient and review of her radiographs suggested the esophageal etiology of her cough. This case reinforces the observation that chronic persistent cough, although common, may present a very perplexing problem. A systematic approach considering the anatomy of the cough reflex, and an awareness of the esophageal and other nonpulmonary causes of cough, can aid in diagnosis and management of these patients.

Persistent cough is a common problem which is most often caused by postnasal drip, chronic bronchitis, or asthma.1 Gastroesophageal reflux may account for 10 percent of the cases despite the absence of classic symptoms.1 There are numerous reports of other esophageal and nonpulmonary diseases presenting predominantly with persistent cough.14

We recently encountered a girl with persistent chronic cough due to an esophageal duplication cyst, a previously unreported occurrence. The presence of a long history of allergic rhinitis, bronchitis, and asthma with objective evidence of hyperreactive airways caused confusion and a delay in diagnosis.

CASE REPORT

A 15-year-old nonsmoking, white girl was referred for evaluation of persistent cough. The patient had a four-year history of bronchitis (one to two episodes per year), allergic rhinitis, "asthma" and an intermittent cough. She had been receiving weekly desensitization shots for two years. Four months prior to admission, she developed an acute episode of cough productive of small amounts of white sputum followed by a persistent residual nonproductive cough. She was evaluated locally with a chest radiograph and pulmonary function testing, both of which were reported as normal. Symptomatic treatment with bronchodilator drugs, narcotic cough suppressants and a short course of prednisone therapy in unknown doses were unsuccessful, and she presented to the authors for evaluation. The patient described her cough as dry, nonproductive, hacking, persistent throughout the day but worse in the recumbent position and just after eating. She complained of frequent palpitations and denied hoarseness, dysphonia, heartburn, hemoptysis, dyspnea on exertion, or weight loss.

Initial physical examination revealed a healthy appearing, 15-year-old white girl with a hacking, paroxysmal, bark-like cough. Blood pressure was 130/80 mm Hg; pulse rate was 120/min, bounding and regular; respirations: 18/min; temperature: 37°C (98.6°F). Head, eye, ear, nose and throat examination was unremarkable, including indirect laryngoscopy and nasopharyngoscopy. Lungs were clear, chest symmetric, and heart without murmur, rub, or gallop. The

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