Pneumocystis carinii Pneumonia During Steroid Taper in Patients With Primary Brain Tumors

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***Pneumocystis carinii* causes life-threatening pneumonitis (PCP) in immunocompromised individuals. In the non-AIDS (acquired immunodeficiency syndrome) population, PCP is frequently associated with corticosteroid therapy, and the rodent model uses corticosteroid-induced immunosuppression to provoke PCP. Although patients with intracranial tumors are frequently treated with long courses of corticosteroids, there have been very few descriptions of PCP in this population. We report the diagnosis and treatment of PCP in four patients over a 12-month period with intracranial neoplasms who developed symptoms during corticosteroid taper. Effective prophylaxis against PCP exists and should be considered for patients with intracranial neoplasms receiving long-term steroids.**

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Manuscript submitted May 15, 1991, and accepted in revised form July 31, 1991.

Pneumocystis carinii is a unicellular eukaryote capable of causing life-threatening opportunistic pneumonitis (PCP) in immunocompromised hosts [1,2]. Prior to the acquired immunodeficiency syndrome (AIDS) epidemic, the most common clinical scenerio for sporadic infections in adults was in patients with hematologic malignancies treated with chemotherapeutic regimens that have almost always included steroids [3]. More recently, an increasing number of cases of non-AIDS PCP have been seen in organ transplantation recipients receiving a variety of immunosuppressive agents, including long-term steroids [4–7]. Early clinical observations suggested a relationship between the presentation of PCP and the tapering of corticosteroids [8,9]. In the laboratory, murine models have been used to study the relationship between steroid administration and PCP; the administration of corticosteroids to rats and mice is associated after 6 to 8 weeks with pneumonitis thought to be due to activation of latent infestation with *P. carinii* [10,11].

Patients with intracranial neoplasms are frequently treated with long courses of corticosteroids to reduce cerebral edema. There has been only one previous detailed description of PCP in patients with primary brain tumors [12]. Over a 1-year period, we have diagnosed and treated PCP in four patients with intracranial neoplasms who developed respiratory symptoms during corticosteroid taper. None of these patients had risk factors for PCP other than steroid therapy. Antibiotic prophylaxis for PCP should be considered in patients with intracranial neoplasms receiving long-term steroids.

CASE REPORTS

Patient 1

VP is a 55-year-old man who underwent partial resection of a left parietal glioblastoma multiforme 10 weeks prior to admission. Eight weeks prior to admission, radiotherapy was initiated. Dexamethasone, begun perioperatively, was tapered from 4 mg orally four times a day to 1 mg orally twice a day over the ensuing 8 weeks. One week prior to admission, the patient developed a nonproductive cough

with progressive shortness of breath and intermittent fevers. On the day of admission, a chest radiograph revealed bilateral interstitial infiltrates, and arterial blood gas values with the patient breathing air were pH = 7.5, partial carbon dioxide pressure (PCO_2) = 34 mm Hg, and oxygen partial pressure (PO_2) = 51 mm Hg. The alveolar-arterial oxygen gradient ([A-a]O_2 gradient) was 58 mm Hg. The lactate dehydrogenase (LDH) concentration was 330 U/L. The patient was admitted and treated with intravenous trimethoprim/sulfamethoxazole and erythromycin. On the second day of hospitalization, a specimen of sputum induced with nebulized 3% saline revealed *P. carinii* on toluidine blue staining. Treatment with trimethoprim/sulfamethoxazole alone was continued, and the patient recovered uneventfully.

