

Title: First reported case of acute Chagas' disease presenting with a suprasellar mass and panhypopituitarism

Authors: Hoon-Ji Helen Choi, MD¹; Marcia Cornford, MD, Ph D⁴; Lina Wang, MD²; Julie Sun, MD³; Theodore C. Friedman, MD, PhD¹

Institutions:

Department of Endocrinology, Metabolism, and Molecular Medicine ¹

Department of Pathology ²

Department of Radiology ³

Charles Drew University of Medicine & Science

1731 East 120th Street

Los Angeles, CA 90059

Department of Pathology ⁴

Harbor-UCLA Medical Center

1000 West Carson Street

Los Angeles, CA 90509

Running Title: Suprasellar Mass in Chagas' Disease

Address reprints to:

Theodore C. Friedman, MD, PhD

Department of Endocrinology, Metabolism, and Molecular Medicine

Charles Drew University of Medicine & Science

1731 East 120th Street

Los Angeles, CA 90059

(310) 668-5197

(323) 563-9324 (fax)

tefriedm@cdrewu.edu

Abstract

Although intrinsic pituitary lesions are the most common cause of hypopituitarism, suprasellar masses can produce similar symptoms. The differential diagnosis of a suprasellar mass includes cystic lesions, tumors, granulomatous disease, and infection. The etiology is not always obvious, and despite extensive work-up, may remain elusive. A 28-year-old Mexican man presented with complaints of headache and weakness for two weeks duration. He became increasingly lethargic and an MRI revealed a two centimeter suprasellar mass. Testing of the hypothalamic-pituitary axis suggested panhypopituitarism. He was prescribed treatment with hydrocortisone, DDAVP, and levothyroxine. Open craniotomy and biopsy of the hypothalamus revealed marked inflammation with plasma cells, histiocytes, and small lymphocytes. Light microscopy revealed macrophage-contained leishmania-like organisms although results were not immediately available. Pathological data was consistent with acute infection by *Trypanosoma cruzi*. Despite supportive efforts, the patient expired two months after presentation.

This case illustrates the difficulty of diagnosing and the potential rapid mortality of a suprasellar mass. Because of the wide consideration of etiologies, a tissue diagnosis is needed. However, as this case illustrates, a definitive tissue diagnosis is not always possible, even following biopsy during open craniotomy.

Key words: Chagas' disease, suprasellar, hypothalamus, hypopituitarism

Introduction

Although pituitary adenomas are the most common cause of a sellar mass, nonpituitary sellar or parasellar masses can present similarly (1). The differential diagnosis of nonpituitary sellar and parasellar masses includes embryonic remnant cystic lesions (2), primary and metastatic tumors, granulomatous infectious processes (3, 4) and abscess formation (5). Appropriate treatment requires correct diagnosis, which may be elusive due to nonspecific imaging characteristics and the difficulty of obtaining an adequate biopsy from the hypothalamus/suprasellar region.

In the present report, we describe a young, previously healthy male who presented with a two-week history of headache and malaise. MRI revealed a 2-cm suprasellar mass associated with panhypopituitarism. An infectious disease workup was negative. Biopsy was performed to determine the etiology. The unusual biopsy findings are reported to expand the possible etiologies to be considered in similar cases.

Case Report

A 28-year-old Mexican man presented to the emergency department with complaints of severe bitemporal headache for two weeks duration. Associated symptoms included generalized weakness, poor sleep and subjective dizziness. He denied any photophobia, neck pain, nausea, vomiting, abdominal discomfort, or any alleviating or exacerbating factors. His past medical history was significant for type 2 diabetes, for which he took no medications. He had no history of previous surgery. The patient was a college-educated computer engineer who lived with his immediate family and denied any ethanol abuse, illicit drug use or tobacco use. Recent travel

history revealed a trip to Mexico five months prior to presentation. Family history was unknown.

