

## Case History

# Cryptococcal Thyroiditis and Hyperthyroidism

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We report a case of cryptococcal thyroiditis presenting with hyperthyroidism that evolved through a transient euthyroid phase to hypothyroidism and finally recovered to normal function. This four-phase clinical presentation is similar to that of subacute thyroiditis, and it is unusual in the setting of infectious nonviral thyroiditis. Cryptococcal thyroiditis is rare; only three cases have been reported. Our patient is the first who survived the disseminated cryptococcal infection with thyroid involvement, thus enabling longitudinal clinical and endocrinologic follow-up.

### Introduction

FUNGAL INFECTIONS of the thyroid gland are uncommon. A review of the English language literature from 1900 to 1980 identified only 31 cases of fungal thyroiditis; the majority (26 cases) was caused by *Aspergillus* species; there were three cases of *Coccidioides immitis*, one of *Allescheria boydii* and one of *Candida* (1). Subsequently, reports of fungal thyroiditis published from 1980 to 2002 included: three cases of *Cryptococcus neoformans* (2–4), three of *Candida* (5–7), two of *Coccidioides immitis* (8), one of *Histoplasma capsulatum* (9), and one of *Aspergillus fumigatus* (10). Cryptococcal thyroiditis has resulted from hematogenous spread in the setting of positive cerebral spinal fluid (CSF) and blood cultures (2–4).

We describe a case of cryptococcal thyroiditis that was unusual in that hyperthyroidism was a presenting feature that evolved through a transient euthyroid phase to hypothyroidism and finally a recovery of normal function, a pattern typical of subacute or viral thyroiditis. The case was reviewed and obtained Institutional Review Board (IRB) clearance for publication.

### Case Report

A 39-year-old man on long-term immunosuppressive therapy for kidney and pancreas transplants was evaluated in the outpatient clinic for low-grade fever (37.5°C), dry cough, and rhinorrhea; he then exhibited painless thyroid gland enlargement. His past medical history was significant for type 1 diabetes mellitus for 27 years complicated by the

development of peripheral somatic neuropathy, diabetic retinopathy and diabetic nephropathy leading to end-stage renal disease. Eight years previously the patient received a kidney transplant from a living-related donor, and subsequently a cadaver pancreatic transplant. His immunosuppressive regimen for the past several years consisted of tacrolimus 6 mg twice daily, mycophenolate mofetil 1000 mg twice daily, and prednisone 10 mg daily.

On admission to the hospital the patient presented with fever (38.5°C), headache, weakness, nausea and vomiting, tachycardia (97 beats per minute) and blood pressure of 160/90 mm Hg. His thyroid gland was asymmetrically enlarged (right lobe larger than left lobe), approximately 3 times normal size, of firm consistency and nontender to palpation. There were no discrete nodules nor areas of fluctuency in the thyroid gland; cervical lymphadenopathy was absent. Laboratory studies revealed: normal white blood cell count of 8100 cells per microliter with lymphopenia and relative monocytosis: neutrophils 67.8%, lymphocytes 11.2% and monocytes 19.9%; hemoglobin was 11.5 g/dL and platelets 309,000 cells per microliter. Erythrocyte sedimentation rate (Westergren method) was 14 mm/hr (normal range, 0–15).

Tests of thyroid function indicated hyperthyroidism (Table 1). Absence of anti-thyroid peroxidase (TPO) antibodies (< 20 IU/L; reference range < 20) and antithyroglobulin antibodies (< 1:100) indicated that preexisting thyroid autoimmune disease was unlikely. Thyroglobulin levels of 15.3 µg/L subsequently declined to 4.9 µg/L.

Because of persistent headache associated with retrobulbar

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TABLE 1. THYROID FUNCTION TESTS

Time	Day 1	Day 9	Day 12	Day 18	Day 25	Day 39	Day 56	Day 94
TSH (mU/L)	<0.01	<0.01	<0.01	<0.01	0.02	0.09	7.3	2.8
FT <sub>4</sub> (ng/dL)	3.8	5.2	3.9	3.0	1.6		0.5	
FT <sub>3</sub> (pg/mL)			6.3	4.6			3.3	

Hyperthyroid phase: ~3 weeks; transient euthyroidism: ~3 weeks; thyroid hormone levels fall in the normal range while TSH is still suppressed; hypothyroid phase: ~3–4 weeks: TSH rebound, low FT<sub>4</sub>; recovery phase: return to euthyroidism.

