Coccidioides Thyroiditis in an HIV-Infected Patient

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We report a case of Coccidioides thyroiditis in an HIV-infected patient with a history of recent Coccidioides pneumonia but with negative Coccidioides serology determined by enzyme immunoassay at presentation. Diagnosis of Coccidioides thyroiditis was made based on histopathologic examination and culture of thyroid abscess material obtained by fine-needle aspiration biopsy.

CASE REPORT

The patient, a 44-year-old man living in Bakersfield, California, diagnosed with HIV infection in 1988, had antiretroviral therapy initiated in 2008 with efavirenz-emtricitabine-tenofovir disoproxil fumarate (Atripla). His medical history is also significant for hemophilia and an episode of Pneumocystis jirovecii pneumonia in 2008. He had been taking daily trimethoprim-sulfamethoxazole (double strength) since 2008 until the current presentation, in light of a CD4 count of 170/mm³. The patient also had a history of pulmonary coccidioidomycosis in January 2011, diagnosed by serology, from which he recovered well after being treated with amphotericin B lipid complex followed by fluconazole (400 mg/day) for chronic suppressive therapy. His follow-up serum antibody, using an enzyme immunoassay (EIA) for Coccidioides species, was negative in September 2011, compared to positive EIA and positive IgM and IgG titers (both 1:32) by complement fixation in January 2011, when the patient initially presented with pulmonary coccidioidomycosis.

In October 2011, he presented to his primary care physician with neck pain and swelling. The patient was still taking the same antiretroviral medications, as well as trimethoprim-sulfamethoxazole and fluconazole, as noted above. On examination, his vital signs were normal: temperature, 98°F; respiratory rate, 20 breaths/min; heart rate, 75 beats/min; blood pressure, 115/77 mm Hg; and oxygen saturation, 97% in room air. His thyroid was diffusely enlarged and firm, with no tenderness on palpation. Chest examination was remarkable for diffuse wheezing. Complete blood count showed a white blood cell count of 10,300 cells/mm³ (63% neutrophils), hemoglobin of 12.3 g/dl, and a platelet count of 425,000/mm³. CD4 count was 170/mm³ with 6% CD4 helper T cells. Other investigation results were remarkable: thyroid-stimulating hormone (TSH), 276 mIU/ml (normal range, 0.550 to 4.780); free triiodothyronine (T3), 0.12 pg/ml (normal range, 2.30 to 4.20); free thyroxine (T4), 0.13 pg/ml (normal range, 0.44 to 1.66); partial thromboplastin time (PTT), 56.7 (normal range, 25.8 to 37.3); erythrocyte sedimentation rate, 69 mm/h (normal level, <15 mm/h); and creatinine, 1.5 mg/dl. Liver function tests were normal. Chest X ray showed a severe, diffuse bilateral interstitial disease pattern, which was unchanged from his previous chest X-ray finding. Computed tomography (CT) scan of the neck revealed a markedly abnormal thyroid gland, which was hypodense and enlarged, with large loculated abscesses in the isthmus and in both lobes (Fig. 1). The patient underwent a fine-needle aspiration (FNA) of the right lobe of the thyroid; purulent material was readily aspirated. Histopathology of the aspirated material showed necrotic proteinaceous material and acute and chronic inflammation, consistent with infection. There were few thyroid follicular cells. Numerous Coccidioides spherules in various stages of development were identified in cell block sections by hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and Gomori methenamine silver (GMS) stains (Fig. 2), and a diagnosis of coccidoidal thyroiditis was made. Culture using Sabouraud’s dextrose agar supplemented with chloramphenicol and cycloheximide (mycobiotic agar; Hardy Diagnostics, Santa Maria, CA) was incubated at 24°C and yielded growth of a mold after 2 days, which was identified after further incubation as Coccidioides species based on the presence of arthroconidia in alternate hyphal cells. Identity of the culture as Coccidioides species was confirmed by DNA probe (AccuProbe; Gen-Probe, San Diego, CA), which was performed at the Health Department in Bakersfield, CA. The patient was admitted to a local hospital and underwent incision and drainage of the thyroid abscesses without complications. He was discharged home on day 7 of admission and was treated with amphotericin B lipid complex (400 mg, 3 times a week) for 16 weeks, followed by therapy with oral fluconazole (800 mg/day). The patient is clinically doing well 20 weeks after his surgery.

Of note, EIA testing of the patient on presentation, performed at the Physician’s Automated Laboratory in Bakersfield, CA, was negative, although subsequent testing 7 days after presentation was positive, with complement fixation titers of 1:16 for both IgM and IgG.

