Cytomegalovirus Infection of the Thyroid in Immunocompromised Adults

THOMAS S. FRANK, M.D., VIRGINIA A. LiVOLSI, M.D., AND ANN MARIE CONNOR, M.D.

Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Received April 18, 1986

Cytomegalovirus (CMV) inclusions were discovered at autopsy in the thyroid follicles in five immunocompromised adults, four of whom had acquired immune deficiency syndrome (AIDS). Although reports of viral infections of the thyroid are uncommon in adults, our experience suggests that the thyroid gland may be commonly involved in patients with disseminated CMV, and the possibility exists that CMV infection of the thyroid has the potential to cause clinical dysfunction.

INTRODUCTION

Cytomegalovirus (CMV) is a herpesvirus typically linked to infections in neonates as well as in immunocompromised adults. Increasingly, CMV is recognized as one of the hallmark infective agents in the acquired immune deficiency syndrome (AIDS). In this patient population, the pathologic findings of CMV infection have been characterized for several target organs including lung [1], eye [2], and gastrointestinal tract [3]. Somewhat less common are reports of CMV infections of endocrine organs, and the potential for endocrine dysfunction due to CMV is as yet unknown. There have been infrequent reports of CMV inclusions of the thyroid; most of these describe inclusions within endothelial rather than epithelial cells [4] or fail to specify which [5]. A recent case report of a patient with AIDS [6] included the incidental finding of CMV inclusions in thyroid epithelial cells, but there was no discussion of this patient’s thyroid function. Our experience suggests that CMV inclusions in thyroid epithelial cells may be a common phenomenon in immunocompromised patients with disseminated CMV infection. We wish to report five recent cases of immunocompromised adults (four of whom had established AIDS) in which infection of the thyroid by CMV was documented.

MATERIALS AND METHODS

The records of nine hundred adult autopsies performed at our institution between January 1, 1980, and June 15, 1985, were reviewed, showing twelve patients with AIDS (and one severely immunocompromised patient with idiopathic thrombocytopenic purpura) who had pre- or post-mortem evidence of CMV infection of at least one organ system. Where available, routinely fixed, paraffin-embedded, hematoxylin- and eosin-stained sections of thyroid gland were examined for morphologic evidence of CMV infection of epithelial cells. Cells were considered infected if they demonstrated characteristic morphologic changes (discussed below). To confirm that this infection...
was due to CMV and not herpes simplex virus (HSV), the tissue sections were stained for HSV antigens, utilizing a sensitive immunoperoxidase method which has no cross-reactivity with CMV, according to the manufacturer (Ortho Diagnostic Systems Inc., Raritan, New Jersey).

Where cited, thyroxine (T₄) and 3,5,3'-triiodothyronine (T₃) uptake were measured by competitive and non-competitive radioimmunoassay, respectively. The free thyroxine index is calculated by multiplying the ratio of patient:control T₃ uptake by the patient's T₄ level, thus representing a relative index of circulating free thyroxine. Thyrotropin (thyroid stimulating hormone, TSH) levels were determined by radioimmunoassay in cases 3 and 4, and by radioiodinated monoclonal antibodies in case 5.

Where reported, T lymphocyte helper:suppressor assays (OKT4:OKT8) were performed with murine monoclonal antibodies stained with fluorescein-labeled antimouse immunoglobulin and enumerated with laser flow cytometry (Ortho Spectrum III, Ortho Diagnostic Systems).

In case 2, anti-CMV serology was assayed by complement fixation, using whole-virus antigen (MA Biologic Products). In case 5, CMV was cultured in a human cell line, MRC-5.

