Video-assisted thoracoscopic surgery for patients with pulmonary coccidioidomycosis

Awais Ashfaq, MD,^a Holenarasipur R. Vikram, MD,^b Janis E. Blair, MD,^b and Dawn E. Jaroszewski, MD^a

Objective: The study objective was to evaluate the use of video-assisted thoracoscopic surgery for removal of pulmonary sequelae of the fungal infection coccidioidomycosis.

Methods: Retrospective chart review of all patients with pulmonary coccidioidomycosis treated surgically at our tertiary care center between January 1, 2009, and August 31, 2012.

Results: Of 2166 patients treated for pulmonary coccidioidomycosis, 58 (2.7%) (median age, 52 years [range, 18-84 years]) required surgical treatment. Surgical resection was performed for diagnosis (n = 28 [48%]); 17 with positive positron emission tomography findings); persistent or progressive symptoms despite antifungal therapy (n = 23 [40%]); or complications (n = 7 [12%] of cavity rupture/infection). Of 33 patients (57%) who had serology performed, 23 (70%) had positive results. Video-assisted thoracoscopic surgery was used for most (95%; n = 55) procedures, including 38 (67%) wedge resections, 14 (24%) segmentectomies, and 6 (11%) lobectomies; 4 patients also required additional decortication. Major (8%), including 1 death, and minor (12%) complications occurred in 12 patients postoperatively. Median hospitalization was 3 days (range, 1-8 days). Postoperative antifungal therapy was administered to 50% of patients for a median duration of 2 months. No patient had recurrent coccidioidomycosis at a median follow-up of 19 months.

Conclusions: Although rarely necessary for pulmonary coccidioidomycosis, surgical intervention may be indicated. Specific indications include refractory symptomatic disease and complications of the infection, such as cavity rupture. Excisional biopsies also may be required for diagnostic confirmation of indeterminate pulmonary nodules. With video-assisted thoracoscopic surgery, diagnostic and therapeutic intervention can be undertaken with a low risk of complications and shorter length of hospital stay. (J Thorac Cardiovasc Surg 2014;148:1217-23)

Often called “valley fever,” the fungal infection coccidioidomycosis affects an estimated 150,000 persons in the United States annually.¹⁻³ The infection is caused by inhalation of soil-dwelling spores of the fungus *Coccidioides* species, which is endemic to the southwestern United States.^{1,2,4,5}

The Centers for Disease Control and Prevention has documented a substantial increase in the incidence of reported coccidioidomycosis in endemic states (Arizona, California, Nevada, New Mexico, and Utah) from 5.3 per 100,000 population in 1998 to 42.6 per 100,000 in 2011.⁶ With the increasing mobility of patient populations, clinicians in regions outside the coccidioidal endemic area also have been faced with the responsibility of identifying and treating this disease and its sequelae. Coccidioidal infection typically manifests as a flu-like illness, and it is

a common cause of community-acquired pneumonia in endemic areas.^{1,4} Typical symptoms include cough, fatigue, chest pain, fever, hemoptysis, weight loss, dyspnea, malaise, night sweats, and chills.^{1,2,5,7}

Approximately 5% to 10% of coccidioidal infections result in residual pulmonary sequelae, such as nodules and cavities.^{1,4} Most coccidioidal infections are self-limited and resolve with or without antifungal treatment; however, a small percentage of patients require surgery as definitive or adjunctive treatment.^{3,5,8} The most common surgical indications are symptomatic nodules or cavities that do not resolve (Figure 1) and, less frequently, cavitary lesions (Figure 1) that rupture. Persistent or enlarging coccidioidal nodules or masses also may present a diagnostic dilemma for patients who are at risk for carcinoma or who have nondiagnostic or unobtainable biopsies (Figure 2). Serum antibody testing also may be negative in these patients, which contributes to diagnostic complexity.

Since 1995, video-assisted thoracoscopic surgery (VATS) has been used in select cases for lung resection. VATS has become the standard approach in diagnostic procedures and for the treatment of many benign diseases⁹⁻¹⁴ (Figure 3). The role of VATS in the excision of coccidioidal lesions has not been well studied. The inflammatory response and potential pleural adhesions inherent in coccidioidal infection led many surgeons to use open resection.