On physical examination, the patient appeared to be well-developed, with normal secondary male features. He was afebrile, heart rate 98, respiratory rate 20, and blood pressure 117/79. He appeared alert and was oriented to person, place, time, and situation. Head and neck exam revealed normal pupillary reactions to light, and cranial nerve functions were intact. His neck was supple and there was no lymphadenopathy noted. Chest exam was clear to auscultation, and abdominal exam revealed no palpable masses or hepatosplenomegaly. There were no visible skin lesions or abnormal pigmentation noted.

Initial laboratory test results are shown in Table 1.

On admission the patient underwent CT scanning of the head without contrast, which was initially read as negative for mass or intracerebral hemorrhage. Lumbar puncture was also performed on the first hospital day with the following results: glucose 42 mg/dL, protein 172 mg/dL, RBC 1/mm³, WBC 48/mm³ (1% polymorphonuclear cells, 97 lymphocytes, 2 monocytes). Gram stain, India ink, AFB stains, cultures and cryptococcal antigen were negative. The patient was admitted and started on treatment with ceftriaxone, ampicillin, and acyclovir for probable meningitis.

The patient's mental status began to decline despite treatment and MRI of the brain was performed one week after admission. MRI revealed a suprasellar poorly defined mass of approximately 2 cm diameter, described as an area of enhancement extending symmetrically from the region of the optic chiasm into the hypothalamus, both medial temporal lobes, left greater than right, and midbrain (Figure 1). Repeat MRI imaging several weeks later revealed

enlargement of the lesion which involved the hypothalamus, with further extension into the left temporal lobe (Figure 2).

Testing of the hypothalamic-pituitary axis is shown in Table 1. The patient developed intermittent episodes of diabetes insipidus. He was placed on hydrocortisone 50 mg IV q 12 hours, DDAVP, and levothyroxine.

Further studies included a normal testicular ultrasound. CT of the chest/abdomen/pelvis did not reveal any tumor, lymphadenopathy, or other mass. A PPD was placed and was positive at 20 mm induration. HIV testing was negative. An extensive infectious disease work-up including multiple bacterial, acid-fast bacilli (AFB), viral, and fungal cultures of blood and cerebrospinal fluid were all negative.

Serological studies of plasma and cerebrospinal fluid were negative for antibodies against *Coccidioides*, *Toxoplasma*, *Histoplasma*, *Trypanosoma cruzi*, *Bartonella*, *Borrelia burgdorferi*, *Leishmania* (*L. donovani*, *L. braziliensis*, *L. mexicana*, *L. tropica*), West Nile virus, Arbovirus, Coxsackie A virus, Epstein-Barr virus, Echovirus, Herpes 1 and 2 viruses, syphilis, Varicella virus, adenovirus, and enterovirus. Serum and CSF ACE (Angiotensin-1-converting enzyme) levels were within normal range. The patient was placed on empiric antifungal (Amphotericin B), four drug anti-tuberculosis, and broad-spectrum antibiotic (vancomycin, imipenem, metronidazole) therapy early in the hospital course, without clinical response.

The patient's condition continued to deteriorate, and he became obtunded by the third week of hospitalization. On hospital day 30, hypothalamic biopsy by open craniotomy using a lateral frontal approach was performed. The meningeal and parenchymal biopsy revealed a solid sheet of plasma cells, admixed mature and reactive lymphocytes, macrophages in focal necrosis, and scattered large reactive-appearing astrocytes in small numbers (Figure 3). The inflammation

was centered predominantly around small vessels with disrupted basement membrane and hypertrophic endothelial cells. Immunohistochemistry demonstrated polyclonality of the B-cells and numerous T cell lymphocytes. Toxoplasma and Herpes Simplex antigens were negative by immunohistochemistry. Markers of Langerhans cell histiocytosis were negative (CD1a and S100).

Several slides stained with hemotoxylin and eosin, Giemsa, and period acid shift (PAS) showed multiple oval to round predominantly extracellular trypanosome-like parasites, 2-4 microns in diameter (Figure 4). There were occasional intracellular microorganisms in histiocytes. The trypanosome-like parasites showed a clear membrane limited structure with a round nucleus and a bar-shaped kinetoplast which are typical of the amastigote form of *Trypanosoma cruzi* in the acute stage of infection (6).

