AIDS-related extrapulmonary *Pneumocystis carinii* infection presenting as a solitary rectal ulcer

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EM YOSHIDA, D FILIPENKO, P PHILLIPS, JSG MONTANER, JS WHITTAKER. AIDS-related extrapulmonary *Pneumocystis carinii* infection presenting as a solitary rectal ulcer. *Can J Gastroenterol* 1996;10(6):401-404. Extrapulmonary infection with *Pneumocystis carinii*, although uncommon, is increasingly recognized. Use of aerosolized pentamidine versus a systemic medication is thought to be a contributing factor due to the low concentrations of drug that are incapable of suppressing systemic infection. Infection with *P carinii* has been reported in every organ system including the gastrointestinal system. A 28-year-old acquired immunodeficiency syndrome patient receiving prophylaxis with aerosolized pentamidine who presented with a solitary rectal ulcer is reported. Initial biopsy was characteristic of extrapulmonary *P carinii* infection, with numerous organisms present. Occasional cytomegalovirus inclusion bodies were noted which may have been a copathogen but which were not treated. Treatment with intravenous pentamidine resulted in documented eradication of *P carinii* and complete resolution of the ulcer. Although lower gastrointestinal pneumocystosis has been described without ulceration, this is the first description of rectal ulceration presenting as the initial manifestation of extrapulmonary pneumocystosis.

Key Words: *Acquired immunodeficiency syndrome, Extrapulmonary Pneumocystis carinii, Rectal ulcer*

Infection extra-pulmonaire à *Pneumocystis carinii* liée au SIDA sous la forme d'un ulcère rectal solitaire

RÉSUMÉ : L'infection extra-pulmonaire à *Pneumocystis carinii*, bien que rare, est de plus en plus observée. L'utilisation de la pentamidine en aérosol versus un médicament systémique pourrait être un facteur contributif à cause des faibles concentrations du médicament qui sont incapables de supprimer l'infection systémique. L'infection à *P. carinii* a été signalée dans tous les organes, y compris dans l'appareil digestif. Nous décrivons ici le cas d'un patient de 28 ans atteint du syndrome de l'immuno-déficience acquise ayant reçu en prophylaxie de la pentamidine en aérosol et qui a présenté un ulcère rectal solitaire. La biopsie initiale a été caractéristique de l'infection extra-pulmonaire à *P. carinii* avec présence de nombreux organismes. D'occasionnels organismes d'inclusion à cytomégalovirus ont été notés et auraient pu être des pathogènes concomitants, mais n'ont pas été traités. Le traitement par pentamidine intraveineuse a permis une éradication documentée de *P. carinii* et la résolution complète de l'ulcère. Bien que la pneumocystose des voies digestives basses ait été décrite sans ulcération, il s'agit du premier cas d'ulcération rectale décrit comme manifestation initiale d'une pneumocystose extra-pulmonaire.

Since the widespread adoption of prophylaxis against *Pneumocystis carinii*, the incidence of infection as an indicator disease for acquired immunodeficiency syndrome (AIDS) has declined from 53% in 1989 to 16% in 1993 (1). Despite this, *P carinii* still remains a significant problem in human immunodeficiency virus (HIV)-infected patients and *P carinii* pneumonia (PCP) remains the leading diagnostic indicator for the new diagnosis of AIDS in the United States

(1). Extrapulmonary infection with *P carinii*, although uncommon, has been more frequently reported in the past few years (2-17). Aerosolized pentamidine has been considered a contributing factor in the development of extrapulmonary *P carinii* infection in many of these reports (5-17). As aerosolized pentamidine achieves high pulmonary concentrations with minimal systemic absorption (18), it is hypothesized that pulmonary infection is suppressed without the benefit of

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Figure 1) **A** High power photomicrograph of the granulation tissue comprising the ulcer base with capillary loops separated by foamy material (arrow) (hematoxylin and eosin; bar = 10 µm). **B** Oil immersion photomicrograph of the arrowed region showing typical cup-shaped cysts of *Pneumocystis carinii* (Grocott's methenamine silver stain; bar = 10 µm)

significant systemic suppression. Not all cases of extrapulmonary pneumocystis infections, however, have preceded aerosolized pentamidine administration (12,14) and reported cases of disseminated *P carinii* infection predate the AIDS era (12).