TSH, thyroid stimulating hormone, normal range, 0.3–5.5 mU/L; FT<sub>4</sub>; free thyroxine, normal range, 0.73–1.79 ng/dL; FT<sub>3</sub>: free triiodothyronine, normal range, 2.8–5.3 pg/mL.

pain and photophobia, a lumbar puncture was performed and produced CSF containing numerous yeast forms. The diagnosis of cryptococcal meningitis was confirmed by CSF cryptococcal antigen titer of 1:1024 and CSF fungal cultures identifying numerous *Cryptococcus neoformans*. Widespread systemic cryptococcal infection was documented by serum cryptococcal antigen titer of 1:512 and growth in blood cultures. Serologic testing for human immunodeficiency virus type 1 (HIV-1)/human immunodeficiency virus type 2 (HIV-2) was negative; additional fungal serologies for blastomycosis, coccidioidomycosis, and histoplasmosis were also negative.

Thyroid uptake of radioactive iodine performed on day 3 of hospitalization was 0.7% (normal range, 7–30). Whole body scan after administration of 185 MBq of <sup>67</sup>Ga-citrate portrayed intense concentration of radioactivity in the thyroid gland at 24 hours (Fig. 1) that was still apparent at 4 days. There were no other areas of focal <sup>67</sup>Ga concentration throughout the body, indicating that the thyroid gland was the only extrameningeal tissue focally involved. Ultrasound imaging on day 5 showed an enlarged and diffusely heterogeneous thyroid gland. Ultrasound-guided fine needle aspiration (FNA) of the right thyroid lobe produced numerous yeast forms on direct smear (Fig. 2) and fungal cultures of the aspirate grew *Cryptococcus neoformans*.

### Cytologic Methods and Observations

Both air dried Diff-Quik™ (Dade Behring, Deerfield, IL) stained and alcohol-fixed Papanicolaou stained slides were prepared. The smears contained numerous follicular cells, fragments of colloid, numerous lymphocytes and other inflammatory cells, and scattered multinucleated histiocytes. In addition, occasional budding organisms were seen in the background and within the histiocytic cytoplasm. Hemorrhage-laden macrophages indicative of old hemorrhage were also noted. With Diff-Quik the organism stained pale blue with a surrounding clear halo representing the unstained capsule. With the Papanicolaou stain (Fig. 2), the organisms stained variably bluish-green or pink as oval structures with minimal coloration of the capsule. A GMS (Grocott's methenamine silver nitrate) fungal stain performed on a ThinPrep™ (Quest Diagnostics, Teterboro, NJ) demonstrated the organisms black-stained.

The patient received parenteral antifungal therapy (amphotericin B and flucytosine) for 17 days. His thyrotoxic symptoms (tachycardia, anxiety, insomnia) were treated with propranolol. His clinical condition gradually improved, and, after 22 days, he was discharged home on long-term suppressive therapy with fluconazole 400 mg/d. Persistent thyrotoxic symptoms were evident on cytology and cultures from a second FNA of the thyroid gland done on day 18.

When reevaluated in the endocrine clinic 1 month after discharge from the hospital, the patient's thyrotoxic symptoms had completely resolved, but he now manifested fatigue, mild cold intolerance and weight gain (approximately 10 pounds). The thyroid gland exhibited persistent asymmetric nontender enlargement but was less firm. Thyroid tests reflected resolution of hyperthyroidism by day 25 (normal free thyroxine [T<sub>4</sub>] level), hypothyroidism on day 56 and spontaneous recovery to euthyroidism 3 months after the initial presentation (Table 1). The mild TSH elevation despite clearly low free T<sub>4</sub> levels on day 56 may reflect suboptimal pituitary response to hypothyroid state in the setting of chronic disseminated infection.

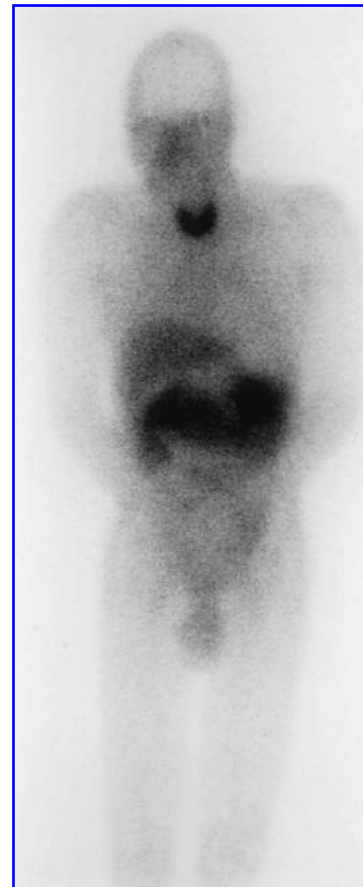


FIG. 1. Anterior body image made 24 hours after 185 MBq of <sup>67</sup>Ga-citrate. The thyroid gland appears enlarged and concentrates radioactivity diffusely. No other abnormal focus of radioactivity is present; physiologic activity is seen in the liver, kidneys and intestine within the abdomen.