From the Divisions of Cardiovascular and Thoracic Surgery,^a and Infectious Diseases,^b Mayo Clinic Hospital, Phoenix, Ariz.

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Address for reprints: Dawn E. Jaroszewski, MD, Division of Cardiovascular and Thoracic Surgery, Mayo Clinic Hospital, 5777 E. Mayo Blvd, Phoenix, AZ 85054 (E-mail: jaroszewski.dawn@mayo.edu).

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Abbreviations and Acronyms

- CT = computed tomography
 PET = positron emission tomography
 VATS = video-assisted thoracoscopic surgery

Previous publications have commonly described open resection for treatment of fungal-based disease.¹⁵⁻¹⁷ We therefore conducted a retrospective review of the medical records of patients with pulmonary coccidioidomycosis who were surgically treated using VATS at our tertiary care academic medical institution to determine whether VATS was safer and more effective compared with open surgery.

MATERIALS AND METHODS**Study Design**

A retrospective review was conducted to identify all patients with documented coccidioidal infection who were treated at Mayo Clinic, Scottsdale, Arizona, between January 1, 2009, and August 31, 2012. The study was approved by the Mayo Clinic Institutional Review Board, which waived consent on de-identification of patients. Patients with coccidioidal infections were selected by reviewing all cases of coccidioidomycosis reported to the Arizona Department of Health Services by our institution. Reports were compiled on the basis of microbiological cultures of any source of *Coccidioides* sp, positive pathologic results, or positive serologic results. The medical records of these patients were retrospectively reviewed, and the following information was abstracted: site of coccidioidal infection (right or left lung) and characteristics of the first radiographic findings (nodule, cavity, pneumothorax, or empyema). Patients underwent surgery following our proposed treatment algorithm in previous publication.¹⁵ For patients who underwent surgery, further details included clinical and radiologic indications for surgery, diagnostic methods, type of surgical treatment (wedge resection, segmentectomy, or lobectomy), postoperative complications, preoperative and postoperative antifungal treatment, and follow-up. Complications were reported in accordance with the definitions established by The Society of Thoracic Surgeons.

Statistical Methods

Categorical variables were analyzed as numbers and percentages. Continuous variables were summarized as medians and ranges. Differences among categorical variables were determined by the chi-square test. All data entry and analysis were conducted using SPSS version 16.0 (SPSS Inc, Chicago, Ill).

RESULTS**Patients**

A total of 2166 patients were identified with a diagnosis of coccidioidomycosis who were evaluated at our tertiary care academic medical institution between January 1, 2009, and August 31, 2012. Of this total, 58 patients (2.7%) underwent thoracic surgical procedures. The median age of the surgical patients was 52 years (range, 18-84 years). Thirty-two patients (55%) were women, and 26 patients (45%) were men. Patients were categorized by their radiographic findings at the time of presentation for surgical consultation. Of the 58 patients, 34 (59%) had lung

nodules, 17 (29%) had cavitary disease, and 7 (12%) had complications of disease that included empyema, hydrothorax, or pneumothorax. Twenty-three (40%) of the 58 patients had intractable coccidioidal symptoms (chest pain, dyspnea, fever, or fatigue) refractory to antifungal therapy at the time of surgery. Surgery resulted in complete resolution of symptoms in all but 1 patient (improved but not completely resolved).

Preoperative Antifungal Therapy

Before surgical resection, 24 (41%) of the 58 patients had preoperative antifungal therapy (Table 1), with treatment duration ranging from 3 weeks to 1 year. The most common antifungal medication was fluconazole (n = 20 [83%]). In select cases, itraconazole, posaconazole, or voriconazole was subsequently used because of organism resistance or intolerance to medication side effects. Treatment choices were based on the preference of the physician, the tolerance profile of the patient, and the health insurance coverage of the patient. No conclusions can be drawn about the optimal length of antifungal therapy on the basis of disease advancement or progression to complications. Thirty-three patients (57%) had serology performed before surgery, with only 23 (70%) exhibiting positivity (Table 1).

