

# An Autopsy-Proved Case of AIDS in Taiwan

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At no other time in the history of medicine has so much progress been made in so short a time on so complicated a disease as the acquired immunodeficiency syndrome (AIDS). However, the incidence of AIDS continues to increase worldwide. Infection with human immunodeficiency virus (HIV)\* has been recognized in all areas of the world, except for Antarctica. AIDS has also been reported from many Asian countries around Taiwan, causing great public anxiety about the possible invasion of this Island by the illness.

In December 1984 an American, transiting Taiwan, with fullblown AIDS triggered our first major concern over this fatal disease.<sup>1,2</sup> One native homosexual with "possible" AIDS was reported in August 1985 further heightened our concern over the spread of this disease to the Island.<sup>3</sup> A seroepidemiologic study for HIV infection in Taiwan revealed that individuals infected with HIV do exist among the homosexual population and among hemophiliacs in Taiwan.<sup>4</sup> This report presents the clinicopathological features of the first autopsy-proved case of AIDS in a Taiwan resident with emphasis on inherent local problems in diagnosis.

**SUMMARY** The first case of AIDS positively identified in a non-foreigner in Taiwan was a 25-year-old unmarried male who had practiced homosexuality for ten years. The patient began to have abdominal pain accompanied with loose stools and weight loss in June 1985, followed by fever, cough, headache, dizziness, and loss of memory. Facial hyperpigmentation and extensive oroesophageal candidiasis were noted. Laboratory studies showed severe lymphopenia with a reversed T-helper to T-suppressor ratio, cutaneous anergy and polyclonal gammopathy. Human immunodeficiency virus (HIV) antibodies were positive by ELISA and Western blot, and the virus was isolated from the blood. At autopsy, disseminated cytomegalovirus infection, extensive CNS toxoplasmosis and early lesions of Kaposi's sarcoma were demonstrated. The detection of HIV in the adrenal medulla supports the consensus that the virus is neurotropic.

## CASE REPORT

### Clinical features

A 25-year-old unmarried male was admitted to the National Taiwan University Hospital (NTUH) on January 29, 1986 with a several-day history of severe headache, dizziness, vomiting and loss of memory.

The patient had practiced homosexuality for more than ten years with more than 100 sexual partners. In the past five years he had not traveled abroad and had had 50-60 partners among whom were three foreigners: one Swede, one American, and one of unknown nationality. His last sexual contact with foreigners

had been two years previously. Relationships with sexual partners were usually anonymous and of short term, lasting no more than a week. He usually had receptive anal intercourse, and he also practiced anilingus and fellatio. He used saliva as a lubricant, but never a condom. The patient also denied use of recreatives and devices, and of immunosuppressive drugs or blood/blood product transfusions.

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\* Previously referred to as HTLV-III/LAV, and subsequently referred to in this report as HIV in accordance with emerging and recommended usage.



He had been in good health until June 1985 when he began to have mild abdominal pain accompanied with loose stools. Medical care was not immediately sought, and the symptoms continued intermittently for approximately one month before they resolved without therapy. He stopped sexual activity at the onset of symptoms for fear of having contracted AIDS. In September 1985, intermittent fever, headache, and cough began. On November 5, he developed a high fever, chills, and a dry cough which were treated as influenza by practitioners. Gradually, but steadily, he developed lethargy and intermittent loss of memory. On November 17, 1985, he was hospitalized at the Tri-Service General Hospital because of two episodes of transient loss of consciousness accompanied with upward gazing of the eyes and extension of extremities. A total of 5-6 kgs of body weight was lost in several months, and oral thrush was noted on admission. Coarse breath sounds were heard over both lung fields. The hemoglobin was 11 gm/dl and WBC 3,800/cmm with 86% neutrophils and 2% lymphocytes. Acid-fast stain and bacterial cultures of sputum were negative. Cold agglutinins were negative. Chest x-ray showed infiltrative lesions over the right middle and left upper lung fields. No studies for *Pneumocystis carinii* were performed. He was treated with trimethoprim-sulfamethoxazole (TMP-SMX) for pneumonia of unknown etiology and with ketoconazole for oral candidiasis. He was discharged on December 18, but was readmitted on December 22 because of recurrent high fever. Therapy with TMP-SMX was resumed but side effects featuring skin rash and spiking fever developed. He was discharged on December 31 and stayed home until worsening fever, headache, vomiting and confusion brought him to NTUH on January 29, 1986.