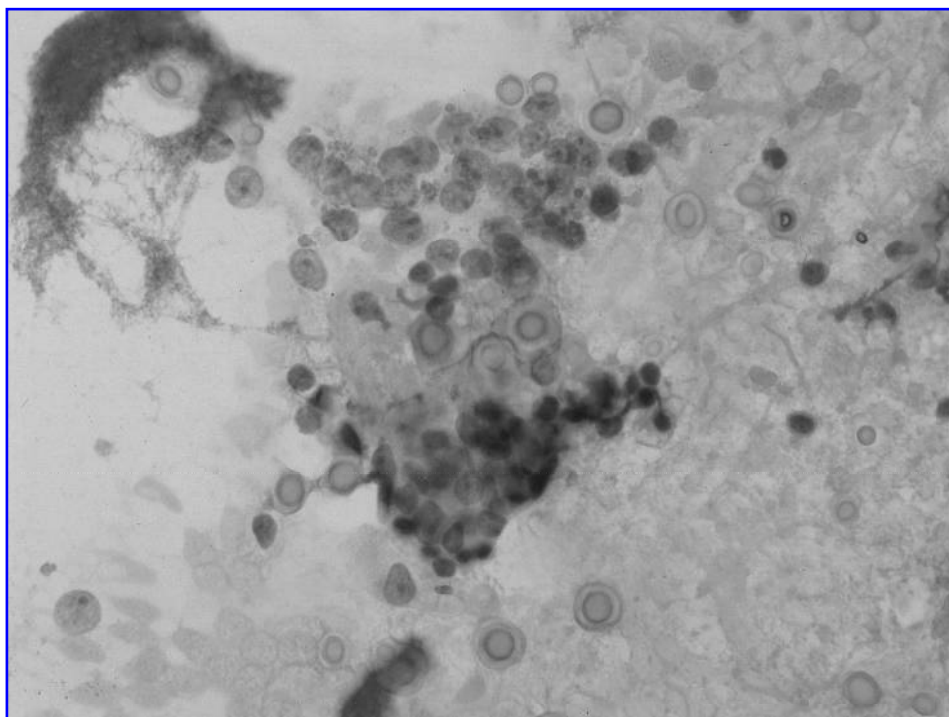


FIG. 2. Numerous eosinophilic forms with thick capsule are cryptococcus organisms. In the center are cryptococci engulfed by a large blue staining histiocyte. To the left is an aggregate of hemosiderin-laden macrophages. To the right are deeply stained follicular thyroid cells. Papanicolaou stain, 400 $\times$ .

TABLE 2. CLINICAL FEATURES OF PATIENTS WITH CRYPTOCOCCAL THYROIDITIS

Author, yr.	Patient age/gender outcome	Underlying disease	Cryptococcal infection	Diagnosis of infection	Features of thyroid involvement
Szporn et al. (2) 1984	47/M died	Type 2 DM, ethanol abuse, IV drug abuse, hepatic failure	Disseminated, cryptococcal meningitis	CSF cultures, thyroid FNA, autopsy histologic sections	Enlarged, tender thyroid Thyroid scan: no uptake Gallium scan: diffuse, increased uptake over thyroid gland
Machac et al. (3) 1985	40/M died	Chronic hepatitis, recurrent sepsis	Disseminated, cryptococcal meningitis	Blood and CSF cultures; autopsy histologic sections of thyroid	Normal size, nontender thyroid no signs/symptoms of thyroiditis <sup>67</sup> Gallium scan: intense uptake in the thyroid gland
Vaidya et al. (4) 1990	54/F died	Type 2 DM, HTN, ARDS	Disseminated	Blood and thyroid aspirate cultures, thyroid FNA	Left thyroid lobe enlargement, <sup>99</sup> Tc thyroid scan: no uptake in the left lobe
Present case	39/M survived	Type 1 DM, immunosuppression for kidney and pancreas transplant	Disseminated, cryptococcal meningitis	Blood and CSF cultures, thyroid FNA and thyroid aspirate cultures	Diffuse thyroid enlargement, right lobe greater than left, no nodules; RAIU 0.7% <sup>67</sup> Gallium scan: intense uptake in the thyroid; clinical evolution with hyperthyroidism, hypothyroidism and recovery to euthyroidism

ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; HTN, hypertension; Tc, technetium; IV, intravenous; CSF, cerebrospinal fluid; FNA, fine-needle aspiration; RAIU, radioiodine uptake.