Patients With Nodular Radiographic Findings

Thirty-four (59%) of the 58 patients underwent surgical excision after a suspicious nodule was noted on imaging. Of the 18 patients who underwent positron emission tomography (PET) imaging, 17 (94%) had lesions with positive uptake of ¹⁸F-fluorodeoxyglucose (Table 1). Nodules were noncalcified in 10 patients (56%) and spiculated in 11 patients (61%). Of 9 of 18 patients (50%) who underwent computed tomography-guided transthoracic biopsy, 7 had indeterminate findings on pathology. Two patients with multiple nodules were found to have cancerous pathology (1 carcinoid and 1 adenocarcinoma), in addition to coccidioidomycosis nodules. The remaining half of the patients (n = 9) did not undergo transthoracic biopsy mainly because of the technically difficult location of the nodule. One patient with a negative PET scan had a smooth calcified nodule and underwent resection because the nodule was enlarging. Among 17 PET-positive patients, 12 had a previous or current diagnosis of cancer: lung cancer and oral pharyngeal cancer (2 patients each); and carcinoid, melanoma, colon cancer, retroperitoneal sarcoma, endometrial sarcoma, breast cancer, post-stem cell transplant, and chronic lymphocytic leukemia (1 patient each). Coccidioidal serology was positive for 10 (29%) of the 34 patients with nodular disease (Table 1).

Patients With Cavitary Lesions

Cavitary lesions that progressed or failed to resolve despite adequate antifungal therapy affected 17 (29%) of

FIGURE 1. Computed tomography scan of the chest showing 2 cavitary lesions with pleural thickening (arrows) in a patient presenting with pulmonary coccidioidomycosis.

the 58 patients. The primary symptoms were chronic fatigue (14 [16%]), chest pain (11 [12%]), chronic cough (10 [11%]), dyspnea (8 [9%]), and hemoptysis (8 [9%]) (Table 2). Thirteen (76%) of these 17 patients had positive coccidioidal serology results.

Patients With Complications Due to Coccidioidomycosis

Seven patients presented with complications related to their pulmonary coccidioidomycosis lesions that required operative intervention. All had cavitary lesions that ruptured, creating empyema (n = 5) or hydropneumothorax (n = 2).

Procedures

Surgical resection was performed using VATS in 95% of patients (n = 55). The types of procedures performed are summarized in Table 3. In addition, 4 of these 55 patients required decortication, with 2 being converted to open thoracotomy for completion.

Morbidity and Mortality

Major (8%) and minor (12%) complications, including 1 death, occurred postoperatively in 12 patients (Table 4). One patient required readmission and reoperation on postoperative day 12 because of hydropneumothorax. A previous wedge resection had been performed for a cavitary lesion. Reoperation with VATS showed necrosis in the residual lung segment, and a complete segmental resection was performed. Pathology revealed no abnormalities other

FIGURE 2. A 55-year-old man with a history of hepatocellular carcinoma presented with positive findings on PET of a new right lower nodule. Final pathology after VATS excision identified coccidioidomycosis. CT, Computed tomography; PET, positron emission tomography.

FIGURE 3. A, Intraoperative image of a cavitary lesion (arrow) in a patient undergoing VATS for resection of pulmonary coccidioidomycosis. B, Resected specimen from a patient with pulmonary coccidioidomycosis complicated by empyema (arrow).

than partial necrosis in the residual specimen. The sole death occurred in a 79-year-old woman with a biopsy-proven adenocarcinoma in the upper lobe and a second ipsilateral undiagnosed nodule in the lower lobe. Resection was performed of both the cancer (segmentectomy) and the secondary nodule (wedge resection), which was found to be coccidioidomycosis. Postoperatively, the patient had a significant left hemispheric stroke. After review of her advance directives and discussion with the family, care was withdrawn.

