Candida Septic Thrombosis of the Great Central Veins Associated with Central Catheters

Clinical Features and Management

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Candida septic thrombosis of the great central veins is rarely diagnosed during life, and reports of survival with this condition are exceedingly rare. Eight patients with Candida septic thrombosis of the central veins, with six survivors, are reported. Seven of eight patients had multiple organ system failure following surgery or trauma. All patients had received broad spectrum antibiotics and total parenteral nutrition *via* a central catheter. Every patient showed features of venous thrombosis with localizing extremity edema and high grade candidemia. Intensive amphotericin B therapy (mean daily dose: 0.7 mg/kg) in all patients, combined with 5-fluorocytosine in five cases, resulted in cure and long-term survival in six patients who received 1600 to 3435 mg (mean: 26 mg/kg) total dose. None of these patients developed renal failure, while four showed improving renal function during treatment. In contrast to Candida endocarditis, septic central vein thrombosis caused by Candida appears to be curable medically in the majority of cases with intensive amphotericin B therapy (total dose: ≥ 22 mg/kg), combined when feasible with 5-fluorocytosine.

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SUPPURATIVE THROMBOPHLEBITIS has been recognized to be a significant complication of intravenous therapy. Endovascular infection within a peripheral vein is best treated by surgical excision of the involved segment, whether the offending organism is bacterial or fungal.[1-3] Central venous infection poses a greater problem, however, due to the formidable undertaking to surgically remove clot from the central veins.

Central venous catheters are now used widely in the care of critically ill patients, for total parenteral nutrition, drug therapy, and hemodynamic monitoring. Autopsy and prospective angiographic studies have demonstrated thrombosis formation, often of major degree yet clinically inapparent, within cannulated central veins in up to one-half of all patients.[4] Infected venous thromboses are found at autopsy in one-third of patients dying of major burns.[5] It is reasonable to expect a similarly high proportion of infected central venous thromboses.

Septic thrombosis of the great central veins—the internal jugular or subclavian veins and vena cavae—has rarely been diagnosed during life. Survival with Candida septic great vein thrombosis has been exceedingly rare. The first successfully treated case was reported in 1978.[6] We report now the unique clinical features of Candida septic thrombosis of the great central veins in eight patients, six of whom survived with intensive antifungal chemotherapy, without surgical intervention.

Methods

Over the past 8 years at the University of Wisconsin Hospital, approximately 60 patients had two or more blood cultures positive for Candida species. Eight patients fulfilled the following criteria for intravenous catheter related septic thrombosis: (1) high grade candidemia; (2) a central venous catheter in place prior to and up through the onset of candidemia; (3) no plausible extra-endovascular source; (4) candidemia persisted for more than 2 days after removal of the culpable catheter; and (5) clear-cut evidence of obstruction of the involved vein, edema of the extremity or extremities or the side of the neck and face.

Supporting evidence was considered, if obtained: Doppler examination (5 patients), radionuclear scanning (3 patients), histologic examination of clot adherent to the catheter tip (4 patients), autopsy findings (2 patients), and echocardiography negative for heart valve vegetations (6 patients).

Patients not fulfilling these criteria were excluded from consideration.

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TABLE 1. *Features of Candidemia*

Major Diagnosis	Age	Sex	Positive Cultures (N)	Vein Involved*	Duration of Positive Cultures (Days)
Survivors					
75% burn	27	M	7	IVC	6
Sacral ulcer following total hip replacement	74	M	10	SVC	19
Spontaneous splenic artery rupture	38	F	10	L Subclav	16
40% burn	46	M	7	SVC	14
Aortic aneurysm resection	59	M	11	R Subclav	6
Pneumonia/ morbid obesity	46	F	28	L IJ	24
Nonsurvivors					
Peritonitis with Crohn's colitis	56	F	20	Bilat Subclav, SVC	11
Electrical injury	62	M	12	L Subclav, SVC	9

* IVC = inferior vena cava; SVC = superior vena cava; IJ = internal jugular vein.