CASE REPORTS

Case 1

The first patient was a 47-year-old bisexual white male who was found to have disseminated Kaposi's sarcoma in December 1982; the following month he developed Pneumocystis carinii pneumonia, which was successfully treated at that time. Over the following year his Kaposi's sarcoma progressed despite radiation and chemotherapy. In April 1984, he presented with a complaint of progressive dyspnea. Chest radiography demonstrated severe interstitial lung disease as well as bilateral pleural effusions; this was thought clinically to represent pulmonary involvement by Kaposi's sarcoma. On his second hospital day thoracentesis was performed. The pleural fluid contained 600 WBC/mm³ (93 percent mononuclear, 6 percent lymphocytes, 1 percent neutrophils) and 30,000 RBC/mm³, and total protein of 3.3 g/dl (serum = 4.7 g/dl). No abnormal cytology was seen, and cultures of the pleural fluid were negative. The patient received one cycle of chemotherapy for his Kaposi's sarcoma as well as aggressive antimicrobial therapy for Klebsiella sepsis. Although he became afebrile, his dyspnea worsened. His mental status declined and he became unresponsive. On hospital day 27, he became severely hypotensive and subsequently expired. The patient showed no clinical evidence of thyroid dysfunction, and no thyroid function tests were performed during his hospitalization. CMV infection was not documented pre-mortem.

Case 2

The second patient was a 28-year-old bisexual black male who was diagnosed as having AIDS after presenting in June 1983 with Pneumocystis carinii pneumonia. At that time his T-cell subsets were measured, demonstrating T₄ = 15.0 percent (normal = 43.5 percent ± 7.9 percent) and T₈ = 51.2 percent (normal = 22.6 percent ± 6.2 percent), with a T₄:T₈ ratio of 0.20 (normal = 2.0 ± 0.8). He also had documented anergy. Although his pneumonia was initially treated successfully, it recurred several months later. In June 1984, M. avium-intracellulare was isolated
from bronchial tissue, cerebrospinal fluid, and stool. He experienced episodes of severe candidal esophagitis. Anti-CMV titers increased from 1:32 in early September to 1:256 three weeks later. Biopsy of tongue ulcerations in early October showed cytomegalovirus nuclear inclusions as well as herpetic inclusions. The patient expired three days later. The patient had no clinical signs of thyroid dysfunction, and no thyroid function tests were performed during his hospitalization.

Case 3

The third patient was a 28-year-old bisexual black male who was diagnosed as having AIDS in May of 1984 when he presented with *Pneumocystis carinii* pneumonia. Measurement of his T-cell subsets demonstrated T4 = 2.0 percent, T8 = 53.9 percent, and T4:T8 ratio = 0.31 (normal values as above), and he was anergic. He had evidence of prior hepatitis B infection, and he suffered at that time from oral candidiasis and herpes labialis. The patient's pneumonia eventually resolved, but seven months later (January 1985) the patient was readmitted when chest radiography demonstrated increased interstitial markings. Bronchoscopic washings and biopsy disclosed recurrent *Pneumocystis carinii*; cells demonstrating morphologic evidence of cytomegalovirus infection were also seen. Thyroid function tests were performed February 19, 1985, for hypothermia, demonstrating T₄ = 11.1 µg/dl (normal 4.2–11.5 µg/dl), T₃ uptake = 0.92 (normal 0.85–1.17), free thyroxine index (FTI) = 10.2 (normal 3.8–11.8), and thyroid stimulating hormone (TSH) = 2.4 µIU/ml (normal <6.5 µIU/ml). Thyroid function tests were repeated on March 26, 1985, for undocumented reasons, and showed T₄ = 4.9 µg/dl, T₃ uptake = 1.19, FTI = 5.8, and TSH =1.2 µIU/ml. The patient experienced progressive dyspnea and hypoxia despite aggressive oxygen supplementation and expired on April 7, 1985.