Complication rates for patients with nodular disease ($n = 8/34$ [24%]) were similar to those of patients with cavitary lesions ($n = 4/17$ [24%]). Complications ($n = 11/55$ [20%] vs $n = 1/3$ [33%]; $P < .05$) and length of hospitalization (3.3 ± 1.65 days vs 6.0 ± 1.25 days; $P < .05$) were significantly different among patients who had VATS ($n = 55$) than in those who had open surgical procedures ($n = 3$) (Table 5). The median hospitalization for all patients was 3 days (range, 1-8 days). Patients with complications due to cavitary rupture had a longer median hospitalization of 5 days (range, 3-8 days).

Postoperative Antifungal Therapy

Postoperatively, antifungal therapy was continued in 50% ($n = 29$) of the patients at the discretion of their

referring physician. The median duration of the antifungal therapy for all patients was 2 months (range, 1 month to 1 year), and continued antifungal therapy was most commonly based on monitoring of coccidioidal serology (Table 1). The most common antifungal therapy was fluconazole ($n = 24$ [83%]). Patients with intolerance to the side effects of fluconazole ($n = 5$) were administered voriconazole.

Follow-up

Patients had a median follow-up of 19 months (range, 7-104 months). None experienced recurrent pulmonary coccidioidomycosis.

DISCUSSION

The incidence of pulmonary coccidioidomycosis seems to be increasing in the southwestern United States. Therefore, thoracic surgeons should be aware of the disease and its manifestations and the need for potential operative management of such patients. Symptoms range from a mild, self-resolving respiratory syndrome to persistent pulmonary infections that may result in sequelae.¹ The strategies for optimal patient management vary widely, depending on the severity of illness and the presence of risk factors (eg, African or Filipino ancestry, suppression

TABLE 1. Diagnostic and therapeutic variables categorized by type of coccidioidal lesion

Variables	Known coccidioidal nodule	Indeterminate nodule	Known coccidioidal cavity	Total no. of patients
Antifungal therapy				
Preoperative duration, median, mo	6*	5.5	12	N/A
No or limited response to antifungal treatment	9	1	24	34
Persistent symptoms despite antifungal therapy	8	0	15	23
Postoperative duration, median, mo	2	2	3	N/A
Preoperative diagnostic evaluation				
PET/CT-positive uptake	1	16	0	17
Serology testing	5	11	17	33
Serology positivity	5	5	13	23
Interventional biopsy†	1	8	0	9

CT, Computed tomography; N/A, not available; PET, positron emission tomography. *Values are number unless indicated otherwise. †Interventional biopsy was always CT guided, with the approach determined by the preference of the radiologist.

TABLE 2. Signs and symptoms of pulmonary coccidioidomycosis in 58 patients undergoing thoracic surgery

Sign or symptom	Patients, no.* (%)
None	33 (36)
Fatigue	14 (16)
Chest pain	11 (12)
Cough	10 (11)
Dyspnea	8 (9)
Hemoptysis	8 (9)
Fever	4 (4)
Night sweats	2 (2)
Myalgia	1 (1)

*The patients who had signs/symptoms experienced more than 1 sign/symptom, so numbers total more than 58.

of cell-mediated immunity, advanced age, and diabetes mellitus) that portend complicated, severe, or disseminated infection. In most patients, the infection will resolve without antifungal therapy. Management of persistent disease includes periodic examinations every 3 to 6 months for as long as 2 years, with documentation of radiographic resolution or identification of potential pulmonary or extrapulmonary complications as early as possible.¹ When deemed necessary, our practice is to initiate antifungal treatment with fluconazole (400-800 mg/d administered orally) for most coccidioidal infections, whether pulmonary or extrapulmonary infection. Although itraconazole has better antifungal activity than fluconazole in vitro, we typically reserve itraconazole (200 mg orally twice or thrice daily) for patients who do not tolerate (or infection that is refractory to) fluconazole because of itraconazole's drug interactions, the difficulty with oral absorption, and the requirement to monitor serum levels. In situations in which a patient's course is rapidly declining or particularly severe, we treat with lipid formulations of amphotericin B (2.0-5.0 mg/kg or more per day given intravenously).¹ The newer azoles, such as voriconazole or posaconazole, are effectively used as salvage treatment.¹⁸