On physical examination, the patient was a thin, chronically-ill-

appearing young man with dull reaction. Respiration was smooth. The blood pressure was 130/80 mmHg and pulse rate 78/min. The face was hyperpigmented but no skin nodules or plaques were detected. There was no lymphadenopathy. The pupils were isocoric and reacted to light promptly. There were multiple whitish patches over the oropharyngeal mucosa. The neck was supple and there was no lymphadenopathy. Lung fields were clear to auscultation. No heart murmur was heard. The abdomen was flat and soft. Neither abdominal tenderness nor hepatosplenomegaly was noted. Bowel sounds were slightly hyperactive. There was no lower leg edema. The anal sphincter tone was moderate. Neurologically, he had mild papilledema, bilateral hyperreflexia in the limbs and a right-sided Babinski's sign.

He was treated with steroids, TMP-SMX and ketoconazole. TMP-SMX was discontinued the next day because of a drug reaction consisting of skin rash and fever. After the acute skin rash and systemic toxicity had abated, the brownish hyperpigmentation of the face and upper extremities intensified and the patient was progressively debilitated. He became less and less responsive to calls, and gave nearly no verbal response. An episode of apnea and cardiac arrest occurred on March 1 and he expired the next day.

#### Laboratory findings

CBC showed a hemoglobin of 11.9 gm/dl, WBC of 3,800/cmm with 82% neutrophils, 10% monocytes, 7% lymphocytes, and 1% basophils. The absolute lymphocyte count was 266/cmm. Routine urinalysis was negative. Arterial blood gas analysis was normal. Repeated studies using acid-fast stains and sucrose floatation failed to demonstrate *Cryptosporidium* or other parasites in the stool. Endoscopic examination showed severe esophagitis with whitish plaques in

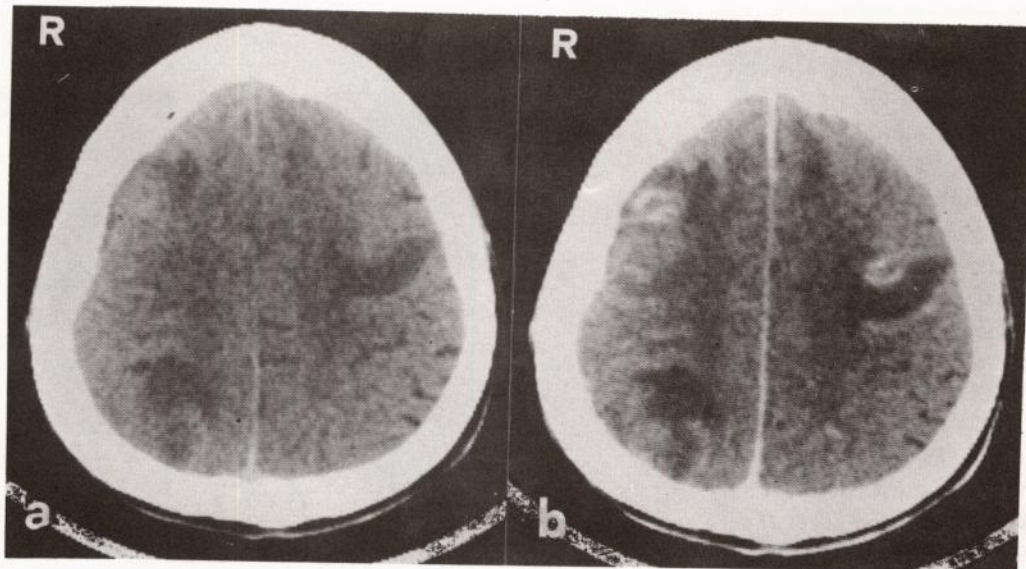
the upper esophagus, and ulcers and erosions with irregularity and thickening of mucosa in the lower part of the esophagus. Examination of biopsy specimens proved esophageal candidiasis. Lumbar puncture showed an opening pressure of 160 mm/H<sub>2</sub>O, protein 120 mg/dl, glucose 53 mg/dl, and cell count of 10/cmm, all lymphocytes. India ink preparation was negative.