Results

Eight patients, 5 males and 3 females, were found to have had Candida septic thrombosis of the great central veins during the past 8 years. Table 1 gives features of the patients and their candidemia. Six patients survived with intensive medical treatment. Seven patients had undergone surgery or had major burns. All patients were in an intensive care unit at the onset of the syndrome with seven patients ventilator dependent. All patients had received total parenteral nutrition *via* the involved vein. All patients had received broad spectrum antibiotics for polymicrobial sepsis, with an average of five antibiotics given for 6 days each. Patients developed candidemia an average of 21 days after onset of antibiotic therapy. Two patients had received corticosteroids and two were diabetic (Table 2). All patients developed clinical signs of edema corresponding to the involved vein, although in some cases edema did not develop until a week after the first positive culture. Five patients had Doppler examination of the vessel, in all cases confirming thrombosis. Only one of three patients who had an indium-labeled white blood cells scan had a positive study. Five patients were seen by an ophthalmologist during the period of candidemia; three were confirmed to have had Candida retinitis. Six patients had an echocardiogram performed, which showed no evidence of valvular infection. A seventh patient had no endocarditis at autopsy (Table 3).

TABLE 2. *Associated and Possible Predisposing Clinical Conditions in the 8 Patients*

Conditions*	Number of Patients
Major burn or postsurgery	7 (83%)
Pneumonia/ARDS	1
Central venous catheter	8 (100%)
For TPN or hemodynamic monitoring	
For mean 14 (6–21) days	
ICU	8 (100%)
TPN	8 (100%)
Previous bacterial sepsis	8 (100%)
Multiple antibiotics	8 (100%)
Ventilator-dependent	7 (83%)
Corticosteroid therapy	2
Diabetes or glucose intolerance	2

* ICU = intensive care unit; TPN = total parenteral nutrition.

TABLE 3. *Diagnostic Findings*

Finding	Number of Patients
Localized edema	
Extremity/extremities, ipsilateral face/neck	8/8
Doppler evidence venous occlusion	5/5
Infected clot adherent to catheter tip	4/4
Indium-labeled PMN scan showed increased local uptake	1/3
Echocardiography negative for vegetations in heart	6/6
Retinal lesions	3/5

Anticoagulation was used in treatment of three surviving patients and one fatal case. Three patients cleared their candidemia and recanalized the thrombosis without use of anticoagulation. No patient had clinical or radiologic evidence of a pulmonary embolus.

Amphotericin B (Fungizone®) was given to all of the patients, to the six survivors in doses ranging from 22 to 28 mg/kg total (mean: 26 mg/kg). Duration of therapy ranged from 42 to 75 days (mean: 52 days) with a mean daily dose of 0.7 mg/kg. No patients developed renal failure induced by amphotericin. Four patients showed improvement in their serum creatinine during the course of treatment. No surviving patients had an abnormal serum creatinine on discharge from the hospital. Both patients who died received less than 350 mg of amphotericin total and both developed renal failure. Table 4 shows the effect of amphotericin on renal function in the eight patients. The time required to achieve negative blood cultures following initiation of amphotericin B therapy ranged from 4 to 21 days in the survivors. Negative blood cultures were never achieved in the two fatal cases.

5-fluorocytosine (5FC) was also used in treatment of five survivors and one fatal case. One survivor and the treated fatal case required discontinuation of 5FC because

of deteriorating liver function tests. A second survivor's Candida strain became resistant to 5FC, necessitating discontinuation of the drug (Table 5).

In no case did we discontinue antibacterial therapy specifically to treat candidemia. Two survivors had antibacterial therapy discontinued during the course of the Candida septicemia because coincidental bacterial infection had cleared. One of these patients had prompt cessation of candidemia, and a second patient had candidemia for 2 days after antibiotic discontinuation. The remaining four survivors resolved their candidemia despite continuation of a broad spectrum antibiotic therapy.

TABLE 4. *Effect of Amphotericin on Renal Function*

Case Number	Amphotericin B: Daily Maintenance	Amphotericin B: Duration of Therapy (Days)	Amphotericin B: Total Dose mg (mg/kg)	Serum Creatinine (mg/dl): Onset	Serum Creatinine (mg/dl): Completion
Survivors					
1	75 mg	40	1600 (28)	0.9	0.9
2	40 mg	75	2476 (26)	0.7	0.7
3	35 mg	50	1383 (27)	2.5	1.1
4	55 mg	42	1936 (24)	1.6	1.1
5	40 mg	44	1626 (22)	1.2	.9
6	100 mg	61	3425 (28)	2.9	1.5
Nonsurvivors					
7	40 mg	10	300 (6)	0.6	1.2
8	35 mg	8	336 (4)	1.2	5.0

Discussion

In-dwelling venous catheters are subject to thrombosis and infection depending on catheter material, insertion technique, duration of catheterization, and host factors. The vast majority of central catheter thromboses are occult and may not present clinically. Infectious organisms may be introduced percutaneously along the catheter, hematogenously from another site, or with contaminated intravenous solution.

