REVIEW ARTICLE

Candida Arteritis in Patients Who Have Not Received Organ Transplants: Case Report and Review of the Literature

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Fungal arteritis is a rare entity, associated with significant morbidity and mortality, that typically involves graft arteries in solid organ transplant recipients. Here, we report the first case of *Candida* carotid arteritis and review 22 other cases of *Candida* arteritis reported since 1966 in patients who have not received transplants. Most patients had serious underlying conditions. All cases were anatomically characterized by pseudoaneurysm formation. Patients presented with fever ($n = 17$), local pain ($n = 13$), and an expanding pulsatile mass ($n = 4$), with subsequent rupture and hemorrhage ($n = 7$). Evidence of *Candida* colonization or infection was present in 15 patients before arteritis occurred. Treatment typically included a combined surgical and antifungal approach. The outcome was favorable in 11 patients, but follow-up was limited. A high index of suspicion, early diagnosis, and prompt antifungal and surgical treatment seem crucial to efforts to avoid life-threatening arterial rupture and hemorrhage.

The term "mycotic endarteritis" was coined by Osler [1] in 1885 to indicate infection of blood vessel walls due to septic embolization in patients with infectious endocarditis. This term is a misnomer, because the vast majority of arterial aneurysm infections are bacterial in origin [2–4], typically occurring in the context of arterial trauma due to injection drug use [5] or cardiogenic bacterial emboli.

Arterial infection associated with *Candida* species is an emerging problem in solid organ transplant (SOT) recipients, in whom it generally occurs as anastomotic site infection of graft vessels [5–8]. In several cases, the infection has been transmitted from the donor, most often via contaminated kidney graft infusate (reviewed in [8]). Graft loss and/or severe hemorrhage are common complications [6, 7, 9–13]. In addition to SOT recipients, 22 cases of *Candida* arteritis in patients who have not received SOTs have been published [2, 3, 7, 13–22]. Here, we report the first case, to our knowledge, of carotid arteritis due to *Candida albicans* and review the 22 published non-SOT cases, to describe the clinical and microbiological features of this entity.

METHODS

We searched the PubMed database (1966–2006; all languages) using the terms "candida," "pseudoaneurysm," "aneurysm," and "arteritis." Cases were considered to be definite if yeast elements were present microscopically, if *Candida* was grown in culture of a surgical artery-wall specimen or vascular graft [2, 3, 6, 8–10, 14–18, 20, 23–31], or if *Candida* organisms were present in culture of an aneurysm vegetation [32]. Probable cases were defined as those in patients with candidemia who had radiographic evidence of a new vascular (pseudo)aneurysm, in the absence of other

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compatible pathogens in blood or artery-wall culture [4, 6, 33, 34].

Six possible cases were excluded from our review: 4 were in patients who had polymicrobial infection; thus, it was unclear which symptoms and signs were attributable to *Candida* and which were due to the other organism [19, 35–37]. Two cases were excluded because *Candida* organisms were cultured from the urine or other sites but not from the blood or artery wall [38, 39].

CASE REPORT

A 75-year-old man presented in December 2002 with hoarseness and an enlarging, painful, pulsatile mass in the right side of his neck. He had end-stage diabetic and hypertensive nephropathy and had been hemodialysis dependent for the previous 5 years, with an arteriovenous prosthesis of the forearm in place. The patient had severe peripheral arterial disease, with multiple previous arterial leg bypass operations and with endoscopic insertion, in August 2002, of an intra-arterial prosthesis because of an internal iliac aneurysm. Ultrasound examination of the neck mass showed a pseudoaneurysm of the right common carotid. Surgical resection and insertion of a prosthetic graft was done. Two days later, pneumonia and empyema due to *Enterobacter cloacae* developed, which was treated with chest tube drainage and imipenem administered intravenously.