A small subset of patients may require surgical intervention if they do not respond to medical therapy or if

TABLE 3. Type of surgical procedure categorized by type of radiographic abnormality found in patients with pulmonary coccidioidomycosis

Surgical procedure*	Radiographic finding, no. (%)		
	Nodule (n = 34)	Cavitary (n = 17)	Complications secondary to disease (n = 7)
Wedge	23 (68)	8 (47)	5 (72)†
Segmentectomy	6 (17)	7 (41)	1 (14)
Lobectomy	4 (12)	0 (0)	1 (14)†
Thoracotomy with wedge	1 (3)	1 (6)	0 (0)
Thoracotomy with lobectomy	0 (0)	1 (6)	0 (0)

*VATS unless stated otherwise. †Four of 6 patients also required decortication.

complications develop.¹⁵ Patients with coccidioidomycosis are typically managed by pulmonary medicine or infectious diseases specialists. The timing of surgical intervention is optimally based on input from a multidisciplinary team.¹⁵ In our patients, referral for surgical consultation occurred for (1) definitive diagnosis of a suspicious nodule, (2) refractory symptomatic disease despite optimal antifungal therapy, or (3) complications secondary to the fungal lesions. An algorithm has been published for our institution.¹⁵

Definitive Diagnosis of a Nodule

Recent technologic advances have reduced the likelihood that patients presenting with a suspicious lung nodule will require surgical biopsy for a diagnostic dilemma. However, the diagnostic yield of many testing modalities in patients with coccidioidomycosis is often inadequate. Percutaneous needle biopsy has been attempted for such nodules, but definitive diagnosis is relatively low.¹⁷ Likewise, PET has been found to have low specificity and negative predictive value in endemic regions.^{19,20}

In our population of patients undergoing surgical biopsy for diagnostic purposes, 7 of 9 (78%) had unsuccessful interventional biopsies and 17 of 18 (94%) had PET-positive lesions suspicious for carcinoma. Coccidioidal serology can be used as an adjunct diagnostic modality when evaluating a lung nodule. Typically, such serology is most likely to be positive in the first months of symptomatic coccidioidal illness and then negative as symptoms resolve.²¹ False-negative and false-positive serologic results are common. Therefore, it is not surprising that 22 (88%) of the 25 patients with indeterminate nodular disease in our study had negative serology.

In such cases, excisional biopsy may be recommended for definitive diagnosis, especially when malignancy is suspected. The VATS biopsy can be undertaken for complete diagnostic accuracy and rapid patient recovery.

Surgical Treatment for Refractory Disease

A small subset of patients underwent surgical excision when they continued to manifest clinically significant symptoms or when their disease progressed despite adequate antifungal therapy. On average, patients were treated for 6 months before referral for surgical consultation. In most patients, symptom relief correlated with surgical resection of lesions.

Complications Secondary to Pulmonary Lesions

Complications related to cavity rupture were most often treated with surgical intervention. Although clinically significant morbidity is rare, when complications occur, they can lead to lengthy hospitalization. A prolonged hospital stay was common for patients presenting with complications associated with ruptured nodules/cavities (mean, 5 days) versus uncomplicated resection (mean, 2 days). The goal for surgical intervention is to identify

TABLE 4. Morbidity and mortality in patients with pulmonary coccidioidomycosis undergoing surgical intervention

Patient no.	Disease type	Procedure*	Morbidity
Major morbidity			
1	Nodule	Segmentectomy	Reoperation with VATS wedge of necrotic lung
2	Cavitary	Wedge	Empyema requiring reoperation
3	Cavitary	Wedge	Pneumothorax requiring chest tube reinsertion (19 d)
4	Nodule	Lobectomy	Pneumothorax requiring chest tube reinsertion (6 d)
Minor morbidity			
5	Cavitary	Segmentectomy	Venous thrombosis subclavian vein
6	Nodule	Lobectomy	Intercostal pain requiring pain management
7	Nodule	Wedge	UTI
8	Cavitary	Segmentectomy	Intercostal pain
9	Nodule	Wedge	Acute kidney injury self-resolved
10	Nodule	Wedge	Prolonged air leak (8 d)
11	Nodule	Lobectomy	UTI, treated as outpatient; patient had a history of recurrent UTI
Mortality			
12	Nodule	Segmentectomy and wedge	Adenocarcinoma with coccidioidomycosis; status epilepticus developed postoperatively; entire left hemispheric cerebrovascular accident with internal carotid artery occlusion; withdrew care on POD 13

