Therapy of *Candida* peritonitis: penetration of amphotericin B into peritoneal fluid

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Summary

Candida albicans peritonitis developed in a 48-year-old man with a perforated gastric ulcer who subsequently was treated with intravenous amphotericin B. The drug penetrated well into the inflamed peritoneal cavity and eradicated the organism from the peritoneal fluid. Nevertheless, at post-mortem, *Candida* organisms were demonstrated in a gall-bladder empyema and within the gall-bladder wall. Because intra-abdominal organs may be involved in *Candida* peritonitis, the use of high dose amphotericin B administered either intravenously, intraperitoneally, or both intravenously and intraperitoneally is recommended.

Introduction

Peritonitis due to *Candida* has recently been reviewed by Bayer *et al.* (1976). Their report and that by Bortolussi *et al.* (1975) suggested that short-term therapy with amphotericin B administered intravenously, intraperitoneally, or by a combination of these routes was effective in the treatment of *Candida* peritonitis.

A patient with peritonitis due to *C. albicans* is now described who received only intravenous amphotericin B. Simultaneous serum and peritoneal fluid levels of this antifungal agent were determined, and in spite of adequate peritoneal fluid concentrations of amphotericin B, *Candida* organisms were demonstrated microscopically in the gall-bladder at post-mortem.

Case report

A 48-year-old barman was transferred to the Minneapolis Veterans Administration Hospital for evaluation of abdominal pain and haematemesis. During the three weeks before transfer he had been

treated continuously with either tetracycline for pneumonitis or trimethoprim-sulfamethoxazole and nitrofurantoin for urinary tract infection. A series of upper gastrointestinal tests done four days before transfer revealed a large gastric ulcer on the lesser curvature with no evidence of perforation. Three days before transfer, *C. albicans* was cultured from his sputum.

The patient's complaints were limited to haematemesis and mild upper abdominal distress. He denied any past history of ulcer disease or significant abdominal pain, but did admit to heavy cigarette smoking accompanied by a productive cough and to chronic alcohol ingestion.

Physical examination revealed diffuse tenderness and guarding in both upper quadrants and in the right lower quadrant of the abdomen. Also, there was minimal rebound tenderness in the left upper abdominal quadrant. Endoscopy demonstrated a deep, penetrating ulcer on the lesser gastric curvature and multiple small antral ulcers.

Laboratory evaluation revealed a haemoglobin of 13.5 g/dl and a white blood count of $24 \times 10^9/l$ with $21 \times 10^9/l$ neutrophils, $1.2 \times 10^9/l$ lymphocytes and $1.68 \times 10^9/l$ monocytes.

On the second hospital day, right upper quadrant rebound tenderness developed and an exploratory laparotomy was performed. Two perforated gastric ulcers with an associated subhepatic abscess were found. A partial gastrectomy was performed. Cultures of the abscess grew *C. albicans*.

Following surgery the peritoneal cavity was irrigated with 1 g of cephalothin every 6 hr. Two days later the patient developed signs of an acute abdominal catastrophe and a second abdominal exploration revealed infarction of all but 137 cm of the small bowel. The infarcted portion of bowel was removed and revealed diffuse mucosal necrosis, acute peritonitis, patent mesenteric vessels, and no fungal organisms. Free peritoneal fluid contained numerous

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FIG. 1. Photomicrograph showing a portion of the necrotic gall-bladder wall with small budding yeast and pseudohyphae (Gomori's silver impregnation $\times 700$).

neutrophils and budding yeast with pseudohyphae. *C. albicans* was grown from peritoneal fluid obtained at the second operation, as well as from previously placed abdominal drains. Therapy was begun with amphotericin B intravenously. After a 1 mg test dose the amount of drug was rapidly increased to a maintenance dosage of 50 mg every other day.

After 5 days of therapy, specimens of serum and peritoneal fluid were obtained before and after a 10-hr intravenous infusion of 50 mg amphotericin B. Bioassay determination of amphotericin B using appropriate serum and peritoneal fluid standards revealed serum levels to be 0.52 $\mu\text{g/ml}$ before and 1.5 $\mu\text{g/ml}$ after the infusion. Peritoneal fluid concentration ranged from 0.44 to 0.78 $\mu\text{g/ml}$. These levels exceeded the minimum inhibitory concentration for the yeast (0.25 $\mu\text{g/ml}$) and *C. albicans* could no longer be found on smears or cultures of peritoneal fluid. The patient slowly improved for 8 days and then again developed signs of peritonitis. At a third operation he had a leaking jejunocolonic anastomosis and an open duodenal stump. The remaining bowel was cyanotic and poorly perfused. Smears and cultures of the peritoneal fluid were negative for yeast; however, numerous Gram-negative bacilli were isolated. The patient died 2 days later after receiving a total of 471 mg amphotericin B intravenously. At post-mortem, extensive acute and chronic peritonitis was found and budding yeast

with pseudohyphae were found in sections of a gall-bladder empyema (Fig. 1).