Histologic analysis of the endarterectomy material showed an ulcerated, calcified atheromatous plaque involving the arterial intima and media. The plaque was surrounded by fibromuscular tissue displaying chronic inflammation, including lymphocytes, macrophages, and giant cells. Pseudohyphae were seen, and *C. albicans* grew after 5 days in culture of the resected arterial specimens. Culture results were negative for bacteria. Serum candidal antimannan antibodies were positive (41.2 ng/mL; normal, <5 ng/mL). Five sets of blood cultures did not reveal any growth. Fluconazole treatment (200 mg once daily by mouth) was initiated with a plan for long-term treatment because of the prosthetic graft. Two months after the operation, the patient had a cardiopulmonary arrest in the setting of severe hyperkalemia, with no fever or other symptoms suggesting persistent fungal infection. The patient died. Permission to perform an autopsy was not granted.

RESULTS

Since the first description of a case of femoral artery-wall infection due to *Candida* species, by Anderson in 1974 [20], 39 cases of *Candida* arteritis have been described in the literature. Of these cases, 17 occurring in SOT recipients have recently been reviewed [8]. In addition to the case described in the above section, 19 definite and 3 probable cases [4, 33, 34] occurring outside of the SOT setting are the subject of this review (table 1). The mean age of patients was 46 years (range, 1 month–80 years), and 17 patients were male. Clinical presentations included fever ($n = 17$), local pain ($n = 15$), an expanding pulsatile mass ($n = 5$), and major hemorrhage ($n = 7$). *Candida* arteritis occurred in 3 patients admitted to the intensive care unit, of whom 2 received mechanical ventilation.

The arteries involved were the thoracic aorta or its branches ($n = 5$), intracranial arteries ($n = 3$), the abdominal aorta ($n = 8$), the iliac artery ($n = 2$), the femoral artery ($n = 3$), and 1 case each in the pulmonary, brachial, popliteal, and tibioperoneal arteries. In 2 cases, 2 different arteries were involved (the abdominal aorta and brachial artery in one case and the popliteal and tibioperoneal arteries in the other). Native arteries were infected in 19 cases, whereas a prosthetic arterial graft was infected in 2 cases [15, 29], a vein graft was infected in 1 case [14], and an aortic homograft was infected in 1 case [34].

Potentially contributory conditions included advanced cancer ($n = 5$), diabetes mellitus ($n = 4$), major surgery ($n = 4$), injection drug use ($n = 3$), end-stage renal disease/hemodialysis ($n = 2$), advanced HIV infection ($n = 2$), and long-term corticosteroid treatment ($n = 2$). An underlying vascular disease was documented in only 4 patients, including the patient described in the present article [5, 17, 25].

Candidemia was recorded in 11 of 22 cases for which blood cultures were performed. Seven patients had endocarditis documented (4 native valve and 3 prosthetic valve). Seven patients had candiduria; in each case, it is unclear whether this represented the source or a consequence of candidemia. One patient had concomitant *Candida* arthritis. An infected intravenous catheter was diagnosed in 2 cases.

Fifteen of 23 patients had a documented *Candida* infection or colonization before the diagnosis of *Candida* arteritis: 9 patients had candidemia, 4 patients had mucocutaneous or respiratory *Candida* infection or colonization, 1 patient had candiduria, and 1 patient had a proven *Candida* spondylodiskitis 4 months before the diagnosis of fungal aortitis.

Candida arteritis was diagnosed by direct, microscopic examination ($n = 11$) or via growth in culture from surgical artery-wall specimens ($n = 21$). The cultured *Candida* species included *C. albicans* ($n = 14$), *C. tropicalis* ($n = 1$), *C. parapsilosis* ($n = 1$), and *Candida* not further specified ($n = 5$). Pathologic examination of resected surgical tissue showed an inflammatory infiltrate in the 11 patients with histologic results reported, and direct tissue examination revealed yeast elements in all of these cases.

Treatment included antifungal therapy alone ($n = 1$) or combined with surgery ($n = 18$). Multiple antifungal regimens were used (table 1), including amphotericin B ($n = 7$), am-

Table 1. Clinical features of 23 reported cases of *Candida* arteritis in patients who have not undergone solid organ transplantation.