An emergency computed tomography (CT) was performed which showed multiple, near isodense mass lesions with ring-like enhancement and perifocal edema at the cortico-medullary junction of the right frontal, right parietal, and left frontoparietal regions (Fig. 1). However, brain biopsy was inconclusive.

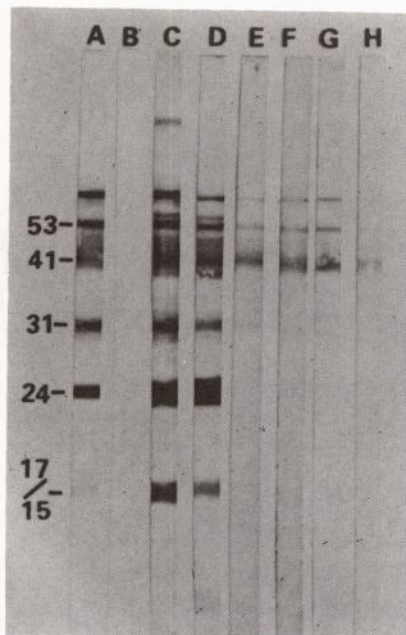
Repeated blood and cerebrospinal fluid (CSF) cultures were negative for fungi, bacteria and viruses. Throat swab yielded *Candida albicans*, *Candida glabrata* and cytomegalovirus (CMV). Stool culture also yielded *Candida glabrata*. Urine culture was positive for CMV. Blood and CSF antibody tests for varicella zoster, herpes simplex, Epstein-Barr virus, adenovirus and *Mycoplasma pneumoniae* were all negative. Serial studies for antibodies to CMV and *Toxoplasma gondii* were positive, but there was no significant fluctuation of titers.

Serum protein electrophoresis showed polyclonal gammopathy with IgG 2208 mg/dl, IgA 684 and IgM 80. HIV antibodies by ELISA (Abbott) was strongly and repeatedly positive: first run patient value 0.954 (cutoff value 0.167), repeated patient value 0.886 (cutoff value 0.189). Western blot (DuPont) gave strong reactions with gp53 and gp41, and a weak but definite reaction with gp64 (Fig. 2). A repeated Western blot (Abbott) demonstrated p24 and p16 bands but no gp41 was seen. Lymphocyte subpopulation studies showed OKT3 23%, OKT4 10%, OKT8 26%, and T4/T8 ratio 0.38; on repeated assay OKT3





**Fig. 1** Disseminated cerebral toxoplasmosis – several near isodense lesions are shown with perifocal edema and broken ring enhancement at the corticomedullary junction of the right frontal, right parietal, and left frontoparietal regions (a. plain CT, b. enhanced CT).



**Fig. 2** Western blot using DuPont strips. A = positive control serum ; B = normal serum ; C,D = sera from hemophiliacs ; E Bleed 1 (January 30) ; F = Bleed 2 (February 17) ; G = Bleed 3 (February 27) ; H = CSF.

56%, OKT4 10%, OKT8 61%, and T4/T8 0.16. Lymphocyte proliferation studies could not be carried out satisfactorily because of an insufficient number of lymphocytes. Delayed type skin tests were negative for PPD (20 U, National Institute of Preventive Medicine, ROC), *Candida albicans* (1:100, Torii, Japan), SKSD (125 U, Lederle, USA) and House dust (1:10, Domestic). However, a 1:10 solution of *Candida albicans* elicited positive skin reaction. By co-culture of the patient's lymphocytes with a lymphoid cell line developed from a local case of adult T-cell leukemia (the control cell line had no detectable virus), type D virus particles were demonstrated (Fig. 3).

#### Autopsy findings

At autopsy, the lymph nodes showed marked lymphoid depletion. A few residual lymphoid follicles remained with central hyaline sclerosis. The interfollicular and medullary areas revealed predominantly plasma cells and a few small lympho-

cytes. In the sinusoids there was reactive histiocytosis with evident phagocytosis of red blood cells, neutrophils and occasional lymphocytes. Immunoperoxidase study demonstrated marked depletion of T4 cells and relative preservation of T8 cells, resulting in a marked decrease of T4/T8 ratio. The thymus was atrophic with characteristic calcification of Hassall's corpuscles. The bone marrow showed reactive histiocytosis with relative preservation of marrow elements. There was mildly increased iron deposition.