Case 4

The fourth patient was a 34-year-old Haitian immigrant who was evaluated during pregnancy. In May of 1981, six months after her arrival in the U.S., she complained of fatigue, malaise, and diarrhea. One month later she was admitted to another hospital with cough, fever, abdominal pain, diminished appetite, and anemia. Chest radiography demonstrated a left lower lobe pneumonia and possible hilar lymphadenopathy. A tuberculin-purified protein derivative (PPD) was nonreactive, but subsequent sputum smears showed acid-fast organisms that proved by culture to be *M. avium-intracellulare*. On August 1, 1981, she was transferred to our hospital with declining respiratory function, anemia, and cachexia. Thyroid function tests were ordered on admission as part of a broad nonspecific endocrinologic evaluation, and showed T₄ = 3.6 µg/dl (normal 4.2–11.5 µg/dl), T₃ uptake = 1.00 (normal 0.85–1.17), and FTI = 3.6 (normal 3.8–11.8). These tests were repeated on August 26 for undocumented reasons and were essentially unchanged; a TSH level was also obtained at that time and was 4.0 µIU/ml (normal <6.5 µIU/ml). In spite of intensive antimicrobial therapy, including four anti-mycobacterial drugs, her respiratory status declined and her fevers continued. She became increasingly cachectic. She underwent spontaneous abortion August 25, heralded by an acute decline in her platelet count. She suffered unremitting bleeding from multiple sites, including the gastrointestinal tract. Her mental status declined rapidly, and she expired September 1, 1980. The diagnosis of AIDS was made retrospectively on the basis of autopsy findings which included Kaposi's sarcoma in the small intestine; CMV infection was not documented until post-mortem examination.
Case 5

The fifth patient was a 30-year-old black female with a history of insulin-dependent diabetes mellitus, hypertension, congestive heart failure, chronic renal failure, and anemia, who was admitted in December of 1984 for evaluation of worsening renal function and lower extremity edema. Shortly before her admission on December 23, 1984, thyroid function tests were performed because of persistent congestive heart failure. At that time, $T_4 = 5.1 \, \mu g/dl$ (normal 4.2–11.5 $\mu g/dl$), $T_3$ uptake = 0.42 (normal 0.85–1.17), FTI = 2.1 (normal 3.8–11.8), and TSH = 1.0 $\mu IU/ml$ (normal 0.5–5.0 $\mu IU/ml$); TSH measured again on January 4, 1985, was 0.9 $\mu IU/ml$. Soon after her admission she was found to have declining platelet counts; a diagnosis of idiopathic thrombocytopenic purpura (ITP) was made and the patient was placed on high doses of intravenous steroids. Her respiratory status declined, which was attributed to cardiogenic pulmonary edema on the basis of an elevated pulmonary capillary wedge pressure (PCWP). After her PCWP was normalized by aggressive fluid management (including peritoneal dialysis), however, chest X-ray indicated a persistent bilateral pulmonary infiltrate, and she experienced continued fever. An open lung biopsy on January 21 showed chronic interstitial inflammation as well as CMV pneumonia with diffuse alveolar damage; cultures of that tissue grew CMV in two days. *Candida albicans* and *tropicalis* were isolated from bronchial brushings, stool, and Tenckhoff catheter. Her respiratory status continued to decline despite aggressive therapy, and she expired on January 31, 1985.

RESULTS

At our institution, autopsy records were available for twelve patients with AIDS who died between January 1, 1980, and June 15, 1985, as well as one severely immunocompromised patient without documented AIDS (case 5). The thyroid gland was available for examination at autopsy in seven of these patients, and of these, five had histologic evidence of CMV infection of thyroid epithelium (see below). The thyroid glands of four of these five patients were grossly unremarkable in appearance, weight (where available), and consistency. In case 5, however, sectioning the thyroid revealed a solitary 2 mm white nodule which proved histologically to be a focus of Aspergillus infection.

Microscopically, CMV inclusions were seen in thyroid epithelial cells in the five patients cited. Several histologic criteria easily distinguish cellular infection by CMV from that caused by other viruses, including other members of the herpesviruses group. Such criteria include cytomegaly; the cells are extremely enlarged to about three to four times the diameter of their uninfected counterpart cells. In addition, CMV infection results in a large basophilic intranuclear inclusion which is homogeneous and surrounded by a clear halo. Last, CMV infection produces morphologically distinct intracytoplasmic inclusions. These inclusions, seen in all of the cited cases, are usually basophilic, smooth, and round, and are composed of aggregated virions and lysosomes (Fig. 1A, B). Infection by CMV is morphologically distinguishable from herpes simplex virus (HSV) by several criteria. Cells infected by herpes simplex virus (HSV) are only rarely cytomegalic, do not show a clear halo around the intranuclear inclusion, and do not contain cytoplasmic inclusions. Reliable immunohistochemical anti-CMV stains for fixed and embedded tissue are not currently available, but immunohistochemical stains for HSV were performed on thyroid tissue from four of the five cases presented above and were negative (tissue was not available from case 4). Thus, we
conclude that the specific diagnosis of cytomegalovirus infection of the thyroid has been established morphologically in our cases.