The patient remained on mechanical ventilation and had no purposeful movements or response to verbal stimuli for the remainder of the hospital course. Unfortunately the biopsy results were not available for several months (while several pathology consults were reviewing the data), and the patient expired two months after initial presentation to the emergency department. The empiric antimicrobial therapy did not include coverage against *Trypanosoma* species {Nifurtimox, available on an experimental basis from the Centers for Disease Control (CDC)}.

A Coroner's autopsy was performed to rule out a contagious infection. Light microscopic studies found that the dominant pathology in the brain was a polymorphous infiltrate composed primarily of lymphocytes, plasma cells, and phagocytic macrophages with superimposed hypoxic encephalopathy (not shown). The findings were primarily seen as perivascular inflammation around small, thin-walled vessels. The hypothalamus was necrotic, but scattered foci of the

inflammatory process had spread into the brain stem and central white matter. Again, PAS-staining demonstrated free and intracellular structures corresponding to the microorganisms of Leishmanoid type. Histiocytosis X was ruled out by immunohistochemistry and electron microscopy. No microorganisms were identifiable in the small amount of autopsy material submitted for electron microscopy from the hypothalamus.

Discussion

This case illustrates the difficulty in diagnosis and the potential mortality of a rapidly enlarging suprasellar mass with panhypopituitarism. Although the patient reported only two weeks of headache, the patient had biochemical evidence of profound central hypothyroidism, central adrenal insufficiency (low cortisol for an acutely ill state) and hypogonadism. Although the majority of patients with severe acute illness have hypercortisolemia, low cortisol levels may be found in 10 - 20% of acutely ill patients (7-9). Thus, low cortisol argues against the possibility, but does not exclude the possibility that the central hypothyroidism and hypogonadism were due to acute illness. The differential diagnosis, including tumor, granulomatous disease and infection was pursued on many fronts. Because of his age and sex, the patient was evaluated for testicular tumor by clinical exam, testicular ultrasound, alpha-fetoprotein, and beta-HCG levels and all were normal. CT scan of the chest, abdomen, and pelvis did not reveal any significant findings such as masses or lymphadenopathy. Although the patient had a positive PPD for tuberculosis, acid-fast bacilli staining of the CSF and biopsy specimen were negative, and the patient did not clinically respond to the standard four anti-tuberculosis medication regimen. Extensive infectious disease work-up did not provide further clues to the diagnosis, and the patient did not improve despite several weeks of therapy with

broad- spectrum antibiotics, antifungal, and anti-tuberculosis medications. After brain biopsy, the patient continued to deteriorate despite maximal supportive therapy and eventually expired.

The finding of trypanosome-like organisms, characteristic of Chagas' disease, in this setting of hypopituitarism has not been reported previously. Acute disease has been reported to cause tumor-like masses of polymorphous chronic granulomatous inflammation in the central nervous system in immunocompromised individuals. (10-13). As the patient traveled to Mexico 5 months prior to presentation, it is possible that he was infected with *T. cruzi* during that trip and developed an acute form of Chagas' disease in the subsequent months, although an incubation time of 5 months is longer than expected. Adults without obvious immunosuppression have not been reported to develop inflammatory pseudotumors with *T. cruzi* infection, as the vigorous inflammatory response may limit the infection in most adults exposed to the organism.

Extensive involvement of the heart and organomegaly of other organs due to chronic destruction and inflammation was not apparent from the coroner's autopsy. This suggests an acute onset in this patient. The negative antigen titer for *T. cruzi* on presentation may have reflected an early humoral response defect in this person. Although the numbers of plasma cells exceeded any other component in the inflammatory infiltrate of the biopsy specimen, there were no plasma cells containing Russell bodies in the biopsy specimen. The vigorous inflammatory response probably reduced the number of identifiable organism in the small hypothalamic biopsy.

