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SHORT REPORT

Two cases of fatal *Pneumocystis jirovecii* pneumonia as a complication of tacrolimus therapy in ulcerative colitis — A need for prophylaxis

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Abstract

Here we report 2 cases of fatal *Pneumocystis jirovecii* pneumonia in patients with severe ulcerative colitis receiving combination immunosuppression including tacrolimus. We discuss the necessity of a *P. jirovecii* prophylaxis especially in elderly patients according to the European evidence-based consensus on the prevention and management of opportunistic infections in inflammatory bowel disease.

1. Introduction

Immunosuppressive therapy is an established risk factor for opportunistic infections. There is increasing evidence for a rising incidence of opportunistic infections under combined immunosuppressive therapy in inflammatory bowel diseases (IBD) especially in the era of anti-TNF-antibodies.[6] Kaur and Mahl reported 84 cases of pneumocystis infection in a large series of patients with rheumatoid arthritis treated with anti-TNF-antibodies.[1] Another study from Japan including 5000 patients with rheumatoid arthritis calculated an incidence of pneumocystis infection of 0.4%.[2] In inflammatory bowel disease 2 cases of *Pneumocystis jirovecii* (formerly *P. carinii*) have been reported in a series of 100 patients with severe ulcerative colitis treated with combination immunosuppression including cyclosporine.[3] Here we describe the first cases of pneumocystis infection in patients with steroid-refractory ulcerative colitis treated with tacrolimus.

2. Case report 1

The first case is a 72-year old male patient with a recent diagnosis of ulcerative colitis three months ago. The patient had received prior Billroth-I-resection more than 20 years ago. Comorbidities included medically controlled arterial hypertension, hyperlipoproteinemia, paroxysmal atrial flutter and moderate but regular alcohol consumption. The patient had received high-dose mesalamine topically and systemically and in addition intravenous steroids without response and was referred to our hospital in January 2009. The patient suffered from severe symptoms with up to ten bloody bowel movements and abdominal pain. Colonoscopy showed severe inflammation extending to the hepatic

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flexure and the histology demonstrated typical findings including crypt distortion with no signs of infective colitis. Viral superinfection with cytomegalo- and herpes simplex virus was excluded by serology and immunohistochemistry. Due to severe activity with rectal bleeding and abdominal pain despite high-dose steroids intravenous tacrolimus therapy was initiated at a dose of 0.01 mg/kg body weight. Six days later the patient started to develop respiratory insufficiency and pulmonary embolism of the right lung was diagnosed. The patient deteriorated despite anticoagulation therapy. Radiologic imaging showed interstitial infiltrations of both upper lobes [Fig. 1]. Mechanical ventilation was initiated and a bronchoscopy with lavage was performed. Immunofluorescence and PCR revealed *P. jirovecii* infection. High-dose trimethoprim–sulfamethoxazole plus a broad antibiotic therapy including piperacilline, combactam, levofloxacin and fluconazole was initiated but the respiratory situation continued to deteriorate and the patient died from multiorgan failure 11 days after diagnosis and 23 days after initiating tacrolimus therapy.

3. Case report 2

The second case is a 74-year old male patient with ulcerative colitis diagnosed 2 years earlier. Previously the patient had an operation for aortic aneurysma, ischemic cardiomyopathia and chronic renal insufficiency. Primarily the patient received steroids and azathioprine. Azathioprine therapy had to be stopped due to gastrointestinal discomfort and nausea. In June 2006 the patient had experienced a severe steroid-refractory flare-up of his ulcerative colitis. Colonoscopy revealed extensive colitis and in addition to steroids tacrolimus therapy was initiated. Combination treatment with steroids and tacrolimus resulted in hyperglycemia but disease activity of the colitis was controlled. Complete weaning from steroids failed several times. In February 2008 6-mercaptopurine was initiated but complete withdrawal of steroids failed again. Although colectomy was strongly suggested the patient refused the operation and therefore triple immunosuppression had to be maintained to control colitis. In July 2008, i.e. 2 years after initiation of triple immunosuppression the patient developed respiratory insufficiency and sepsis. Non-invasive ventilation was initiated and the patient was transferred to the intensive care unit. Because *P. jirovecii* was suspected high-dose trimethoprim–sulfamethoxazole was initiated immediately. A CT-scan showed patchy bilateral infiltrates [Fig. 2] and bronchoscopy confirmed the suspected diagnosis of *P. jirovecii* in bronchial lavage fluid. In the following the patient developed septic complications (renal and hepatic failure, paralytic ileus, and septic cardiomyopathy). Due to respiratory deterioration mechanical ventilation was initiated. The patient died 2 weeks after diagnosis.

4. Discussion

P. jirovecii is a unicellular fungi which is found in the respiratory tract of mammals and humans. Symptoms in patients with *P. jirovecii* pneumonia include, fever, nonproductive cough, weight loss, chills, progressive respiratory insufficiency and rarely hemoptysis.

This organism may cause life-threatening opportunistic infections in patients with advanced HIV infection or other causes of immunosuppression (i.e. patients with cancer treated with chemotherapy or solid organ transplant recipients). Different studies [13–15] report on the risk of *P. jirovecii* infection especially in kidney transplant recipients. Lufft et al. [15] examined the incidence of *P. jirovecii* pneumonia after renal transplantation and showed the highest incidence in patients treated with tacrolimus compared to patients treated with a cyclosporine-based immunosuppressive regime.