Discussion

Clinically significant peritoneal infection with *Candida* has been described, manifest by fever, signs of peritoneal inflammation, positive peritoneal cultures, and purulent ascitic fluid (Bayer *et al.*, 1976). The patient fulfilled all these criteria although fever greater than 38°C was present only on the day of the second laparotomy. There was no evidence of disseminated candidiasis in that all intraperitoneal vessels were patent and no yeast was ever found outside the abdominal cavity.

Intraperitoneal administration of amphotericin B for the treatment of *Candida* peritonitis has been proposed in order to decrease the systemic reactions frequently encountered with the intravenous injection of this agent (Bayer *et al.*, 1976). This method of therapy has been thought to be effective because *Candida* organisms usually remain localized to the abdominal cavity. The dosages recommended have varied widely. Bortolussi *et al.* (1975) used a very small amount of 16 mg in 10 days in the treatment of a young girl with peritonitis due to a very sensitive *C. tropicalis*. Bayer *et al.* (1976) gave much larger total doses ranging from 330 mg in 21 days to 3.0 g in 16 days given either intravenously or both intravenously and intraperitoneally. It is of interest that

the present patient had unsuspected abdominal organ involvement as did two cases in Bayer's series. With low dose therapy by any route it would seem unlikely that sufficient amphotericin B would be available for penetration into abdominal viscera. This problem might be overcome by using the higher doses reported by Bayer, since amphotericin B is well absorbed from peritoneal surfaces. In Bayer's patient, in whom peritoneal levels of amphotericin B were measured, a fluid level of only 2 µg/ml was found while the patient was receiving an average daily dose of 150 mg intraperitoneally and 25 mg intravenously.

Amphotericin B has been reported as penetrating poorly into cerebrospinal fluid, parotid gland fluid, aqueous humour and haemodialysis fluid (Bennett, 1974; Feldman, Hamilton and Gutman, 1973). The present authors show for the first time that intravenously administered amphotericin B penetrates well into inflamed peritoneal fluid, with a peak-fluid: peak-serum penetration ratio of 52%. Increased penetration into aqueous humour has been reported with ocular inflammation in experimental animals (Green, Bennett and Goos, 1965). Because of the possibility of involvement of abdominal organs it appears that full-dose intravenous therapy, as given to the patient described in this report, high dose intraperitoneal therapy alone, or in combination with intravenous amphotericin B, as given by Bayer *et al.* (1976) is a reasonable approach in the treatment of *Candida* peritonitis. This is further supported by the favourable response of *Candida* peritonitis to systemic antifungal therapy recently reported by Barnes *et al.* (1975) and in earlier reports (Montemartini, Specchia and Dander, 1970; Reeves *et al.*, 1972). Oral administration of amphotericin B has been used (Hurwich, 1966) and may be effective in the gut lumen, but the poor absorption of swallowed amphotericin B would make this an unreliable approach for the treatment of *Candida* peritonitis.

Finally, it is noteworthy that the patient here reported received antibiotics for 3 weeks before the onset of *Candida* peritonitis, and that *C. albicans* was recovered from his sputum 4 days before the development of peritoneal signs. The role of

antecedent systemic antibacterial therapy and intra-peritoneal administration of antimicrobials as predisposing factors in the development of peritoneal candidiasis was cited by Bayer *et al.* (1976). It is likely that the colonization of the present patient's upper respiratory tract with *C. albicans* led to the eventual development of *Candida* peritonitis following gastric ulcer perforation.

In summary, the authors have shown that amphotericin B penetrates well into the inflamed peritoneal cavity, and that in the presence of peritonitis *Candida* organisms may infect intra-abdominal organs without specific localizing signs. Therefore, to ensure adequate drug penetration into all infected sites, the authors recommend either high dose intravenous, high dose intraperitoneal or a combination of these two methods of therapy for patients treated with amphotericin B, and continuation of therapy for at least as long as signs of peritoneal infection persist.

Acknowledgments

We gratefully acknowledge the assistance of Evelyn Glatt and Tracy Husing in the preparation of the manuscript.

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