

Brief Report

**TRANSIENT ANGIOLYMPHOID
HYPERPLASIA AND KAPOSI'S SARCOMA
AFTER PRIMARY INFECTION WITH
HUMAN HERPESVIRUS 8 IN A PATIENT
WITH HUMAN IMMUNODEFICIENCY
VIRUS INFECTION**

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DNA sequences of human herpesvirus 8 (HHV-8) have been detected in all forms of Kaposi's sarcoma.¹⁻³ HHV-8 has also been detected in primary effusion lymphomas,⁴ Castleman's disease,⁵ and multiple myeloma⁶ and reported anecdotally in cases of angioimmunoblastic lymphadenopathy and germinal-center hyperplasia.⁷ Indirect immunofluorescence and immunoblot assays, based on antigens from a latently infected lymphoma cell line, have shown that HHV-8 is not a ubiquitous viral infection in humans. The overall seroprevalence of HHV-8 is less than 5 percent in the United States and United Kingdom, up to 35 percent in southern Italy, and over 50 percent in East Africa.⁸⁻¹³ Seroconversion has been documented in stored serum samples from homosexual men enrolled in a large cohort study and was associated with a high risk of Kaposi's sarcoma within two years after seroconversion.¹⁴ It is controversial whether primary infection with HHV-8 produces an acute clinical syndrome. We describe a patient infected with human immunodeficiency virus (HIV) who had a sudden onset of fever, arthralgia, cervical lymphadenopathy, and splenomegaly that spontaneously resolved within eight weeks. Pathological examination of the cervical nodes identified angiolymphoid hyperplasia and foci of Kaposi's sarcoma. Retrospec-

tive study of stored serum demonstrated recent seroconversion to positivity for HHV-8.

CASE REPORT

A 43-year-old homosexual man who had been cared for at our institution because of HIV infection since September 1985 was negative for hepatitis B virus core antigen and antibody to hepatitis C virus. Serologic tests for Epstein-Barr virus (EBV), toxoplasma, and cytomegalovirus suggested past infection. In September 1988, immune thrombocytopenia developed and zidovudine therapy was started. On October 24, 1989, the patient was still asymptomatic and had a CD4 cell count of 392 per cubic millimeter. On December 10, 1989, he was admitted to the hospital because of a two-week history of fever, arthralgia, and a cervical mass. At admission, his temperature was 39.8°C, and physical examination revealed a large, tender, retromandibular unilateral adenopathy (3 cm by 4 cm). Livedo reticularis was present, but the skin was otherwise normal. The spleen was palpable 6 cm below the left costal margin. The patient reported diffuse arthralgia involving his knees, elbows, and shoulders without arthritis. The hematocrit was 39.6 percent; the white-cell count was 4200 per cubic millimeter, with 58 percent neutrophils and 22 percent lymphocytes. The platelet count was 135,000 per cubic millimeter. The serum aspartate aminotransferase concentration was 11 U per liter, the lactic dehydrogenase concentration was 164 U per liter, and the protein concentration was 6.9 g per deciliter (albumin, 3.5 g per deciliter; globulin, 1.7 g per deciliter). A chest film revealed no abnormalities. A computed tomographic scan of the abdomen revealed enlargement of the liver (diameter, 19 cm) and spleen (16 cm). The patient was unsuccessfully treated with broad-spectrum antibiotics for 17 days.

Four weeks after the symptoms began, fever was still present, the patient had lost 6 kg in weight, and there was progression of the cervical adenopathy to a large subcutaneous mass associated with homolateral adenopathies. The white-cell count had dropped to 2900 per cubic millimeter, and the hematocrit to 23 percent. A biopsy of one small adenopathic node was performed. One week later, a second biopsy of the cervical mass and a bone marrow biopsy were performed. Eight weeks after the symptoms began, a spontaneous regression of the mass and fever was noted and the only finding on physical examination was persistent mild splenomegaly, which resolved during week 10. Six months later, in July 1990, large-B-cell non-Hodgkin's lymphoma localized to the right quadriceps muscle developed. Complete remission was achieved after six cycles of combination chemotherapy. In December 1997, triple-antiretroviral therapy was begun and the patient remained asymptomatic without a relapse of non-Hodgkin's lymphoma or the development of Kaposi's sarcoma (Table 1).

METHODS

Histopathological, Immunohistochemical, and in Situ Hybridization Studies

Tissues from the lymph node and the cervical mass were obtained by surgical biopsy. Sections were stained with hematoxylin and eosin and Giemsa stain for pathological examination. Paraffin-embedded sections were examined for intracytoplasmic immunoglobulins with monoclonal antibodies to kappa and lambda light chains (Zymed, Biosoft, Paris) and polyclonal antibodies to alpha, gamma, and mu heavy chains (Dako, Trappes, France). Immunoperoxidase reactions were performed with commercial kits (Dakopatts, Copenhagen, Denmark). Immunophenotyping was performed on frozen sections to detect the expression of surface immunoglobulins and T-cell antigens CD3, CD4, and CD8 (Becton Dickinson, Le Pont de Claix, France).

