Management of Candidal Thrombophlebitis of the Central Veins: Case Report and Review

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Candidemia and major organ candidiasis are problems that emerged in the past 2 decades and that are partially due to medical progress. Catheter-related thrombosis of the central veins is known to be a frequent but mostly subclinical complication of central venous lines. Although candidemia and catheter-related thrombosis are frequent, candida thrombophlebitis of the central veins is rarely reported. We recently successfully treated a 19-year-old polytrauma patient with candidal thrombophlebitis of the innominate vein. Despite catheter removal and therapy with amphotericin B, recurrent candidemia and signs of infection persisted, and a complete resection of the involved vein had to be performed. Only 16 well-documented cases of candidal thrombophlebitis of the central veins in adults have been reported over the past 20 years. An analysis of these 16 patients, together with our patient, is made in relation to risk factors, clinical features, diagnosis, therapy, and mortality.

The incidence of nosocomial candidal infections has increased in the past 2 decades, and these infections now represent ~6.5%–12.5% of bloodstream infections [1–3]. Risk factors for the development of major candidal infections are well known and have been reviewed previously [3–5]. Central venous catheters (CVCs) represent an important predisposing factor for the development of candidemia, especially in combination with total parenteral nutrition (TPN) and multiple antibiotics.

Catheter-related thrombosis is one of the possible complications of CVCs and is a frequent finding in angiographic and autopsy studies [6–8], but it is rarely clinically apparent. Only 0.8%–1.7% of cases are clinically significant [9, 10].

Although catheter-related candidemia and catheter-related thrombosis are relatively frequent findings, candidal thrombophlebitis of the central veins is a rare disorder. Before 1978 it was almost always an autopsy finding [11–13]. Jarett et al. [14] published a report on the first successfully treated patient in 1978; since then, only 15 additional adult cases have been reported in the literature. We describe a patient who developed candidal thrombophlebitis of the innominate vein after admission to the intensive care unit (ICU).

Case Report

A 19-year-old male patient was admitted to our hospital following a motorbike accident. Because of hemodynamic instability and evidence of free intraperitoneal fluid on an abdominal ultrasonogram, an emergency laparotomy was performed, which disclosed hepatic and splenic rupture. Liver packing and splenectomy were performed. Administration of cefazolin (2 g b.i.d) was started as prophylactic antibiotic treatment. Further postoperative investigations disclosed a cerebral contusion in the left temporal hemisphere, a contusion of the right lung, and multiple bone fractures.

On day 3 the liver packing was removed, and a partial hepatectomy was performed. On day 4, administration of cefuroxime (1.5 g t.i.d) was started because ventilator-associated pneumonia was suspected. Blood cultures performed on day 6 yielded *Candida albicans*. All CVCs were removed and placed at other sites and therapy with amphotericin B (AmB) at a dosage of 80 mg/d was started. Findings of transesophageal echocardiography (TEE) and fundoscopy were negative. A culture of the pulmonary artery catheter introducer sheet, removed on day 6, and a sputum culture also yielded *C. albicans*.

Fever persisted and the patient became septic. On day 11 all CVCs were removed again because blood cultures were positive for *Staphylococcus epidermidis*. Administration of teicoplanin (400 mg/d, after a loading dose of 1,600 mg over 12 hours) was started because of increasing hemodynamic instability. On day 13 the catheter tips removed on day 11 again yielded *C. albicans*, but now in combination with methicillin-resistant *Staphylococcus aureus*. All CVCs were removed again. Because of persistent spiking fever, increasing parameters of inflammation (WBC count of 40,000 and C-reactive protein level of 32 mg/dL), and evidence of omniresistant *Acinetobacter calcoaceticus* pneumonia and sinusitis, administration of colistine (1.5 million units t.i.d.) was started on day 18.

On day 20 all blood cultures again yielded *C. albicans*. All CVCs were removed; however, attempts to catheterize the left subclavian and left jugular veins failed. It was impossible to advance the guidewire for >15 cm. A slight degree of bilateral upper-extremity edema was evident. Candidal thrombophlebitis was suspected. An echo doppler examination of the left subcla-
vian vein disclosed a possible obstruction proximally to the subclavian vein. Findings of a TEE and fundoscopy were again negative. Preoperative phlebography performed on day 20 disclosed a complete obstruction of the innominate vein, with various collaterals between the left subclavian vein and the superior vena cava (figure 1).