Extrapulmonary *P carinii* infection has been described in almost every organ system. Gastrointestinal involvement has been reported in the esophagus (2), stomach (2,6,17), small intestine (3,4), appendix (3), liver (2,5,7,8,13), pancreas (15) and rectum, and descending and sigmoid colon (17). Gastrointestinal involvement has been described with both multiorgan disseminated involvement (2,3,5,6,8,13,15-17) and as an isolated extrapulmonary focus of infection (4). We report a patient with AIDS who presented with a solitary rectal ulcer as a manifestation of extrapulmonary *P carinii* infection following aerosolized pentamidine administration. To date, rectal ulceration, either in multiorgan dissemination or as a single focus, has not been reported as a presenting feature of extrapulmonary *P carinii* infection.

CASE HISTORY

A 28-year-old homosexual Caucasian man with AIDS was investigated because of a one-month history of passing blood and mucous per rectum without diarrhea or tenesmus. Previous stool cultures were positive for *Yersinia* species; however, treatment with tetracycline did not improve symptoms. The patient was first found to be seropositive for HIV four years previously. AIDS-related illnesses included oral hairy leukoplakia, recurring oral candidiasis, perianal *Herpes simplex* and molluscum contagiosum. An episode of PCP 10 months previously was treated with aerosolized pentamidine as part of a controlled trial. PCP prophylaxis consisted of aerosolized pentamidine (60 mg) by ultrasonic nebulizer every two weeks after an induction course according to protocol (19). Other medications included zidovudine, oral nystatin and acyclovir. The physical examination did not reveal abdominal tenderness, stigmata of liver disease or hepatosplenomegaly. Rectal examination revealed a non-

tender lesion resembling an ulcer. The rest of the examination was unremarkable. Laboratory investigations revealed hemoglobin of 124/L, leukocyte count $2.6 \times 10^9/L$, platelets $138 \times 10^9/L$, mean corpuscular volume 110 fl, CD4 cells $0.02 \times 10^9/L$ (normal 10.4^3 to $1.36 \times 10^9/L$), CD8 cells $0.28 \times 10^9/L$ (normal 10.25 to $0.90 \times 10^9/L$), CD4:CD8 ratio 0.07 (normal 10.95 to 3.41), aspartate aminotransferase 32 U/L (normal less than 40), alkaline phosphatase 84 U/L (normal less than 105) and total bilirubin 10 µmol/L (normal less than 20).

Flexible sigmoidoscopy was undertaken. A 2 cm raised ulcer was seen on the posterior wall of the rectum. Histological examination of biopsied mucosa from the periphery of the ulcer, revealed acellular eosinophilic material with a honey-combed pattern associated with inflamed granulation tissue (Figure 1A). Staining with Grocott's methenamine silver revealed numerous *P carinii* cysts (Figure 1B). A rare cytomegalovirus (CMV) inclusion body was seen; stains for acid-fast bacilli were negative.

The patient was treated for extrapulmonary *P carinii* proctitis. No therapy for CMV was given. Cotrimoxazole and later clindamycin and primaquine were initiated but resulted in severe skin rashes requiring discontinuation. Four weeks after initial biopsy, treatment was undertaken with intravenous pentamidine 4 mg/kg daily for 13 days. One week after completing therapy, sigmoidoscopy was repeated. The rectal ulcer had diminished in size to 1 cm. Repeat biopsy revealed improvement with no evidence of *P carinii*; again a CMV inclusion body was occasionally seen. Five weeks after completing therapy, sigmoidoscopy was repeated. The ulcer had completely resolved leaving only a small residual scar. Biopsy of the area revealed normal rectal mucosa; no CMV inclusion bodies were seen. Clinically, the patient's symptoms of bloody, mucous stools resolved. PCP prophylaxis was reinstituted with intravenous pentamidine at 4 mg/kg once a month.

Eight months after resolution of the rectal ulcer, repeat sigmoidoscopy was undertaken because of a bloody stool. An anal fissure was seen with no recurrence of rectal ulceration. Pathological examination revealed only condylomatous changes in the anal squamous epithelium. The rectal mucosa was normal. Thirteen months after resolution of the ulcer, sigmoidoscopy was repeated because of perianal pain and bleeding. A perianal ulcer was found. Biopsy revealed inflamed granulation tissue and CMV inclusion bodies. Neither *P carinii* nor its characteristic eosinophilic honey-combed necrotic material were seen. Treatment with ganciclovir and foscarnet was initiated. A few months later the patient was admitted in severe respiratory distress because of PCP. Appropriate treatment was initiated but the patient requested that therapy be withdrawn. He subsequently died; an autopsy was declined.