Case type, reference	Age,[a] sex	Underlying conditions	Clinical features	Artery involved	Native artery/prosthetic graft
Definite cases					
Thomas et al. [14]	29, M	Advanced HIV infection, IDU	Pulsatile popliteal mass, local pain	Femoropopliteal vein graft	Vein graft
Cooley and Burnett [15]	46, M	Dacron graft for aortic dissection; extensive bowel resection	Fever, chills and malaise, back pain	Aortic dacron graft	PG
Mahesh et al. [29]	35, M	Marfan syndrome with dilatation of the aortic root	Fever, pseudoaneurysm of aortic prosthetic root (6 weeks after surgery)	Aortic graft	PG
Barry et al. [16]	80, F	DM	Fever, melena, abdominal pain, weight loss	Abdominal aorta	Native
Manso et al. [2]	35, M	IDU, HIV seronegative	Chest pain, fever, chills, hemorrhage	Descending thoracic aorta	Native
Ikeda et al. [3]	63, M	Esophageal carcinoma, broad-spectrum antibiotics	Abdominal pain, fatigue, fever, hemorrhage	Abdominal aorta	Native
Marty-Ané et al. [23]	73, M	Colonic polyp resection 7 months before	Abdominal pain, diarrhea, fever, tender pulsatile epigastric mass	Abdominal aorta	Native
Roush et al. [24]	62, M	CHF, abdominal surgery	Fever, sweats, dyspnea, cough, hemorrhage	Pulmonary artery	Native
Rubin and German [25]	71, M	DM, radical cystectomy (transitional cell carcinoma)	Low abdominal pain	Abdominal aorta	Native
Woodrum et al. [5]	49, M	DM	Pain, knee swelling	Right common iliac artery	Native
Minami et al. [26]	68, M	Steroid therapy (uveitis)	Back pain, fever	Aortic arch	Native
Tsunezuka et al. [17]	70, M	Gastric cancer	Fever, anorexia, pulsatile mass	Common iliac artery	Native
Goldman et al. [27]	16, F	SLE, prednisone	Headache, fever, irritability, seizures, subarachnoid hemorrhage	Proximal basilar artery	Native
Takeda et al. [18]	67, M	Intestinal cancer	Fever, hemiparesis, coma, subarachnoid hemorrhage	Right middle cerebral artery	Native
Gladstone et al. [32]	31, F	Hysterectomy (carcinoma of the cervix), prior IDU	Fever, pain and coldness of the right foot	Right superficial femoral artery	Native
Anderson et al. [20]	26, F	ESRD, HD	Fever, pain, pulsatile mass	Common femoral artery	Native
Oderich et al. [28]	NR	Primary aortoduodenal fistula	NR	Juxtarenal aorta	NR
Collins et al. [31]	20, M	None	Fever, headache, right hemiparesis, upper arm pain	Brachial artery, abdominal aorta	Native
Rabah et al. [30]	11 months, F	AIDS (CD4 cell count, 6 cells/mm^3)	Prolonged fever, seizures, left arm stiffness, hemorrhage	Basilar meningeal arteries	Native
Present article	75, M	ESRD/HD, DM	Expanding pulsatile neck mass, pain	Carotid	Native
Probable cases					
Zedtwitz-Liebenstein et al. [34]	46, M	Homograft aortic valve replacement	Fever, night sweats	Ascending aorta	Native
Larena-Avellaneda et al. [4]	53, M	*Candida* prosthetic endocarditis	Fever, local pain, leg abscess with compartment syndrome	Popliteal and tibioperoneal artery	Native
Khoss et al. [33]	32 days, M	Prematurity	Apnea, abdominal distension	Abdominal aorta	Native

NOTE. 5FC, flucytosine; AmB, amphotericin B; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; ESRD, end-stage renal disease; HD, hemodialysis; IV, intravenous; IDU, injection drug use; L-AmB, liposomal amphotericin B; NR, not reported; PG, prosthetic graft; SLE, systemic lupus erythematous; UTI, urinary tract infection.