## Discussion

All cases of fungal thyroiditis occurred in immunocompromised patients and associated with disseminated infection (1). The clinical presentations were widely variable including: normal size, nontender gland (3), diffuse painless thyroid enlargement (4), painless thyroid enlargement with discrete nodules (8,9), diffuse or localized tender thyroid enlargement (1,2,6,10) and thyroidal pain and tenderness associated with areas of fluctuancy (5,7,8). One patient with *Candida* thyroiditis manifested hyperthyroidism followed by hypothyroidism (6).

Cryptococcal thyroiditis is rare and occurs in the setting of widespread systemic infection in immunocompromised patients. The demographic and clinical features of three previously reported patients are listed in Table 2. Each died as a result of their disseminated infection (2,3,4), but the diagnosis of cryptococcal thyroiditis was made antemortem based on clinical presentation: thyroid enlargement (4); thyroid enlargement and tenderness (2), imaging studies such as radioiodine or <sup>99m</sup>Tc thyroid scans (2,4) and <sup>67</sup>Ga-citrate scan (3). Confirmation of diagnosis was made by FNA (2,4) and histologic examination of thyroid gland at autopsy (2,3). In these cases the TSH level was normal and serum T<sub>4</sub> and triiodothyronine (T<sub>3</sub>) levels were low, possibly related to hypoproteinemia due to hepatic failure (2), chronic active hepatitis (3), and/or severe illness requiring prolonged intubation (4).

Ours is the only patient reported to survive disseminated cryptococcosis with thyroidal involvement, and thereby offered a unique opportunity to characterize the clinical evolution of cryptococcal thyroiditis. His course closely resembled the classical presentation of subacute thyroiditis, progressing through four distinct phases: initial hyperthyroidism, then transient euthyroidism followed by hypothyroidism and recovery to euthyroidism. Further similarities with subacute granulomatous thyroiditis (de Quervain's thyroiditis) were the firm, diffuse thyroid enlargement and the lack of anti-thyroid antibodies to suggest preexistent thyroid disease (11). However, in contrast to the typical pain and tenderness in glands afflicted with subacute thyroiditis, the thyroid gland in our patient was distinctly nontender; this was also true in two other cases (3,4), and thus more typical of so-called painless or autoimmune injury-type thyroiditis. Both subacute thyroiditis (presumed viral in origin) and cryptococcal thyroiditis have now been shown to manifest an injury-type of release of thyroid hormone sufficient to produce hyperthyroidism. A common feature to each disorder is the formation of granulomas, and it is possible that a relatively rapid (over a few days or weeks) pathologic process of this type will be associated with a transient hyperthyroidism. Gallium scan non-specifically portrays regions of inflammation (and sites of some neoplasms) but will help to confirm an active process in the thyroid and other sites of tissue involvement. Prompt attainment of diagnosis through cytology and cultures, including those from an enlarged thyroid gland, will enable a reasonable probability of successful treatment.

In immunocompromised patients the rate of relapse after primary treatment for cryptococcosis remains high; suppressive antifungal therapy with fluconazole should be continued for a prolonged, but as yet undetermined period of

time. Persistence of *Cryptococcus neoformans* in occult sites of infection (e.g., meninges and prostate) has been demonstrated in recurrent infections (12). In cases of cryptococcal thyroiditis, the thyroid gland may constitute a reservoir of *Cryptococcus*, and repeat FNA for cytology and culture may be the best method to determine the clearance of infection. In cases of persistent fungemia and positive thyroid FNA cultures, thyroidectomy could be considered for removal of a source of continued sepsis. Gallium scan would give reassurance of no additional sites of infection, but would be too nonspecific to determine continuing growth of fungus within a gland pervaded by inflammation.

We conclude that cryptococcal thyroiditis should be considered in the setting of disseminated infection. With early diagnosis and aggressive antifungal treatment more patients are likely to survive, and they may present with evolving symptoms and biochemical findings of hyperthyroidism and hypothyroidism.

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