POD, Postoperative day; UTI, urinary tract infection; VATS, video-assisted thoracoscopic surgery. *All procedures were by VATS.

lesions at risk for rupture and to excise them preemptively to prevent contamination of the thoracic cavity. Of the 7 patients who presented with complications, 3 (43%) had a protracted postoperative course lasting as long as 8 days. We identified no correlation between complications and extent of lung resection (wedge, segmentectomy, or lobectomy). The small number of patients experiencing complications precludes statistical predictions about this group.

Most of our patients were successfully treated surgically with the use of VATS. Although pulmonary fungal infections may increase adhesions and the difficulty of cases,²² only 2 patients required conversion to open procedures, in addition to 1 planned as such because of the surgeon's preference. We do not recommend any soft tissue buttress to staple lines or the bronchial stump unless there is significant inflammation and tissue integrity is of main concern. Most often, the residual pulmonary sequelae requiring surgery for coccidioidomycosis does not create such significant inflammation that residual pleural space becomes an issue. In our experience, we did not have failure of expansion after an anatomic or wedge resection. Decortication was required in cases with empyema to allow for

complete lung expansion. Failure to obliterate residual space or persistent bronchopleural fistula after a resection would necessitate muscle flap or omental flap closure.

The potential advantages of VATS over open thoracotomy include less postoperative pain, fewer pulmonary complications, and a shorter hospital stay.^{16,17,19,20} Our institution shifted to predominantly VATS-based cocci thoracic procedures with the addition of a surgeon with specialty training in this disease (D.E.J.). Our comparison of open procedures performed for coccidioidomycosis in this series with those conducted in prior years¹⁵ showed that patients receiving VATS had a shorter mean length of hospital stay than patients undergoing open surgery (3.3 ± 1.65 days vs 6.0 ± 1.25 days) (Table 5) and fewer complications (33% vs 20%). Other publications on surgery for pulmonary fungal infections also have shown that VATS is at least equivalent to open surgery with regard to safety and efficacy.²³

Study Limitations

Although the study highlights important aspects in coccidioidomycosis treatment, it is limited by being a retrospective review from a single institution that specializes in treatment of fungal diseases. This creates a challenge to expanding generalized results to other institutions. Having the experience of multiple patients with coccidioidomycosis has allowed us a positive learning curve in our surgical expertise; however, the majority of surgeons with thoracoscopic experience should have the expertise that would allow them to perform these types of cases.

CONCLUSIONS

The incidence of coccidioidomycosis seems to be increasing, and thoracic surgical intervention may be

TABLE 5. Comparison of resections of coccidioid lesions using video-assisted thoracoscopic surgery compared with open surgery

Variable	Study period		P value
	2004-2008	2009-2012	
Resections	42	58	
VATS	19	55	
Open surgery	23	3	
LOS for VATS cases, mean $\pm$ SD	3.85 ± 3.9	3.3 ± 1.65	<.05
LOS for open cases, mean $\pm$ SD	8.2 ± 9.6	6.0 ± 1.25	<.05

LOS, Length of hospital stay; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

increasingly necessary. Indications for surgery include the need for definitive diagnosis of a pulmonary nodule, refractory symptomatic disease, and complications related to rupture of pulmonary lesions. Patients may benefit from the use of a minimally invasive approach. The use of VATS for coccidioidomycosis lesions is feasible and safe. Our findings that successful resection of coccidioid lesions with minimal complications is possible using VATS may encourage earlier surgical intervention, which might prevent some patients from having to undergo protracted periods of unsuccessful antifungal therapy with the potential for complications, such as rupture. Disease-free survival and complete resolution of symptoms can be expected in most patients after surgical excision of lesions.

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