[a] Age is given in years, unless otherwise specified.

Table 1. ***(Continued.)***

Histologic evidence of fungal invasion	Artery-wall culture results (source of specimen)	Candidemia/ endocarditis	Candiduria	IV catheter infection	Treatment (duration)	Outcome, comments
+	*Candida albicans* (vein graft)	+/−	NR	NR	Surgery, AmB plus 5FC (1 month), then fluconazole	Pseudoaneurysm over vein graft
NR	*C. albicans* (artery graft)	+/NR	NR	NR	Surgery, L-AmB (2 months), then fluconazole	Died (9 months after of fungal infection)
NR	*C. albicans,* aortic graft	+/+	+	NR	Surgery, AmB plus 5FC (6 weeks), then fluconazole	Favorable evolution
−	*C. albicans* (aortic wall)	−/NR	Vaginal *Candida* infection	NR	Surgery, fluconazole	Died (7 days after aortitis was diagnosed, of pneumonia and stroke); duodenal perforation association (probable aortoenteric fistula)
NR	*C. albicans* (aortic wall)	−/NR	−	NR	Surgery, L-AmB	Mucocutaneous candidiasis 3 months before aortitis
−	*Candida* species (aortic wall)	+ (11 months before aortitis)/ NR	+	+	Surgery, IV miconazole, then unspecified oral antifungal treatment	…
NR	*C. albicans* (aortic wall)	+ (after polyp resection) − (at index admission)/NR	NR	NR	Surgery, AmB, then lifelong fluconazole	*C. albicans* spondylodiskitis 4 months before index admission
+	*C. albicans* (tricuspide valve and pulmonary artery)	+/+	NR	Swan-Ganz 1 year before	Surgery, AmB plus 5FC	Died (day 11 of antifungal treatment) of massive pulmonary hemorrhage
+	*Candida* species (aortic wall)	+ (6 weeks before aortitis)/ NR	+	…	Surgery, AmB, then lifelong fluconazole	Mechanical obstruction of ureteral stents with *Candida* species 8 weeks before aortitis
+	*C. albicans* (artery wall)	−/NR	+	NR	Surgery, AmB (4 weeks)	Intermittent fungal UTI
+	*C. albicans* (aortic wall)	−/NR	NR	NR	Surgery, fluconazole, itraconazole	…
−	*C. albicans* (artery wall)	−/NR	NR	+ (2 years before arteritis)	Surgery, fluconazole (1 year)	Candidemia 2 years before
+	*C. albicans* (artery wall)	−/−	+	NR	…	Necropsy diagnosis; ventricular shunt culture positive for *C. albicans* 3 days before death; oral thrush
+	*Candida* species (artery wall and mitral valve)	NR/+	NR	NR	…	Necropsy diagnosis
NR	*Candida* parapsilosis (artery wall vegetation)	+/+ (mitral endocarditis)	NR	NR	Surgery, AmB plus 5FC	Died of pneumonia (10 months after arteritis)
+	*Candida* species (artery wall)	NR/NR	NR	NR	Surgery, AmB	Operative groin wound from vaginal candidiasis
NR	*Candida* species (artery wall)	−/NR	NR	NR	Surgery, unspecified antifungal therapy (4 months)	Prosthetic graft infection 9 months after surgery; died (11 months after CVA)
+	−	−/+ (mitral endocarditis)	NR	NR	Surgery, AmB	…
+	NR	−/−	+	−	…	Necropsy diagnosis; arteriopathy associated with chronic meningitis
+	*C. albicans* (carotid artery wall)	−/NR	−	…	Surgery, fluconazole	Died of hyperkaliemia (2 months after arteritis was diagnosed)
NR	−	+ (*Candida tropicalis*)/+ (prosthetic aortic valve)	NR	NR	Surgery, 5FC plus fluconazole (1 week), then AmB (45 days)	…
−	−	+ (*C. albicans*)/+	NR	NR	Surgery, AmB plus 5FC plus fluconazole, then fluconazole (6 months)	Recovery; no valvular replacement
−	−	+ *(C. albicans)*/NR	+	Umbilical vein catheter	AmB plus 5FC	Died (42nd day of life)