In conclusion, this is a case report of a rapidly enlarging suprasellar mass that proved to be an inflammatory pseudotumor associated with trypanosome-like organisms in a young, immunocompetent adult. Although rare except in young children and patients with AIDS, brain involvement in acute Chagas' disease may produce tumor-like masses even in the

immunocompetent adult. This suprasellar mass led to hypopituitarism. To our knowledge, this is the first report of a suprasellar mass due to acute Chagas' disease leading to hypopituitarism.

Acknowledgments

T.C.F. is supported by a Center of Clinical Research Excellence grant (U54 RR14616-01) and an NICHD Reproductive Center of Excellence (U54 HD41748) to Charles R. Drew University of Medicine & Sciences.

References

1. Freda PU, Post KD Differential diagnosis of sellar masses. *Endocrinol Metab Clin North Am* 1999; 28:81-117, vi.
2. Okamoto S, Handa H, Yamashita J, Ishikawa M, Nagasawa S Computed tomography in intra- and suprasellar epithelial cysts (symptomatic Rathke cleft cysts). *AJNR Am J Neuroradiol* 1985; 6:515-9.
3. Florakis D, Kontogeorgos G, Anapliotou M, Mazarakis N, Richter E, Bruck W, Piaditis G Isolated pituitary granuloma by atypical Mycobacterium in a nonimmunosuppressed woman. *Clin Endocrinol (Oxf)* 2002; 56:123-6.
4. Mohazab HR, Langer BG, Ramsey RG Intracranial blastomycosis presenting as a suprasellar mass: MR findings. *J Comput Assist Tomogr* 1997; 21:845-7.
5. Erdogan G, Deda H, Tonyukuk V Magnetic resonance imaging and computerized tomography images in a case of pituitary abscess. *J Endocrinol Invest* 2001; 24:887-91.
6. Koneman EW, Allen SD, Janda WM, Schreckenberger PC, Winn J, W.C. 1997 Color Atlas and Textbook of Diagnostic Microbiology, 5th ed. Lippincott, Philadelphia
7. Cooper MS, Stewart PM Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348:727-34.
8. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf)* 2004; 60:29-35.
9. Hamrahian AH, Oseni TS, Arafah BM Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 2004; 350:1629-38.
10. Del Castillo M, Mendoza G, Oviedo J, Perez Bianco RP, Anselmo AE, Silva M AIDS and Chagas' disease with central nervous system tumor-like lesion. *Am J Med* 1990; 88:693-4.
11. De Queiroz AC Tumor-like lesion of the brain caused by Trypanosoma cruzi. *Am J Trop Med Hyg* 1973; 22:473-6.
12. Pitella JE, Meneguette C, Barbarosa A Histopathological and imunohistochemical study of the brain and heart in the chronic cardiac form of Chagas' disease. *Arquiv Neuropsiquiatr* 1993; 51:8-15.
13. **Vinters HV, Anders KH, Browning RA** 1989 Neuropathology of AIDS. CRC Press, Boca Raton

Figure Legends

Figure 1. Axial FLAIR sequence of the MRI of the brain at the upper midbrain level demonstrates edema and slight mass effect (arrows) in both medial temporal lobes, left greater than right, and also in the hypothalamus (grey arrow) and midbrain. There is also very mild edema in the inferior left frontal lobe.

Figure 2. Post-biopsy post-contrast coronal T1WI of the MRI of the brain reveals enhancement (white arrows) in bilateral hypothalamic (grey arrow), thalamus, right caudate head, and bilateral medial temporal lobes, left greater than right. There is post surgical change in the right temporal region from recent biopsy and compression of the right lateral ventricle (checkered arrow). As figure 2 is a coronal cut and figure 1 is an axial cut, the two MRIs cannot be directly compared.

Figure 3. Lower power view of the biopsy sample revealed mixed chronic inflammation with predominant plasma cells, lymphocytes, histiocytes, and gliocytes (H&E stain. 40X).