Patient 2

FW is a 74-year-old woman who underwent a partial resection of a left cerebellopontine angle meningioma 29 months prior to admission. Ten months later, recurrent tumor was noted in the left posterior fossa. Twelve weeks prior to admission, the patient was treated with stereotactic radiosurgery for recurrent tumor. Two weeks later, dexamethasone, 4 mg twice daily, was begun because of worsening ataxia. Dexamethasone was subsequently tapered to 2 mg every day, but, 4 weeks prior to admission, the dexamethasone was increased to 4 mg three times a day because of recurrent ataxia. Two weeks prior to admission, the patient was hospitalized for steroid-induced diabetes and myopathy. The dexamethasone was decreased to 2 mg twice a day and then changed to prednisone 15 mg every day. The patient was discharged 3 days prior to admission on prednisone 10 mg every day. One day prior to admission, the patient noted the onset of a nonproductive cough and intermittent fevers. On the day of admission, a chest radiograph revealed bilateral interstitial infiltrates, and arterial blood gas values obtained while the patient was breathing air were pH = 7.50, PCO_2 = 33 mm Hg, and PO_2 = 45 mm Hg. The (A-a)O_2 gradient was 65.2 mm Hg. The LDH concentration was 410 U/L. The patient was admitted and treated with intravenous trimethoprim/sulfamethoxazole. On the second day of hospitalization, sputum induced with nebulized 3% saline and stained with toluidine blue revealed *P. carinii*. The patient recovered uneventfully.

Patient 3

JW is a 50-year-old man who had a right frontal astrocytoma resected 12 weeks prior to admission. Postoperatively, he was treated with dexamethasone 4 mg orally three times a day. He was hospitalized 8 weeks prior to admission for seizures, and his dexamethasone was increased to 4 mg orally four times a day. Radiotherapy was initiated, and, over the ensuing 8 weeks, the dexamethasone was tapered to 1 mg orally daily. One day prior to admission, the patient developed fevers, shortness of breath, and an exacerbation of a chronic nonproductive cough that had been present over the preceding few weeks. On the day of admission, a bilateral interstitial infiltrate was noted on chest radiograph, and arterial blood gas values obtained while the patient was breathing 100% oxygen via a high-flow mask were pH = 7.46, PCO_2 = 32 mm Hg, and PO_2 = 73 mm Hg. The (A-a)O_2 gradient was 608 mm Hg (100% oxygen). The LDH concentration was 420 U/L. The patient was admitted and treated with intravenous trimethoprim/sulfamethoxazole and erythromycin. The patient was too ill to tolerate sputum induction, and, on the second day of hospitalization, he was transferred to the medical intensive care unit because of hypoxia and hypotension. On the third day of hospitalization, an open lung biopsy was performed, and antibiotic therapy was broadened to cover possible resistant *Staphylococcus* and *Mycobacterium* species. On hospital Day 6, sections of biopsied lung stained with methenamine silver revealed *P. carinii*, and all antibiotics were discontinued except for trimethoprim/sulfamethoxazole. The patient recovered fully.

Patient 4

JC is a 75-year-old man who had a right parietal glioblastoma multiforme diagnosed by stereotactic biopsy 10 weeks prior to admission. Postoperatively, he received dexamethasone 4 mg orally four times a day. Eight weeks prior to admission, radiotherapy was initiated. Six weeks prior to admission, his dose of dexamethasone was gradually tapered to 2 mg orally twice a day because of the development of a steroid myopathy. In the 4 weeks prior to admission, he developed a nonproductive cough. Two days prior to admission, he developed bloody diarrhea and fever. Blood cultures obtained on the day of his admission grew *Listeria monocytogenes*, and treatment with intravenous ampicillin and gentamicin was started. His chest radiograph on admission was clear, but sputum obtained on the fourth hospital day revealed *P. carinii* on toluidine blue staining. The LDH concentration was 474 U/L. Arterial blood gas values with the patient breathing air were pH = 7.48, PCO_2 = 34 mm Hg, and PO_2 = 89 mm Hg. The (A-a)O_2 gradient was 20.0 mm Hg. The patient's antibiotics were changed to intravenous trimethoprim/sulfamethoxazole, and he re-

covered uneventfully from his PCP and *Listeria* bacteremia, although his neurologic condition deteriorated.