We here report two cases of *P. jirovecii* pneumonia in patients with ulcerative colitis and combined immunosuppression with steroids and tacrolimus, the second case receiving triple immunosuppression with additional 6-mercaptopurine. Despite an immediate therapy with high-dose trimethoprim–sulfamethoxazole and a calculated broad-spectrum antibiotic therapy both patients died due to progressive respiratory failure. It is our common practise to add tacrolimus in case of steroid-refractory flares of ulcerative colitis.[11,12] During the past 10 years we have

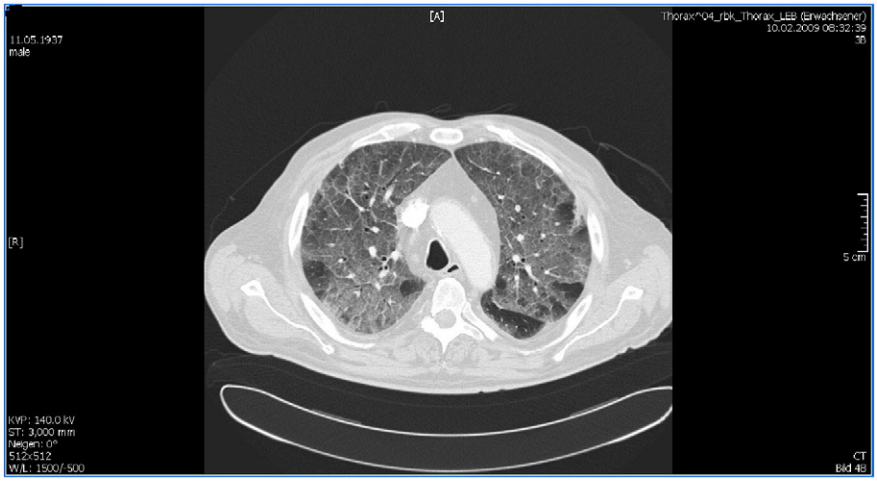

Figure 1 Thoracic CT from patient case 1 with bilateral pulmonary infiltrations.

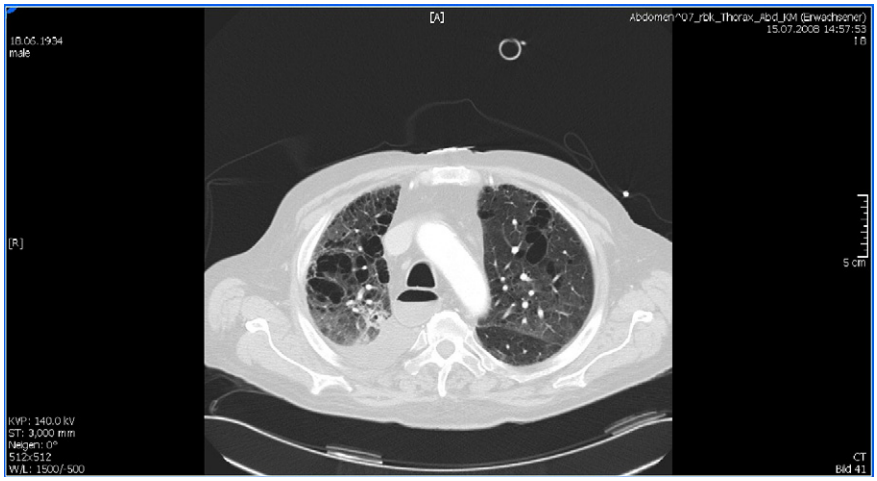

Figure 2 Thoracic CT from patient case 2 with bilateral pulmonary infiltrations and bullous emphysema.

treated approximately 200 patients with tacrolimus. The reported patients are the only cases of *P. jirovecii* infection during this period giving an estimated frequency of about 1% similar to that reported for cyclosporine in UC.[3]

Independent risk factors contribute to opportunistic infections in patients receiving immunosuppressive therapy. A case control study of 100 patients with inflammatory bowel disease showed an age above 50 to be an independent risk factor for opportunistic infections.[5] Furthermore comorbidities have been associated with an increased rate of opportunistic infections in patients with rheumatoid arthritis. In particular these were chronic lung disease, alcoholism, organic brain disease and diabetes mellitus.[7] Patients with a flare of IBD and need for a combined immunosuppressive therapy often suffer from malnutrition. Malnutrition seems to be another independent risk factor for opportunistic infections.[10] Some of these additional factors apply to our reported cases and may have contributed to the progressive course and the fatal outcome of disease.

Prophylaxis with trimethoprim–sulfamethoxazole significantly decreases the risk for *P. jirovecii* pneumonia. A meta-analysis in patients with hematological cancers or transplant recipients reported a 91% reduction in the incidence of *P. jirovecii* pneumonia if prophylaxis with cotrimoxazole was given.[8] HIV-infected patients with a CD4+ count less than 200/ml had significantly fewer infections with cotrimoxazole prophylaxis.[9] It remains speculative if the application of chemoprophylaxis to our patients could have prevented pneumocystis infection or had resulted in a more favourable outcome.

5. Conclusions

This case report strongly demands careful consideration of applying combination immunosuppression to patients at increased risk for opportunistic infections especially advanced age and comorbidities. Furthermore we would like to underline the recommendations on chemoprophylaxis in triple or even double immunosuppression particularly if anti-TNF-alpha agents or calcineurin inhibitors are used. According to the ECCO consensus primary chemoprophylaxis of *P. jirovecii* infection can be performed with 3 different regimes (Table 1).[4]

Table 1 Regimes of chemoprophylaxis of *Pneumocystis jirovecii*.

TMP–SMZ 80–400 mg	Once daily
TMP–SMZ 160–800 mg	Half-dose daily
TMP–SMZ 160–800 mg	Three times per week

TMP: trimethoprim, SMZ: sulfamethoxazole.

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