Although reports of CMV infection of other organs have described inclusions in endothelial cells, the thyroid inclusions in our cases were seen only in epithelium. There was some variation from case to case in the number of follicular cells that showed these changes; cases 1, 2, and 4 had zero to one infected cells per 10 high-power field (hpf, 400 ×), while cases 3 and 5 had two infected cells per 10 hpf overall as well as several focal areas showing 5 per 10 hpf. The large intranuclear inclusions made identification of most of the infected cells possible at lower magnification (50–100 ×). No inflammatory response to the CMV-infected cells was seen in any of the organs, although, in case 5, numerous abscesses due to Aspergillus were present. Other organs infected included the adrenal glands (case 1), tongue (case 2), lung and parathyroids (case 3), lungs, pituitary, and adrenal glands (case 4), and lungs, stomach, and endocervix (case 5).

Of the thirteen immunocompromised patients whose records were reviewed, nine had post-mortem evidence of CMV infection. In four cases (cases 1, 2, 4, and 5) this evidence consisted solely of the histologic findings as described above; no cultures were
obtained at autopsy. In two patients (including case 3), morphologic findings were confirmed by positive post-mortem cultures of blood or lung tissue. In three cases, post-mortem evidence for CMV infection consisted solely of blood or lung cultures. Overall, four of these patients (three of whom had infection of the thyroid) had pre-mortem documentation of CMV infection consisting of pulmonary histology confirmed by culture in one (case 5), pulmonary cytology alone in another (case 3), a tongue biopsy in the third (case 2), and blood culture in the fourth. In the remaining five patients, CMV infection was unsuspected until autopsy.

Three of the patients with CMV infection of the thyroid had thyroid function tests performed within six weeks of death, and in two (cases 4 and 5), the free thyroxine indices were abnormal (low). However, in neither of these patients were there specific clinical indications of thyroid dysfunction.

The clinical and pathologic findings of the patients with CMV infection of the thyroid are summarized in Table 1.

**DISCUSSION**

Reports of viral infections of the thyroid gland, including infection by cytomegalovirus, are extremely uncommon in adults. Some European studies have implicated viral infection of the follicular epithelium in patients with subacute thyroiditis [7,8]. However, many authors believe that actual infection does not take place, but that the pathologic and functional changes of subacute thyroiditis reflect the thyroid’s response to systemic viremia [9]. There have been only scattered case reports of adults with disseminated CMV who were found at autopsy to have inclusions in the thyroid

**TABLE 1**

Autopsy and Laboratory Findings in Patients with Thyroid Cytomegalic (CMV) Inclusions

| Case | Thyroid Function Tests* | Interval Between Thyroid Function Tests and Death | Other Sites of CMV Inclusions |
|------|------------------------|-----------------------------------------------|------------------------------|
| 1    | ND                     | —                                             | Lungs, adrenal medulla       |
| 2    | ND                     | —                                             | Tongue                      |
| 3    | T₄ = 11.1 µg/dl, T₃ uptake = 0.92, FTI* = 10.2, TSH² = 2.4 µIU/ml | 48 days                         | Lungs, liver, kidneys, adrenals, pancreas, large intestine, small intestine, para-thyroids |
|      | T₄ = 4.9 µg/dl, T₃ uptake = 1.19, FTI = 5.8, TSH = 1.2 µIU/ml | 12 days                         |                              |
| 4    | T₄ = 3.6 µg/dl, T₃ uptake = 1.00, FTI = 3.6 | 30 days                         | Lungs, small intestine, pituitary, adrenals, hilar lymph nodes |
|      | T₄ = 3.5 µg/dl, T₃ uptake = 1.02, FTI = 3.5, TSH = 4.0 µIU/ml | 6 days                         |                              |
| 5    | T₄ = 5.1 µg/dl, T₃ uptake = 0.42, FTI = 2.1, TSH = 1.0 µIU/ml | 39 days                         | Lungs, stomach, endocervix  |
|      | TSH = 0.9 µIU/ml       | 27 days                        |                              |