A complete venectomy of the involved vein was performed. Fever and parameters of inflammation decreased promptly following the operation. Cytological examination and cultures of the thrombus yielded *C. albicans*. Invasion of the thrombus by *Candida* could not be confirmed by histologic examination, however, even after silver staining. Treatment with AmB was continued until a total dose of 3.5 g had been given. The patient was discharged 6 weeks after admission. No recurrence of candidal infection occurred during the 6-month follow-up.

### Analysis of the Literature

After an extensive search in MEDLINE, we found 16 well-documented cases of candidal thrombophlebitis in adult patients that had been described in the literature over the past 20 years [14–22]. We analyzed these patients, together with our patient, in relation to risk factors, clinical features, diagnosis, therapy, and mortality (see table 1). There were seven men and 10 women. The mean age was 49 years (range, 19–74 years).

**Risk factors.** Risk factors included CVCs (17/17; 100%), multiple antibiotics (17/17; 100%), TPN (16/17; 94%), admission to the ICU (15/17; 88%), abdominal surgery (9/17; 52%), extensive burns (3/17; 17%), and corticosteroids (3/17; 17%).

**Location of the thrombosis.** In 11 patients (65%) the innominate vein or the superior vena cava was affected, and in five patients (30%) the right atrium was affected.

**Clinical features.** At the time of diagnosis, 17 patients (100%) had persistent fever during or after use of antibiotics and 12 (70%) had edema of the affected limb; these were in combination with candidemia (15/17; 88%) or candidemia that was recurrent (8/15; 53%) despite catheter removal and AmB therapy. Five patients (29%) had spiking fever, two (11%) had fever of unknown origin, and 10 patients had fever that was not described. Two patients had clinically presumed pulmonary emboli, and in one patient the condition was proven. In two patients thrombophlebitis of the central vein was discovered after attempts to catheterize the affected vein had failed. One patient had blurred vision due to proven candidal endophthalmitis.

**Candida species.** Fourteen cases of central vein thrombophlebitis were due to *C. albicans* and three to *Candida glabrata*.

**Diagnosis.** For 16 patients, diagnosis was made while they were alive; five of the 16 had a histologically proven diagnosis. For seven of the 16 patients, *Candida* grew on the catheter tip or on the clot adherent to the catheter tip. Four patients’ diagnoses were highly suspected because of a “high” grade of candi-
Table 1. Data from the 17 reported cases of candidal thrombophlebitis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient no./age (y)/sex</th>
<th>Diagnosis and/or related procedure/condition</th>
<th>Risk factors</th>
<th>Implicated Candida species</th>
<th>Location</th>
<th>Presentation</th>
<th>Therapy (total dose)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[14]</td>
<td>1/27/F</td>
<td>75% Burns</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>IVC</td>
<td>Fever, edema, sepsis</td>
<td>AmB (1.6 g)</td>
<td>Survived</td>
</tr>
<tr>
<td>[15]</td>
<td>2/27/M</td>
<td>70% Burns</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>IVC</td>
<td>Fever, edema</td>
<td>AmB* (1.6 g)</td>
<td>Survived</td>
</tr>
<tr>
<td>[16]</td>
<td>3/74/M</td>
<td>Sacral ulcer, hip replacement</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>SVC</td>
<td>Fever, edema</td>
<td>AmB* (2.5 g)</td>
<td>Survived</td>
</tr>
<tr>
<td>[17]</td>
<td>4/38/F</td>
<td>Rupture of splenic artery</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>albicans</td>
<td>LSubV</td>
<td>Fever, edema</td>
<td>AmB* (1.4 g)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>5/46/M</td>
<td>40% Burns</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>SVC</td>
<td>Fever, edema</td>
<td>AmB* (1.9 g)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>6/59/F</td>
<td>Aortic aneurysm</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>RSSubV</td>
<td>Fever, edema</td>
<td>AmB* (1.6 g)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>7/46/F</td>
<td>Obesity, pneumonia</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>LJugV</td>
<td>Fever, edema</td>
<td>AmB* (3.4 g)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>8/56/F</td>
<td>Crohn's disease, peritonitis</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>albicans</td>
<td>SVC, L + RSSubV</td>
<td>Fever, edema</td>
<td>AmB* (0.3 g)</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>9/62/M</td>
<td>Electrical injury</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>SVC, LSubV</td>
<td>Fever, edema</td>
<td>AmB* (0.3 g)</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>[16]</td>
<td>Gastrectomy, splenectomy</td>
<td>CVC, TPN, ICU, AB, surgery</td>
<td>albicans</td>
<td>SVC/LIV, LJugV</td>
<td>Fever, edema, sepsis</td>
<td>AmB (1.5 g), surgery</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>11/56/F</td>
<td>Scleroderma, gastrointestinal bleeding</td>
<td>Hickman catheter, TPN, AB</td>
<td>glabrata</td>
<td>SVC/LIV, RA</td>
<td>Fever, edema, shoulder pain</td>
<td>None (died)</td>
<td>Autopsied</td>
</tr>
<tr>
<td></td>
<td>12/59/M</td>
<td>COPD/peritonitis, diverticulitis</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>glabrata</td>
<td>L + RSSubV, SVC/RA</td>
<td>Fever, sepsis</td>
<td>AmB (1.6 g)</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>13/35/M</td>
<td>Femoral fracture, osteomyelitis</td>
<td>Hickman catheter, TPN, AB</td>
<td>albicans</td>
<td>LIV</td>
<td>Fever, chest pain, dyspnea</td>
<td>AmB (1.0 g), urokinase, surgery, heparin</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>14/50/F</td>
<td>Laparoscopic cholecystectomy</td>
<td>CVC, TPN, AB, abdominal surgery</td>
<td>albicans</td>
<td>RA</td>
<td>Fever, dyspnea</td>
<td>Surgery, heparin</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>15/63/F</td>
<td>Rectum dissection, fistulization</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>albicans</td>
<td>SVC, RA</td>
<td>Fever, sepsis, sight loss</td>
<td>AmB (2.5 g), surgery</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>16/58/F</td>
<td>Gastrectomy, pancreatitis</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>glabrata</td>
<td>SVC, RA</td>
<td>Fever, sepsis</td>
<td>AmB (3.5 g), surgery</td>
<td>Survived</td>
</tr>
<tr>
<td>[PR]</td>
<td>17/19/M</td>
<td>Polytrauma</td>
<td>CVC, TPN, ICU, AB, abdominal surgery</td>
<td>albicans</td>
<td>LIV</td>
<td>Fever, sepsis, edema</td>
<td>AmB (3.5 g), surgery</td>
<td>Survived</td>
</tr>
</tbody>
</table>