The role of antibiotics in allowing fungal gut overgrowth with subsequent persorption through intact epithelium may explain candidemia and fungal superinfection in some injured, septic patients.[7-9] It has been well documented that candidemia is associated with TPN, antibiotic use, prolonged venous catheterization and many conditions resulting in immunosuppression.[7,10-13,15-18] Antibiotic therapy seems to be the most important risk factor in development of serious Candida infections. TPN or steroid administration becomes significant only when given in combination with antibiotics.[14] On the theory that continued seeding from the gut prevents elimination of Candida without cessation of antibiotics, Stone[9] urges withdrawal of antibacterial agents when treating serious fungal infection. We agree that antibiotics should be discontinued at the earliest opportunity, but not if there is a significant bacterial infection requiring treatment. Our successful treatment of septic thrombi in four patients during continued antibiotic administration supports this viewpoint.

Diagnosis of Candida septic thrombosis may be difficult. Serologic tests may be misleading in up to 50% of documented cases of disseminated disease.[15] Candida endophthalmitis, although significant when found, was present in only three of five of our patients examined, despite high-grade candidemia. Our experience suggests that indium-labeled white cell scans are unreliable for diagnosis of septic great vein thrombosis. The presence of Candida in the urine is nondiagnostic, being neither sensitive nor specific. It may simply reflect Candida cystitis, or it may represent candidemia from a significant infection. Furthermore, actual autopsy proven cases of renal candidiases produced positive cultures in only 81% of cases.[16] Blood cultures may be negative in significant proportion of candidemias, although the likelihood of positive cultures may be increased by taking arterial blood for culture.[9,17] Because of these diagnostic problems, there must be a very high level of awareness whenever a patient has the risk factors for Candida septic thrombophlebitis. We found the most important risk factors to be surgery or trauma, prior bacterial sepsis requiring multiple broad spectrum antibiotics, and total parenteral nutrition given *via* a central venous catheter.

The surgical concept of venous excision is based on the principle that an endovascular infection behaves as an abscess, in which bactericidal or fungicidal levels of therapeutic agents are unable to reach the focus of infection. Excision is clearly indicated for peripheral veins and for central Candidal infections involving heart

TABLE 5. *Management and Outcome*

Treatment	Survivors (N = 6)	Nonsurvivors (N = 2)
Amphotericin B		
Daily dose	0.7 mg/kg (0.4–1.3)	0.7 mg/kg (0.5, 0.9)
Number days therapy	52 (42–75)	10 (9, 11)
Total dose	26 mg/kg (22–28)	5 mg/kg (4, 6)
5 Fluorocytosine	5/6	1/2
Onset of therapy until blood cultures negative	12 days (4–21)	Never (8, 10)*
Anticoagulation	3/6	1/2
Surgical attack on septic thrombosis	0/6	0/2

* Candidemia persisted 8 and 10 days, until death.