photericin B combined with flucytosine ($n = 4$), fluconazole alone ($n = 3$), amphotericin B combined with both flucytosine and fluconazole ($n = 2$), fluconazole and itraconazole ($n = 1$), and miconazole alone ($n = 1$). No patient underwent surgical management without antifungal treatment. Of the 7 patients with diagnoses of *Candida* endocarditis, 5 underwent valve replacement and antifungal therapy, and 1 was treated medically; 1 case was diagnosed postmortem.

Overall mortality was high; 9 of 23 patients died. In 3 cases [16, 28, 32], death was believed to be *not* related to the *Candida* infection. In all patients with intracranial arteritis, the diagnosis was made postmortem.

DISCUSSION

Here we present the first case, to our knowledge, of *Candida* carotid arteritis and review the literature regarding 22 additional cases of *Candida* arteritis that occurred outside of the SOT setting. Patients typically presented with pain at the site of the infected artery and with fever. Documented underlying vascular disease was surprisingly infrequent. The source of *Candida* infection usually remained obscure, even though, in the majority of patients, *Candida* colonization or infection was present before *Candida* arteritis was diagnosed. All patients except 1 had serious concomitant conditions that were similar to those associated with invasive candidiasis [16, 25]. Mortality was high; death was most commonly due to arterial rupture and massive hemorrhage, particularly when aortic or intracranial vessels were involved in the infection.

In all cases, pseudoaneurysms of the infected artery were present. Two mechanisms have been suggested to explain fungal arteritis [20, 23]. First, infection of a preexisting atherosclerotic aneurysm might occur during an episode of candidemia; this was suggested in our patient by the atherosclerotic degeneration seen histologically in the surgical carotid specimen and the absence of endocarditis. Alternatively, localized *Candida* infection of the artery wall (typically via septic microemboli to the vasa vasorum of the artery wall or septic embolization in an artery, or from a contiguous infectious process extending to a nearby artery) may be followed by weakness of the artery wall and secondary pseudoaneurysm formation. It is conceivable that these 2 mechanisms coexist. The relative rarity of preexisting arterial disease in published cases suggests that the second mechanism may be more important.

Only half of the patients with *Candida* arteritis had documented candidemia. This is consistent with the well-recorded difficulty of premortem detection of candidemia in patients who are found to have disseminated candidiasis at autopsy [40]. When *Candida* arteritis is diagnosed, potential complications of candidemia (including endocarditis, endophthalmitis, and spondylodiskitis) should be searched for, even when blood culture results are negative. Another major complication of *Candida* arteritis is massive hemorrhage, perhaps because infected aneurysms are more prone to rupture than are atherosclerotic aneurysms. The diagnosis of *Candida* arteritis was frequently not made before rupture, presumably because of the nonspecific symptoms. Rupture was observed particularly with aortic, pulmonary, and cerebral artery involvement.

Treatment of *Candida* arteritis in most cases included a combination of different antifungal agents and surgery. In the absence of controlled studies, the optimal choice and duration of antifungal therapy is unknown. Prolonged, often lifelong therapy has been used, particularly for patients with prosthetic graft infection. The optimal surgical approach is also not well established but may include excision of all infected tissue and vascular reconstruction, often using extra-anatomic bypass or, more recently, in situ vascular grafting, particularly with aortic infection.

Because *Candida* arteritis is an infrequent entity, a high index of suspicion, early diagnosis, and prompt antifungal and surgical treatment seem crucial to the effort to avoid arterial rupture. Major hemorrhage can be a life-threatening complication, well recorded in the SOT setting and frequently complicating the course of *Candida* arteritis in patients who have not undergone SOT.

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