NOTE. AB = antibiotics; AmB = amphotericin B; COPD = chronic obstructive pulmonary disease; CVC = central venous lines; ICU = intensive care unit; IVC = inferior vena cava; LIV = left innominate vein; LJugV = left internal jugular vein; LSubV = left subclavian vein; PR = present report; RA = right atrium; RSSubV = right subclavian vein; SVC = superior vena cava; TPN = total parenteral nutrition.

* Six of these eight patients were treated with a combination of AmB and 5-fluorocytosine.

demia, the presence of a central vein thrombosis, and response to therapy. An echo doppler examination was performed on six patients and was positive for all. TEE was done on 12 patients, and results were positive for three. In two of three patients, superior caval vein thrombosis was found in combination with right atrial thrombosis. For three of 16 patients the diagnosis was confirmed by phlebography. Fundoscopy disclosed retinal lesions in four of seven patients.

**Therapy.** One patient died before diagnosis. Four of the remaining 16 patients were treated with AmB as monotherapy;
6 with a combination of AmB and 5-fluorocytosine (5-FC); 1 with surgery alone; 1 with a combination of AmB, urokinase, and surgery; and 4 with a combination of surgery and AmB. The average total dose of AmB used was 1.7 g (range, 0.3–3.5 g).

Mortality. Mortality among treated patients was 18% (3/16). The mortality in the group receiving medical therapy alone was 20% (2/10) and in the group treated with a combination of medical therapy and surgery it was zero (0/5). One patient could not be treated with AmB after surgery because of early postoperative death. Therefore, mortality in the surgery group was 16% (1/6).

Discussion

Candidal thrombophlebitis of the central veins is a rare but probably underdiagnosed disorder. In an extensive MEDLINE search we could find only 16 reports of well-documented cases involving adult patients that had been published over the past 20 years. The increasing incidence of candidiasis and nosocomial candidal infections over the past 2 decades [1–3] and the high incidence of catheter-related thrombosis [6–8] suggest a higher frequency of central candidal thrombophlebitis than reported in the literature. This can also explain the low mortality of 18% observed in this review. Since candidal thrombophlebitis of the central veins can be considered a major complication of candidal infections, we would have expected that the mortality noted in this review would be at least 27%–33% [3, 4], which is the generally accepted mortality for nosocomial Candida infections. Thus, physicians should have a higher index of suspicion for this serious Candida-related complication.