There was a widely disseminated CMV infection. The most extensive involvement was seen in the adrenal glands and lungs. Less extensive lesions were also located in the gastrointestinal tract, lymphoreticular system, kidneys and cerebral meninges, preferentially in the endothelial cells. Both cortical and medullary cells of the adrenal glands were affected with marked hemorrhagic necrosis and inflammatory reaction of the medulla. By electron microscopy, besides typical CMV, some virus particles resembling HIV or type D retrovirus were seen in the medullary cells of the adrenal glands; they appeared as 100 nm particles with dense cylindrical cores (Fig. 4). The lung showed focal interstitial pneumonitis with numerous characteristic intranuclear CMV inclusions in the alveolar lining cells (Fig. 5) but no other opportunistic infections such as *Pneumocystis carinii*, *Mycobacterium*, or fungi were detected. Candidiasis of the esophagus diagnosed by endoscopic biopsies must have been treated successfully since there was no evidence of residual infection at autopsy. In addition to CMV infection, the kidneys revealed diffuse acute exudative and proliferative glomerulonephritis with IgA deposition confirmed by immunofluorescence and electron microscopy.

The most unexpected finding was the three small early lesions of Kaposi's sarcoma, one noted in the

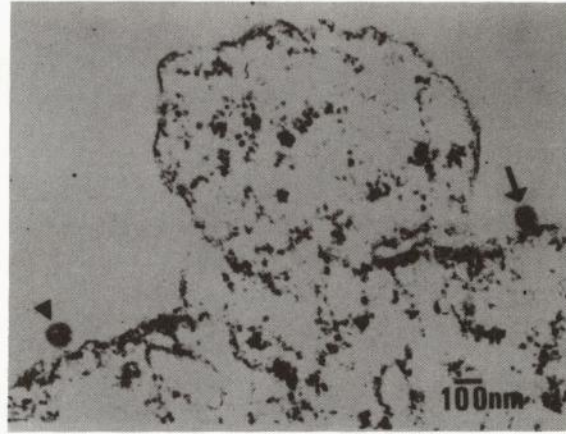


Fig. 3 Typical type D virus particles with a cylindrical core (arrow and arrow head) in a thin-section of the infected lymphocytes.

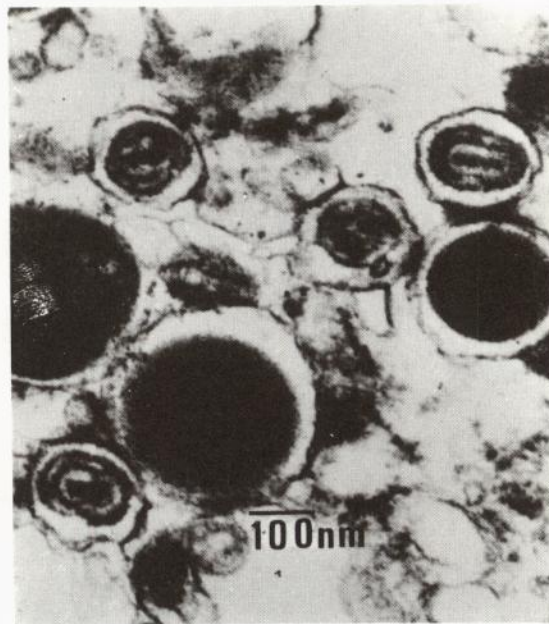


Fig. 4 Intracellular type D retrovirus particles with dense cylindrical cores are shown in the medullary cells of the adrenals.



anterior wall of the stomach and two in the peribronchial lymph nodes. Histologically, characteristic interweaving of atypical spindle cells and slit-like vascular spaces with extravasated erythrocytes were demonstrated (Fig. 6).