*Normal ranges: T₄: 4.2–11.5 µg/dl; T₃ uptake: 0.85–1.17; free thyroxine index: 3.8–11.8; thyroid stimulating hormone: <6.5 µIU/ml (cases 3 and 4), 0.5–5.0 µIU/ml (case 5)

ND, Not Done

*FTI, free thyroxine index

²TSH, thyroid stimulating hormone
follicles [6,10], including one patient with AIDS [6]. Our experience suggests, however, that the thyroid gland is frequently involved in immunocompromised patients with disseminated CMV.

At first the presence of CMV in the thyroid glands of severely immunocompromised individuals with CMV infection elsewhere may not seem remarkable. When viewed from the context of the rarity of documented viral infections of the thyroid, however, these observations may indeed be significant. It is unclear exactly how CMV infects the thyroid. The cases in which cytomegalovirus infection was documented before death (cases 2, 3, and 5) may represent reawakening of latent infection or reactivation, but it seems more likely that they instead signify primary CMV infection. Since anti-CMV antibody titers were not generally available in these cases, however, it was impossible to distinguish between primary infection and reactivation at autopsy. The cases in which pulmonary manifestations were most prominent presumably represent cases in which the focus of primary infection (or reactivation) was pulmonary. CMV is known to produce viremia, probably by travelling within leukocytes (specifically monocytes) in the blood [11]. It thus seems likely that, in most of our cases, CMV infection of the thyroid results from hematogenous spread from the lung. In one of our cases in which CMV infection of the thyroid was present, however, no cytomegalic inclusions were seen in the examined sections of lung (case 2). This might represent so-called "histologically occult" cytomegalovirus infection in which demonstrably infected cells can appear histologically normal [12]. Such a process might also account for some cases in which cytomegalovirus can be cultured from tissue that lacks the histologic manifestations of CMV infection.

The clinical importance of our observations lies in the potential of CMV infection of the thyroid to lead to compromised function. Currently, the evidence that suggests a correlation between CMV inclusions in the thyroid gland and clinical dysfunction is scant and unconvincing [13]. Of the three cited cases in which thyroid function tests were obtained, two (cases 4 and 5) had demonstrably low free thyroxine indices; however, these values must be interpreted cautiously. The temporal relationship between the thyroid function tests and actual infection is unknown; hence, the thyroid function tests may not truly reflect post-infected thyroid status. More important, it is impossible to determine whether the cytomegalovirus infection of the thyroid follicular epithelial cells was overwhelming enough to cause hypothyroidism on the basis of epithelial destruction. Such a mechanism would be analogous to that proposed for subacute granulomatous thyroiditis. In this disorder, presumed viral infection causes cytolysis of thyroid epithelium with subsequent release of stored thyroid hormone (and thus a phase of hyperthyroidism), followed by hypothyroidism as the remaining follicular epithelial cells are unable to produce sufficient thyroid hormone. Although it is possible that a similar mechanism is the cause of the abnormal thyroid function tests reported here, it should be noted that severely ill patients sometimes manifest the so-called " euthyroid sick syndrome," in which thyroid function tests indicate hypothyroidism but the patients are in fact euthyroid. The exact mechanism by which this occurs is still uncertain, although Melmed and associates have indicated that severe systemic illness may lower T₃, T₄, and the free thyroxine index by reducing extra-thyroidal mono-deiodination of T₄ [14]. It has been reported that measurement of serum reverse T₃, can discriminate between patients who are truly hypothyroid and those who are euthyroid sick [15]; in the appropriate setting this test would be of benefit in determining the presence of actual thyroid dysfunction due to CMV.
Another factor that could potentially account for some of the abnormal thyroid function tests in the cases cited is malnutrition, which often accompanies severe systemic illness. Malnutrition results in diminished thyroxine binding globulin levels, thus artificially lowering the concentration of T₃. The free thyroxine index should be unaffected by malnutrition, however, so the low FTI values seen in two of the patients cited are not explicable by this mechanism. In the absence of any identifiable process to account for the measured abnormalities in thyroid function, the possibility that CMV infection of the thyroid epithelium is responsible still exists.