Risk factors for development of candidal thrombophlebitis are largely the same as reported for nosocomial candidal infections [3–5]. At the time of diagnosis all patients had a CVC, all received multiple antibiotics or had prior treatment with multiple antibiotics, the majority of patients received TPN, and the majority were also admitted to the ICU. More than half of the patients had previous abdominal surgery. Other risk factors were extensive burns and use of corticosteroids.

Persistent fever during or after use of broad-spectrum antibiotics, candidemia that was recurrent despite AmB use (50% of the patients), and edema of the affected limb (70% of the patients) were prominent clinical features. Clinically significant pulmonary embolisms were not common, despite systematic removal of the CVCs. The combination of these features seems to be highly suggestive of candidal thrombophlebitis of a central vein and should enable the physician to make an early diagnosis.

More than half of the cases of central vein thrombosis were detected by ultrasonography. Since TEE can easily be performed at the bedside, even in the ICU setting [23], it should be the first diagnostic method used. Repetitive TEE should be performed for every recurrence of candidemia, not only to disclose possible endocarditis but also to search for a catheter-related right-atrial thrombus. In the absence of valvular vegetations or a thrombus, special attention should be drawn to the superior vena cava and if possible to the innominate vein. When TEE results are negative, an echo doppler examination of all previously catheterized central veins should be performed. However, since such procedures are not highly accurate in detecting central venous thrombosis and because of the risks of therapy, phlebography should always be considered before treatment [24].

Although radical excision of the affected vein(s), in combination with administration of AmB, is the rule in the treatment of peripheral candidal thrombophlebitis [25, 26], systematic excision of central vein thrombophlebitis is much more controversial [14, 15, 27]. This controversy is due to the fact that medical therapy alone can be effective in some patients [14, 15, 18, 27] and that surgery is not always possible because of the relative inaccessibility of the central veins. In this review we found no therapeutic advantage in the use of surgery; however, all patients who underwent surgery had histologically proven candidal thrombophlebitis [16, 19–22]. This is in contrast to the patients who received only medical therapy, whose diagnosis was mainly by clinical presumption [14, 15, 18].

Hofmann et al. [16] advocated that the latter group probably had only superficial infection of the thrombus and therefore did not need surgery. Although our patient also did not have a histologically proven diagnosis, he clearly needed more than medical therapy alone. Therefore, therapy should be guided by the clinical evolution of the patient, the surgical accessibility of the involved vein, and the perioperative related risk. Although there are not sufficient reliable data to support systematic resection of central vein thrombophlebitis due to Candida species, surgery should probably be performed, when possible, early in the clinical course. This seems to be particularly true when the right atrium is involved [21].

An alternative therapy to surgery is local thrombolysis. It has been successfully used in combination with administration of AmB and 5-FC in pediatric patients [28, 29], but must be used for an appropriate period of time, sometimes exceeding 10 days. This approach was used only for a short time and unsuccessfully in an adult patient described by Kelly et al. [19]. Heparin can be used in cases of bacterial thrombophlebitis [27] but seemed to have no additional beneficial effect in a small retrospective study of eight patients with candidal thrombophlebitis [15].

The average total dose of AmB noted in this review was 1.7 g. A recent study showed that a low dose of AmB (<500 mg) was as effective as a high dose (>500 mg) in nosocomial candidal infections [30]. These low doses of AmB are probably not appropriate in cases of central candidal thrombophlebitis because of the recurrent and protracted character of the candidemia. Of course, when surgery has been performed early, a lower dose of AmB can probably be used. Since administration of 5-FC in combination with AmB is advised for major candidal infections [3], it should be used for thrombophlebitis, especially when surgery cannot be performed [15].
Several reports showed the effectiveness of fluconazole against nosocomial candidal infections [30, 31], but it was used only for a short period in one patient with candidal thrombophlebitis [22].

**Conclusion**

Candidal thrombophlebitis of the central vein(s) is a rare but probably underdiagnosed disorder. Risk factors and clinical features are known and should help the physician to make an early diagnosis. In cases of recurrent candidemia, repetitive TEE should be performed not only to disclose possible endocarditis but also to exclude the presence of a thrombus in the right atrium or in the superior vena cava. In cases of negative TEE, an echo doppler examination of all previously catheterized central veins should be performed to search for a thrombosis that is not clinically apparent.

Treatment should be guided by the clinical evolution of the patient, the accessibility of the central veins, and the perioperative related risk. Administration of AmB, in combination with surgical resection of the affected vein(s), seems to be the treatment of choice. If the perioperative risk seems too high to perform a surgical procedure or if the involved vein is not surgically accessible, local thrombolytic therapy can be an alternative. Otherwise, AmB should be given in combination with 5-FC.

**References**