Figure 4. Higher power view of the biopsy sample showing numerous extracellular (white arrows) and occasional intracellular (grey arrow showing trypanosome-like microorganisms in a histiocyte) 2-4 micron amphophilic globules resembling microorganisms, consistent with Trypanosomal amastigotes (arrows) on H&E-stained slides (H&E stain. 100X oil).

Table 1: Laboratory Evaluations On admission:

Na	135 mEq/L	Ca	8.9 mg/dL	WBC	$9.6 \times 10^3/\text{mm}^3$
K	3.9 mEq/L	Mg	2.1 mg/dL	Hgb	14.3 g/dL
Cl	98 mEq/L			Hct	42.6 %
HCO ₃	27 mEq/L	Albumin	4.0 g/dL	Plt	$301 \times 10^3/\text{mm}^3$
BUN	16 mg/dL	AST	17 U/L		
Cr	0.7 mg/dL	ALT	25 U/L		
Glu	84 mg/dL	Alk Phos	42 U/L		

During hospital course:

Cortisol (time 1400) 6.1 $\mu\text{g/dL}$ (normal PM value 2-10 $\mu\text{g/dL}$)

Prolactin < 0.6 ng/mL (on dopamine for BP support)

Free T4 0.18 ng/dL (0.71-1.85 ng/dL)

TSH < 0.03 IU/mL (0.32-5.0 IU/mL)

Testosterone 15.4 ng/dL (200-1200 ng/dL).

CD4 count $621/\text{mm}^3$ (490-1740/ mm^3)