Exposure to the two known species of Coccidioides, C. immitis and C. posadasii, is extremely common in areas where Coccidioides is endemic, which include the San Joaquin Valley of California and Arizona in the United States (9). Infection is also seen in persons traveling to areas where Coccidioides is endemic (12). Its major presentation is that of pulmonary disease, although extrapulmonary dissemination occurs in approximately 0.5% of patients in the general population. The most common sites of dissemination include skin, joints, bones, and the central nervous system. Thy-
FIG 1  CT scan of the neck showing large loculated thyroid abscesses in the patient. The right lobe measures 4.4 by 2.8 by 2.9 cm in size, the left lobe measures 4.3 by 1.7 by 2.2 cm in size, and the isthmus measures 2.9 by 1.9 by 1.8 cm in size.

FIG 2  Microscopic appearance of a thyroid biopsy specimen showing acute and chronic inflammatory cells with developing and mature Coccidioides spherules, with the absence of any identifiable thyroid tissue. H&E stain, magnification of ×100 and ×200 (a and b); PAS stain, magnification of ×400 (c and d); and GMS stain, magnification of ×400 (e and f).
roid is a rare site of dissemination, with only 5 cases reported (1, 7, 11).

The characteristics of the five reported cases of *Coccidioides* thyroiditis are hereby described. Patients’ ages ranged from 26 to 78 years. Four of the 5 patients were immunocompromised and had diseases including including sarcoidosis, systemic lupus erythematosus, and polyarteritis nodosa. Three of the 4 patients were taking oral prednisone at various doses (15 mg/day to 80 mg/day). The diagnosis was made by culture of thyroid aspirates in three cases and histopathological examination of the thyroid tissue in the other two cases. All cases were treated with antifungal agents, including amphotericin B or fluconazole. Three of the patients required additional surgical interventions such as abscess drainage and partial or total thyroidectomy.

The patient we present developed disseminated coccidioidomycosis involving the thyroid gland while on fluconazole prophylaxis (400 mg/day). It is not clear whether the progression of the disease, despite initial therapy with amphotericin B followed by fluconazole, was associated with initial resistance or development of resistance to fluconazole with noncompliance of the patient with his medications. The latter possibility is unlikely, as the patient’s HIV disease was well controlled by medication and his CD4 count was fairly high. It is possible that disease progression might have occurred due to antifungal prophylaxis failure. There have been at least 2 reported cases of a fluconazole-resistant *Coccidioides* species (5, 10). Antifungal susceptibility testing was not performed on our patient’s isolate, and his serum fluconazole level was not determined, so we are unable to evaluate if these factors were involved.

Diagnostic methods for *Coccidioides* infection include serology, culture, and histopathology. More recently, PCR assays have demonstrated utility but are not commercially available (2). Although serology is probably the method relied on most frequently, neither its sensitivity nor its specificity is clearly known. Specifically, in the early stage of the disease, the test can be falsely negative. The serology results of all 5 previously reported cases of *Coccidioides* thyroiditis were reported to be positive, but none of these patients had HIV disease. In contrast, high false-positive EIA results for IgM have been suggested by several studies (4, 6). Isolating *Coccidioides* species from a clinical sample provides a definitive diagnosis of a coccidioidal infection. Identification of spherules by direct histologic or cytologic examination also provides a definitive diagnosis and is a more rapid method than culture or serology, which typically takes at least 5 to 7 days before the results become available to clinicians. *Coccidioides* species cannot be detected by Gram stains, while spherules can be detected by routine cytologic and histologic stains, including hematoxylin and eosin stains and specialized stains such as Gomori methenamine silver and periodic acid–Schiff stains. In a review of 41 cases of fungal thyroiditis, antemortem diagnosis of fungal thyroiditis was made by direct microscopy and culture of FNA or biopsy in most cases (3). FNA followed by histopathologic examination can be a valuable tool and should be a part of diagnostic workup for thyroiditis.

Our patient developed severe hypothyroidism, requiring levothyroxine replacement therapy. Histopathologic examination of the aspirated material showed necrotic proteinaceous material with a few thyroid follicular cells, and it is likely that the thyroid gland was significantly damaged by the infection. A similar histologic appearance can be associated with tuberculosis, histoplasmosis, and cryptococcosis, with hypothyroidism induced by thyroiditis due to these infections (3, 8).

In conclusion, *Coccidioides* thyroiditis is a rare manifestation of disseminated coccidioidomycosis. Our case illustrates several of the problems associated with this diagnosis, in which serology can be falsely negative. FNA followed by histopathologic examination can be a valuable tool for determining the etiology of suspected thyroiditis. Consideration of infection with *Coccidioides* should be included as part of the management of patients with thyroiditis, especially in immunocompromised patients residing in or having traveled to regions where *Coccidioides* is endemic.

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**REFERENCES**