COMMENTS

P. carinii is a unicellular eukaryote of uncertain taxonomic position, having been classified as a protozoan by some and a fungus by others [1,2]. There have been only two previous reports of PCP in patients with primary brain tumors. One child with a brain stem tumor developed PCP while receiving a prolonged course of corticosteroids as the only immunosuppressive agent [13]. More recently, Henson *et al* [12] described PCP in 10 patients with primary brain tumors seen over an 8-year period at Memorial Sloan Kettering Cancer Center. In eight of these patients, PCP developed during steroid taper. This report describes four additional patients with intracranial tumors who developed PCP during a prolonged taper of corticosteroids.

There are many descriptions of PCP in the renal [4,5] and cardiac [6,7] transplant literature in which corticosteroids, as well as cyclosporine and azathioprine, are used as immunosuppressives. PCP has also been reported in patients with hematologic [3] and solid [14] tumors whose immune function was impaired either because of direct effects of the underlying disease or because of treatment with immunosuppressive chemotherapeutic agents and steroids. Three reports describe PCP as a complication of Cushing's syndrome [15–17].

The mechanisms by which corticosteroids interact with the host immune system and predispose to the development of PCP are poorly understood but may involve steroid-induced attenuation in alveolar macrophage surveillance [11], inhibition of polymorphonuclear leukocyte function [18], or interference with antibody production by lymphocytes [19]. It is unclear why the clinical pneumonitis in humans appears to develop during the tapering of steroids, but it may relate to the histologic changes observed in the rodent model, with alveolar cyst proliferation seen during steroid administration and interstitial mononuclear infiltration and fibrosis seen during steroid taper [11].

Animal studies have shown that the organism is acquired through airborne inoculation of room air [20]. With the increasing number of hospitalized patients with PCP, it is possible that patients become inoculated while in the hospital [21]. However, asymptomatic human infection, as evidenced by the high proportion of healthy individuals with antibodies against *P. carinii* [22], would argue more for activation of latent infection than *de novo* inoculation.

Patients with PCP unrelated to AIDS tend to have a more acute disease than that seen in the AIDS population. Symptoms are present for fewer days (5 versus 28), and patients tend to have higher respiratory rates (34/min versus 22/min) with lower arterial PO_2 values (52 mm Hg versus 69 mm Hg) at the time of presentation [23]. Treatment options are the same as with the AIDS population, except that trimethoprim/sulfamethoxazole is better tolerated in non-AIDS patients. One study documented 12% side effects in patients without AIDS versus 65% in AIDS patients [23]. Both continuous [24] and intermittent [25] oral trimethoprim/sulfamethoxazole (150 mg trimethoprim and 750 mg sulfamethoxazole per square meter per day or 3 times a week) have been shown to be effective prophylaxis against PCP in patients with malignancies.

From February 1, 1990, to January 31, 1991, we have diagnosed and treated PCP in four patients with primary brain tumors undergoing a steroid taper. This represents a 6.2% incidence (4 of 65) in our patients with primary brain tumors who received radiation and corticosteroids over that period. The median duration of steroid treatment at the onset of PCP symptoms in these patients was 10 weeks. It is unclear whether the incidence of PCP in patients with brain tumors receiving long-term steroids is rising, although this possibility is suggested by the fact that in the preceding 5 years we have observed PCP in only one other patient with a primary brain tumor (glioma) and in one patient with a cerebral metastasis from colon cancer. Both patients had been receiving steroids: the patient with the glioma for 12 weeks and the patient with the metastasis for 8 weeks before PCP developed. We were unable to identify any risk factors for PCP within the group of patients receiving steroid therapy, although it is possible that age may be important. The median age of those patients developing PCP (63.5 years) was higher than the median age for the remaining 61 patients who did not develop PCP (51 years), but the difference was not statistically significant ($p = 0.122$), partly as a result of the small number of patients in our series.

The result of this study and that of Henson *et al* [12] suggest that patients with primary brain tumors receiving steroid therapy may be at increased risk of developing PCP. Until the risks and mode of acquisition of PCP in patients with brain tumors become more clearly elucidated, it may be prudent to consider prophylaxis against PCP for such patients receiving prolonged courses of corticosteroids, particularly as steroid therapy is withdrawn. Furthermore, physicians caring for these patients should maintain a high index of

suspicion for PCP to ensure early diagnosis and treatment.

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