Fig. 1



Fig. 2

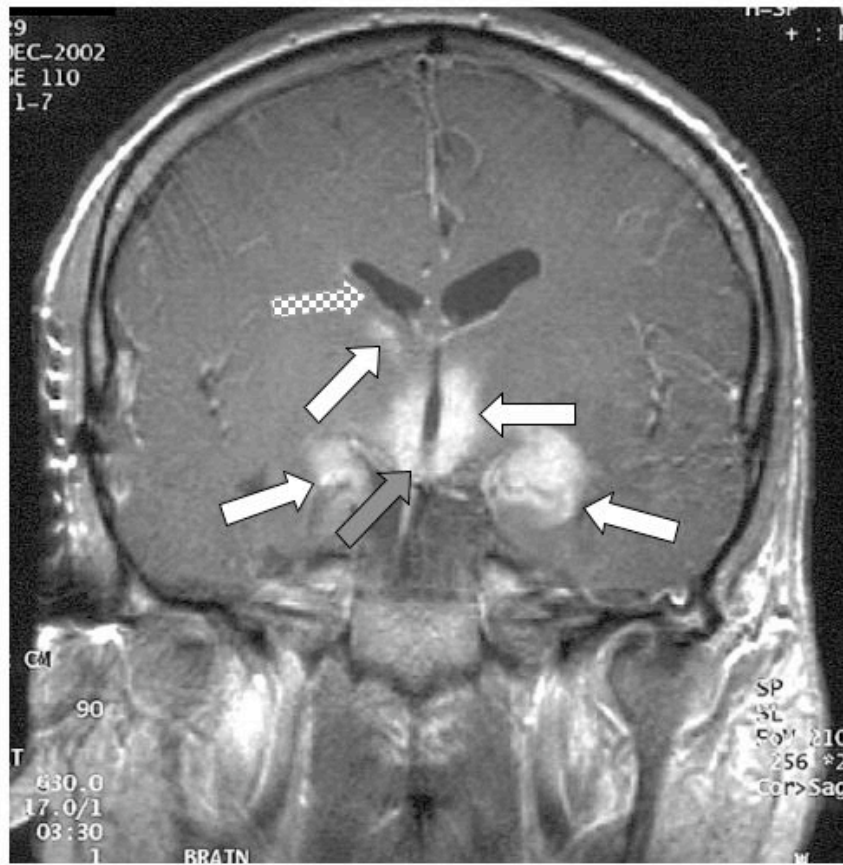


Fig. 3

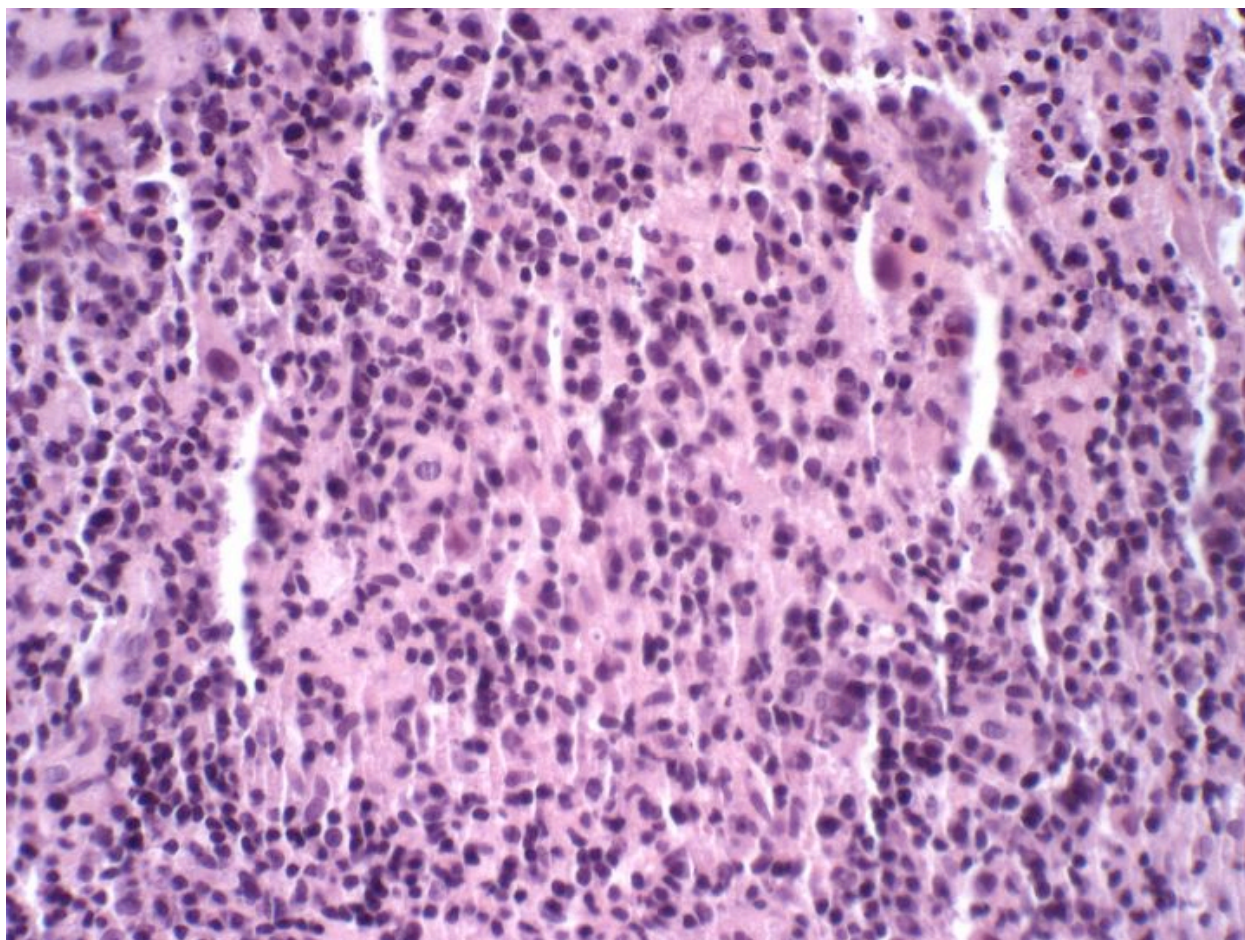


Fig. 4