Our experience indicates that the frequency of CMV infection of the thyroid may be underestimated by pathologists, even though the infected epithelial cells are usually visible at low power. Likewise, systemic CMV infection is often clinically missed in immunocompromised patients [16]. The abnormal thyroid function tests in two of the three infected patients from whom they were obtained indicate that cytomegalovirus infection of the thyroid gland might indeed result in thyroid dysfunction. Although it is not clear what clinical findings prompted the tests in the cases cited, it seems likely that no specific causes of hypothyroidism had been suspected, making interpretation of the abnormal values more difficult. We suggest that in such circumstances both clinician and pathologist be aware of the potential of CMV infection of the thyroid gland.

REFERENCES

1. Craighead JE: Pulmonary cytomegalovirus infection in the adult. Am J Pathol 63:487–504, 1971
2. Palestine AG, Rodrigues MM, Macher AM, Chan CC, Lane HC, Fauci AS, Masur H, Longo D, Reichert CM, Steis R, et al: Ophthalmic involvement in acquired immunodeficiency syndrome. Ophthalmology 91:1092–1099, 1984
3. Meiselman MS, Cello JP, Margaretten W: Cytomegalovirus colitis. Report of the clinical, endoscopic, and pathologic findings in two patients with the acquired immune deficiency syndrome. Gastroenterology 88:171–175, 1985
4. Wong TW, Warner NE: Cytomegalic Inclusion Disease in Adults. Report of 14 cases with review of the literature. Arch Pathol 74:17–36, 1962
5. Welch K, Finkbeiner W, Alpers CE, Blumenfeld W, Davis RL, Smuckler EA, Beckstead JH: Autopsy findings in the acquired immune deficiency syndrome. JAMA 252:1152–1159, 1984
6. Burt AD, Scott G, Shiach CR, Isles CG: Acquired immunodeficiency syndrome in a patient with no known risk factors: a pathological study. J Clin Pathol 37:471–447, 1984
7. Stancekova M, Stancek D, Ciampor F, Mucha V, Hnilica P: Morphological, cytological and biological observations on viruses isolated from patients with subacute thyroiditis de Quervain. Acta Virolog 20:183–188, 1976
8. Werner J, Gelderblom H: Isolation of foamy viruses from patients with de Quervain thyroiditis. Lancet ii:258–259, 1979
9. Volpe R: Subacute (de Quervain's) thyroiditis. Clin Endocrinol Metab 8:81–91, 1979
10. Macasaet FF, Holley DE, Smith TF, et al: Cytomegalovirus studies of autopsy tissue. II. Incidence of inclusion bodies and related pathologic data. Am J Clin Pathol 63:859–865, 1975
11. Myerowitz RL: The pathology of opportunistic infections. In Cytomegalovirus. New York, Raven Press, 1983, pp 161–176
12. Myerson D, et al: Widespread presence of histologically occult cytomegalovirus. Hum Pathol 15:430–439, 1984
13. Salisbury S, Embil JA: Graves disease following congenital cytomegalovirus infection. J Pediatr 92:954–955, 1978
14. Melmed S, Geola FL, Reed AW, Pekary AG, Park J, Hershman JM: A comparison of methods for assessing thyroid function in non-thyroidal illness. J Clin Endocrinol Metab 54:300–306, 1982
15. Chopra II, Solomon DH, Gershon WH, Morgenstein AA: Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. Ann Intern Med 90:905–912, 1979
16. Hui AN, Koss MN, Meyer PR: Necropsy findings in acquired immunodeficiency syndrome: a comparison of premortem diagnoses with postmortem findings. Hum Pathol 15:670–676, 1984