DISCUSSION

This patient presented with a solitary rectal ulcer following a course of aerosolized pentamidine. Rectal mucosal biopsy revealed eosinophilic honey-combed material, the rare

CMV inclusion body and many *P carinii* organisms using a silver stain. The eosinophilic material seen on microscopy is characteristic of the necrotic lesions of active *P carinii* infection (15). Treatment with intravenous pentamidine alone resulted in biopsy proven eradication of *P carinii* followed by complete resolution of the ulcer. This strongly suggests that the ulcer was secondary to *P carinii* and not CMV. Although CMV can cause ulcerations of the gastrointestinal tract (20), its mere presence in the gut may not have etiological significance (20). Nonetheless, it is possible that CMV was a copathogen in this patient's ulcer. A recent review (15) of extrapulmonary *P carinii* infections found coexisting CMV infection in 32 reported cases. It was suggested that CMV may cause endothelial disruption, creating a favourable environment for extrapulmonary *P carinii* infection (15). Alternatively, it has been suggested that CMV can secondarily infect tissue with rapid growth such as endothelial cells in inflammatory tissue (21). If this hypothesis is true, then the situation would be reversed – the presence of CMV would be secondary to the effect of the primary *P carinii* infection. The patient's subsequent perianal ulcer, which occurred more than a year after resolution of the rectal ulcer, was attributed to CMV. Biopsy did not reveal the characteristic necrotic changes associated with *P carinii*. We feel that this perianal ulcer differed etiologically and pathologically from the rectal ulcer.

Interestingly, our patient's rectal ulcer was the only clinically apparent focus of extrapulmonary *P carinii* infection. Presumably, *P carinii* reached the rectum via systemic parasitemia probably from the previous PCP which was treated with aerosolized pentamidine as part of a study protocol. There was no other evidence of disseminated *P carinii* infection. After treatment of the original pneumonia, there were no respiratory symptoms or clinical evidence of pulmonary disease. Fundoscopic examination, likewise, did not reveal evidence of retinal involvement. Liver enzymes were normal and there was no clinical evidence of hepatomegaly. Reported cases of hepatic pneumocystosis have all demonstrated elevation in liver enzymes or clinical evidence of

liver involvement if liver enzymes were not reported (5-8,13,14).

As previously mentioned, *P carinii* has been described in numerous areas of the gastrointestinal tract. Endoscopically, in the upper gastrointestinal tract, focal superficial ulceration and exudate have been described in the esophagus (2), whereas nodules and linear nodular ulcerations have been described in the stomach (6,17) and duodenum (6). Although *P carinii* infection has been described in the colon (16), in the reported case, the mucosa appeared normal endoscopically. Biopsies of the normal appearance mucosa, however, revealed *P carinii* and the characteristic eosinophilic exudate of *P carinii* infection within the lamina propria. Our case is thus the first to describe rectal ulceration as the presenting manifestation of extrapulmonary *P carinii* infection. Other infectious pathogens that have been reported to produce rectal ulcerations include syphilis (22), herpes simplex (23) and lymphogranuloma venereum (24), as a result of direct inoculation during sexual transmission and tuberculosis (25) as a consequence of a systemic infectious process. We note that all of these pathogens should be considered in the differential diagnosis of rectal ulcers in patients engaging in anoreceptive intercourse, a high HIV risk activity.

Our patient responded to intravenous pentamidine both symptomatically, with resolution of bloody, mucous stools, and endoscopically with resolution of the ulcer. Extrapulmonary *P carinii* infections are usually treated with the same agents used to treat PCP. A review of extrapulmonary pneumocystis noted a response to these agents of slightly greater than 50% in 30 reported cases (12).

In summary we report the first case of extrapulmonary *P carinii* infection presenting as a rectal ulcer in a patient with AIDS. Diagnosis was made on sigmoidoscopic biopsy, and response to intravenous pentamidine was excellent. This case demonstrates that extrapulmonary *P carinii* infection needs to be considered in AIDS patients presenting with rectal ulceration especially if aerosolized pentamidine has been used for PCP prophylaxis.

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