The brain weighed 1400 gm and appeared swollen, with flattening of cerebral gyri, narrowing of sulci, decrease in size of all ventricles and moderate bilateral tonsillar herniation. The meninges were unremarkable grossly. Serial horizontal sections of the brain revealed multifocal necrotic foci ranging in size from a few millimeters to  $2 \times 1.5$  cm. The lesions were mainly located in the corticomedullary junction of all cerebral lobes and deep nuclei, and a few extended into the very superficial cortex. The cerebellum and brain stem were also involved but the spinal cord was spared. Microscopically, the lesions were characterized by a necrotic center with vasculitis, a prominent leukocytic infiltration, and a peripheral hyperemic zone with neuronal injury. Under high power, there were numerous trophozoites at the junction between viable and nonviable brain tissue (Fig. 7). The extracellular parasites were far more numerous than the intracellular. No calcification related to the protozoa was visible. These rounded or ovoid trophozoites were shown ultrastructurally to be *Toxoplasma gondii* as having anterior "apical complex" consisting of conoid and rhoptries. In addition to the necrotic foci, there were also scattered microglial nodules with or without trophozoites. In the brain, there were also scattered lesions of CMV infection in the endothelial cells of the meninges with minimal inflammatory reaction.

#### DISCUSSION

Since the detection of anti-HIV antibodies in a promiscuous native homosexual in August 1985, it is believed that the introduction of

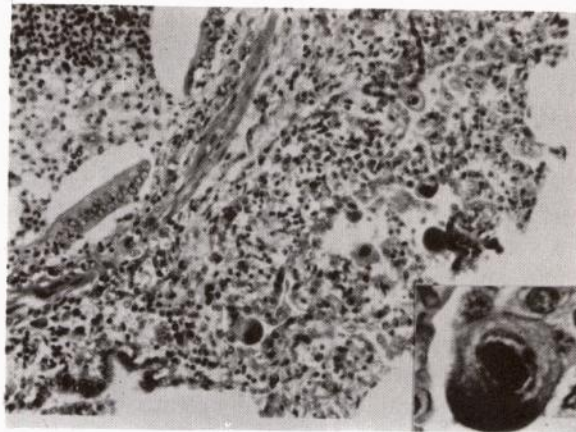


Fig. 5 The lungs show interstitial pneumonitis with multiple intranuclear inclusion cells characteristic of cytomegalovirus infection.

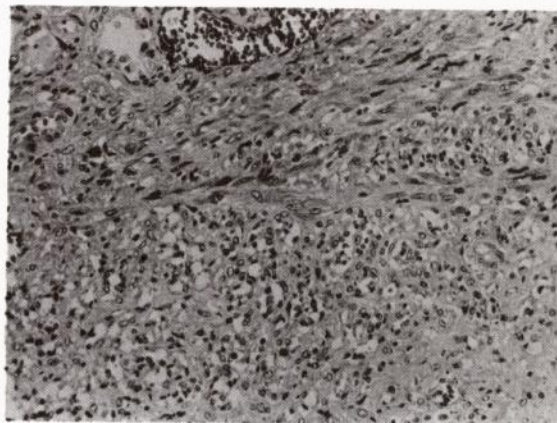


Fig. 6 Kaposi's sarcoma of stomach—characteristic interwoven spindle cells and slit-like vascular spaces with extravasation of red blood cells are shown.

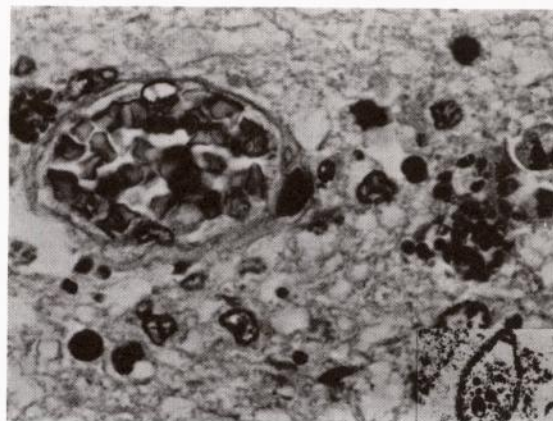


Fig. 7 Cluster of trophozoites of *Toxoplasma gondii* in brain.



AIDS into Taiwan is inevitable.<sup>3</sup> Traditionally and culturally, homosexuality is strictly regarded as a disgrace in Taiwan. Thus, attempts to investigate the true prevalence of AIDS in this group are greatly hampered by the lack of means to approach the most promiscuous segment of the homosexual population.<sup>4</sup> The history of this patient's sexual behavior suggests that he may have been infected by foreigners to whom he was exposed a few years ago. The fact that the patient continued his sexual activities until June 1985, when symptoms developed, suggests that he had probably infected many other homosexuals. Studies from the USA clearly show that detection of AIDS patients is delayed until a large number of individuals in a community have been infected.<sup>5</sup> Thus the appearance of the first case of AIDS in Taiwan indicates that more patients will follow; predictably the future control of the spread of AIDS will be extremely difficult.