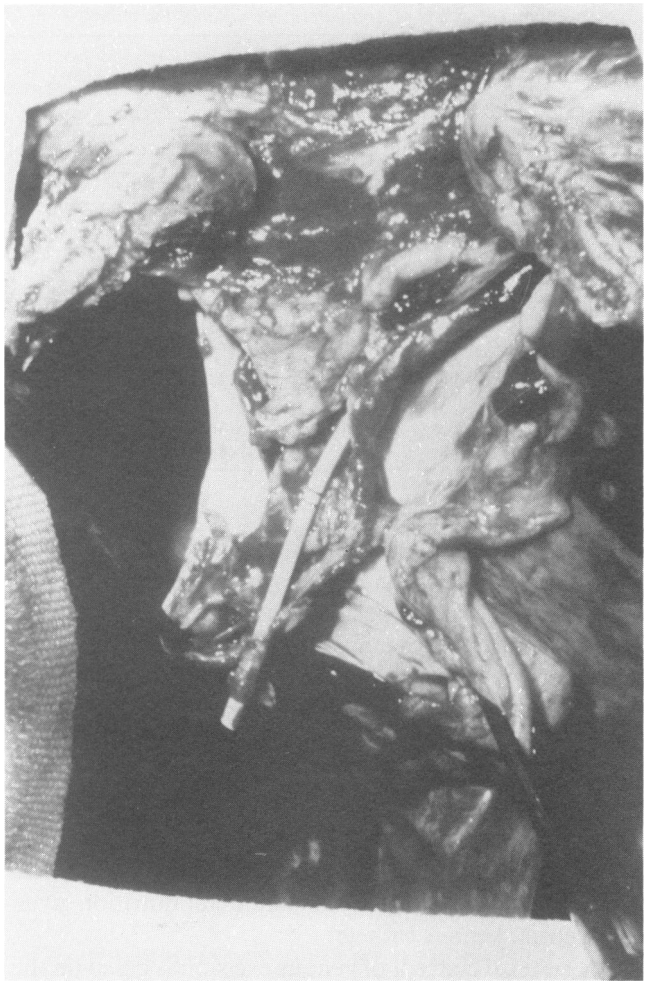

FIG. 1. Autopsy picture of an opened superior vena cava with catheter in place, showing surrounding adherent thrombus, which proved to be infected with *Candida albicans.*

valves.[1-3,18-20] There are, however, no reported cases of successful resection of the great veins. Our data indicate that abscess physiology probably does not exist in Candida great vein infections. Through the process of recanalization and spontaneous fibrinolytic mechanisms, effective levels of antifungal agents can be delivered to sterilize a clot. Figures 1 and 2 demonstrated the gross and histologic features of thrombus infected with *Candida albicans* as found at autopsy.

Amphotericin B remains the cornerstone of antifungal therapy. Because of fear of its formidable nephrotoxicity, many clinicians are reluctant to use amphotericin, even when indicated. We had no cases of renal failure; in fact, four patients showed improvement in their renal function during treatment. Our data support the contention by Solomkin et al.[21] that uncontrolled sepsis rather than amphotericin poses the greatest risk to the kidneys. In one case, we found it necessary to switch to alternate day dosing when the patient's serum creatinine rose, but the creatinine returned to normal when Candida sepsis resolved.

The daily and total dose of amphotericin to use for deep Candida infections has been a source of considerable controversy for over 20 years. The recent studies of Solomkin et al.,[13,21] Marsh et al.,[14] and Tores-Rajas et al.,[3] published over the past 4 years, however, indicate that for most patients with Candida sepsis deriving from peritonitis, pyelonephritis, transient line-related candidemia, or even catheter-related septic thrombophlebitis of a peripheral vein, a daily dose of 0.3–0.5 mg/kg and total dose of 3–6 mg/kg will be curative and rarely result in relapse.

The syndrome we report is a form of deep Candida infection that we believe mandates considerably higher doses of amphotericin B, in the range given for treatment of infections caused by filamentous fungi such as *Aspergillus.* Based on our experience with the eight reported cases, we recommend a daily dose of 0.7 mg/kg because this proved effective in all six surviving patients (Table 5) and because this dose will give maximal therapeutic levels; higher doses do not measurably increment the blood level. All of our successfully treated patients except two yet had candidemia by the time they had received 6 mg/kg, and it was necessary to give up to 15 mg/kg simply to control candidemia. Each of our surviving patients received a total dose of at least 22 mg/kg (Table 5). It must be emphasized that it took an average of 12 days of therapy before candidemia was controlled. The two patients dying had already received an average of 5 mg/kg of amphotericin B at the time of death, and both yet had candidemia.

5-Fluorocytosine is a valuable adjunct to amphotericin but is of limited usefulness in treatment of Candida infections when used alone because of rapid emergence of resistant strains.[22] Unless the isolate is highly resistant to 5-fluorocytosine, we recommend its addition to amphotericin therapy. Inclusion of 5-fluorocytosine in the initial regimen assures therapeutic levels of a candicidal drug during the early phase of therapy when the daily dose of amphotericin B is yet low and being gradually incremented.