The primary targets of HIV are the T4 cells which play a central role in regulating the body's immune system. For reasons that are currently incompletely understood, the process of viral reproduction kills the infected cells. Eventually, the body's T4 cells are depleted, the immune system collapses, and a variety of infections and malignancies supervene. Accumulating experiences have shown that in a single case various organs and systems are involved consecutively or simultaneously, either by HIV itself or by other organisms. With rapidly increasing incidence the revised surveillance definition of the USA Centers for Disease Control (CDC) has also encompassed a broad spectrum of opportunistic infections and malignancies.<sup>6</sup> Without known previous causes for diminished resistance, the first AIDS patient in Taiwan developed successively pneumonia, oroesophageal candidiasis, systemic CMV infection, extensive brain toxoplasmosis and Kaposi's

sarcoma in stomach and lymph nodes, all indicating severe underlying T-cell immunodeficiency and thus fulfilling the CDC case definition.

Clinical manifestations of AIDS have been reported to vary in each area.<sup>7,8</sup> In the Orient, candidiasis has been one of the most common opportunistic infections, but toxoplasmosis has not been reported. When candidiasis is localized in the oral mucosa the appropriate diagnosis is "AIDS-related complex" (ARC), but if it extends to the esophagus, the diagnosis of "full blown AIDS" is more likely. Toxoplasmosis is one of the most characteristic opportunistic infections in the USA, where a significant percentage of patients with AIDS have neurological complications. The CNS is particularly vulnerable to infections with HIV, *Toxoplasma gondii*, *Cryptococcus*, papovavirus, and possibly by *M. avium-intracellulare*. In the present case multiple lesions that contrast-enhanced in both a homogeneous and ring pattern on CT scans strongly suggested CNS toxoplasmosis. In Taiwan although the seropositive rate among the adult population is 7-12%, frank adult toxoplasmosis has never been encountered.<sup>9</sup> The other CNS complications include: (A) neoplasms, (B) vascular complications, and (C) those undiagnosed.<sup>10</sup> Classical skin Kaposi's sarcoma is extremely rare in Taiwan, and the present case is the first case of visceral involvement. Therefore, in studying cases of AIDS every effort should be made to determine the extent of the disease process and the occurrence of rare illnesses.

Many abnormalities of humoral and cellular immunities associated with AIDS can be explained by the preferential infection of the T4 lymphocytes which modulate the whole immune system. Marked functional T-cell defects were well demonstrated in this native AIDS patient. Despite the polyclonal gammopathy, he had diminished ability to respond to CMV

and *Toxoplasma gondii* and serial studies on antibodies against microorganisms did not reveal conclusive clues. It is evident that many of the immune defects of AIDS result from a selective depletion or dysfunction involved in the antigen-specific immune response. This selective functional defect not only makes clinical diagnosis difficult by serological studies, it also accounts for marked susceptibility to a variety of opportunistic infections.

The diagnosis of AIDS has been greatly facilitated by the use of ELISA and Western blot. Combination of these procedures generally offers both satisfactory sensitivity and specificity. However, a significant minority of patients with end-stage AIDS can and do have negative tests, simply because they have no immune system left to make any antibodies. In this patient Western blot studies using two different strips (from DuPont and Abbott) yielded conflicting results; this indicates that sensitivity varies between commercially available tests.

It has been repeatedly reported that conventional therapies often cause unexpectedly frequent or severe drug toxicities in AIDS patients,<sup>11</sup> and TMP-SMX induced systemic reactions occurred twice in this case. The deepening brownish discoloration of the patient's face led clinicians to suspect involvement of the adrenal glands, and severe CMV and HIV infections of the glands were confirmed at autopsy. The demonstration of HIV in the adrenals of AIDS patients has not been previously reported by other investigators. HIV has been shown to be both T4 tropic and neurotropic, and it is therefore not surprising that the virus should infect the adrenal medulla which is of neural origin.

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