There remain several unanswered questions concerning treatment of this formidable disease process. Ketoconazole and miconazole are new agents in the antifungal armamentarium that reportedly have been effective against Candida.[23-25] However, a number of reports of primary drug resistance,[26,27] one report in which Candida became resistant to amphotericin B when cultured in the presence of ketoconazole,[28] and disappointing results[29] when used in Candida sepsis caution against the use of these agents for life-threatening Candida infections.

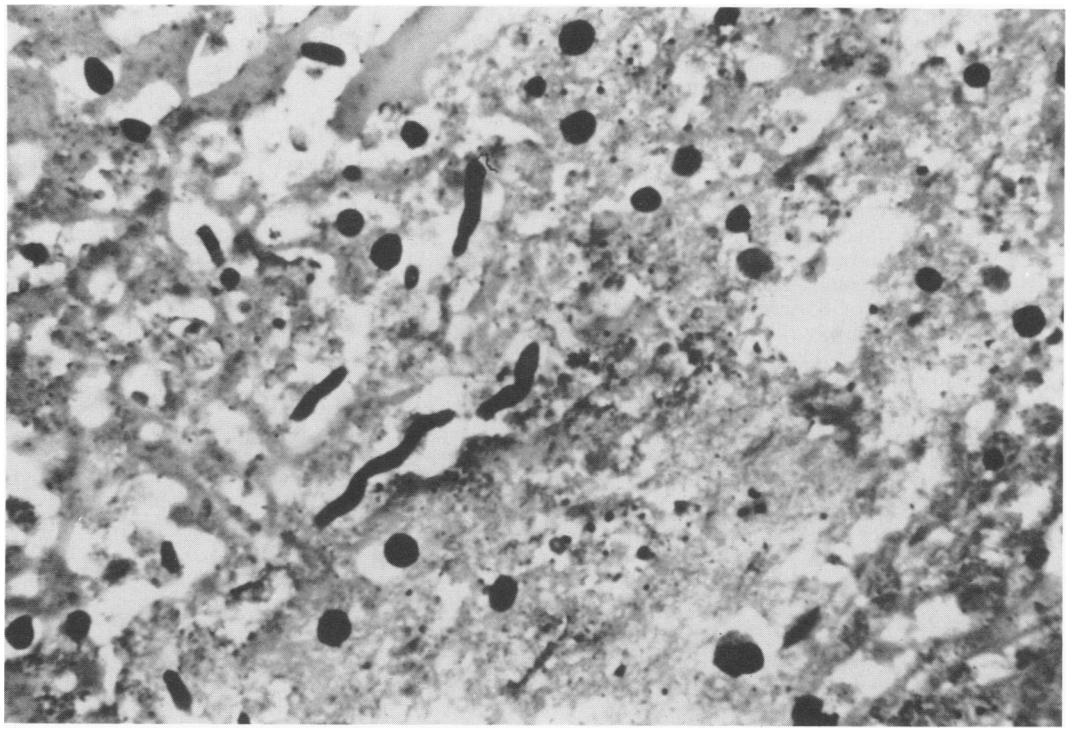

FIG. 2. Microscopy of infected thrombus, demonstrating *Candida albicans*. (H & E staining, high power, magnification ×400.)

Although intuitively desirable, our experience indicates that anticoagulation was not mandatory for successful treatment. Whether anticoagulation would prevent further thrombosis in the setting of endovascular infection awaits further study. Unless there are contraindications, we would recommend anticoagulation as part of the treatment of this syndrome.

Summary

Eight patients were diagnosed with Candida septic thromboses of the great central veins. Risk factors for development of the syndrome are total parenteral nutrition *via* a central catheter, prior surgery or trauma, and treatment for prior bacterial sepsis with multiple antibiotic therapy. Diagnosis can be difficult, although extremity or facial edema corresponding to the involved vein ultimately develops. The hallmark of the disease is high-grade, persistent candidemia. A very high level of suspicion must exist for susceptible patients who develop high-grade candidemia persisting after removal of a central venous catheter.

Removal of the affected catheter followed by intensive amphotericin therapy (mean daily dose: 0.7 mg/kg), combined with 5 FC in five patients, resulted in cure and long-term survival in six patients. No surviving patients developed renal failure, while four showed improved renal function with treatment. Cessation of antibacterial therapy was not required. In contrast to Candida endocarditis, septic central vein thrombosis caused by Candida appears to be curable medically in the majority of patients.

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