Frozen and paraffin-embedded sections were examined for EBV latent membrane protein 1 with CS1, CS2, CS3, and CS4, monoclonal antibodies that recognize this protein. Paraffin-

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TABLE 1. CLINICAL EVENTS AND LABORATORY FINDINGS IN A PATIENT WITH HIV INFECTION AND HHV-8 SEROCONVERSION.*

TIME OF ASSESSMENT	CLINICAL EVENTS	THERAPY	CD4 CELLS	CD8 CELLS	HIV RNA COPIES†	PLATELETS
			cells/mm ³	cells/mm ³	no./ml	×10 ⁻³ /mm ³
Before onset of symptoms						
14 mo	Immune thrombocytopenic purpura	Zidovudine	475	1450	ND	36
7 mo		Zidovudine	360	972	ND	92
4 mo		Zidovudine	408	850	ND	125
5 wk		Zidovudine	392	672	ND	163
Onset of symptoms to 8 wk afterward		Fever, arthralgia, cervical mass, splenomegaly‡	Zidovudine	ND	ND	ND
After onset of symptoms						
3 mo	Non-Hodgkin's lymphoma	Zidovudine	110	814	ND	279
8 mo		Zidovudine	90	720	ND	377
21 mo		Zidovudine	81	570	ND	330
4.6 yr		Zidovudine, didanosine	117	540	ND	112
6.5 yr		Stavudine, lamivudine, ritonavir	71	362	13,000	168
7 yr		Stavudine, lamivudine, ritonavir	144	540	<200	164
8 yr		Stavudine, lamivudine, ritonavir	198	737	<200	184

*ND denotes not done.

†An Amplicor HIV-1 monitor (Roche, Neuilly sur Seine, France) was used.

‡Biopsies were performed on December 28, 1989 (week 4), and January 5, 1990 (week 5). PCR analysis demonstrated polyclonal B-cell and T-cell populations and HHV-8 DNA sequences.

embedded sections were also tested for EBV by in situ hybridization with a probe specific for an EBV-encoded RNA transcript (EBER-1) labeled with fluorescein isothiocyanate, according to the manufacturer's recommendations (Dako).

Amplification and Southern Blotting

Frozen samples from the cervical mass were available for analysis of clonality and molecular detection of HHV-8 DNA sequences with the polymerase chain reaction (PCR). Consensus primers were used for PCR amplification of the variable (V), diversity (D), and joining (J) exons of immunoglobulin and T-cell receptors. For immunoglobulin heavy-chain genes, V-D-J rearrangements were amplified by two sets of PCR, and for T-cell-receptor γ genes, the procedure included three reactions with three mixtures of primers, as previously described.¹⁵ PCR products were analyzed by polyacrylamide-gel electrophoresis, with ethidium bromide staining.

To identify HHV-8 sequences, DNA was extracted from the cervical-mass-biopsy specimen with the primer set for KS330₂₃₃,³ as described by Chang et al.,¹ and subjected to electrophoresis in agarose gel. The PCR products were then transferred to nylon membrane and hybridized with the specific internal oligoprobe 5'GGAACTTGATCTATATACCAC3' and labeled with phosphorus-32.

Serologic Tests for HHV-8

Serum samples obtained 4, 7, and 14 months and 5 weeks before the onset of clinical symptoms and 2 weeks, 8 months, and 7 years after the onset were available for serologic tests. Antibodies to the latent nuclear antigen were measured by immunofluorescence on the BCP-1 cell line as described previously,^{9,11} except that a serum dilution of 1:50 was used for the initial screening. The latent nuclear protein encoded by open reading frame 73 of HHV-8 is the main component of the latent nuclear antigen,¹⁶ and antibodies to a recombinant carboxy-terminal fragment of

this protein¹⁶ were measured by enzyme-linked immunosorbent assay (ELISA). We also measured antibodies to a recombinant "lytic cycle" protein, encoded by open reading frame 65 and associated with the viral capsid,¹¹ and a control antigen (recombinant dihydrofolate reductase protein, the fusion partner of the two recombinant HHV-8 proteins).^{11,16} For the ELISA, serum samples were diluted 1:100 and the assay was carried out as previously described.¹¹

Antibodies to lytic structural HHV-8 antigens were also measured by an immunofluorescence assay with a B-cell line (ISI-1) that harbors HHV-8 in the absence of EBV DNA and was established in April 1996 from a primary effusion lymphoma related to the acquired immunodeficiency syndrome (AIDS). Ten million cells were incubated with 3 mM butyrate in 20 ml of RPMI 1640 medium supplemented with 20 percent heat-inactivated fetal-calf serum and antibiotics for 48 hours. The cells were centrifuged at 4000×g twice for 10 minutes, the resulting pellet was gently suspended in phosphate-buffered saline at a final density of 100,000 cells in 2 μ l, and droplets were placed on slides. The slides were air-dried and fixed in acetone at 5°C for 15 minutes. For the immunofluorescence assay, serum diluted in phosphate-buffered saline (dilution, 1:10 to 1:500) was incubated with the cell smears for 30 minutes, rinsed three times with phosphate-buffered saline, and stained with fluorescein isothiocyanate-conjugated mouse antihuman IgG at a dilution of 1:100 with Evan's blue counterstain (Sanofi Diagnostics Pasteur, Paris). The smears were examined independently by two persons who had no knowledge of the subjects. Serum from patients with Kaposi's sarcoma and serum from the patient with AIDS and primary effusion lymphoma whose cells had been used to establish the ISI-1 cell line were used as positive controls. The positive controls did not stain nuclei from a T-cell line (MOLT4) without the HHV-8 or EBV genomes or Hep2 cells, a human epidermoid carcinoma cell line used for the detection of antinuclear autoantibodies (data not shown). Serum from healthy blood donors was used as a negative control.

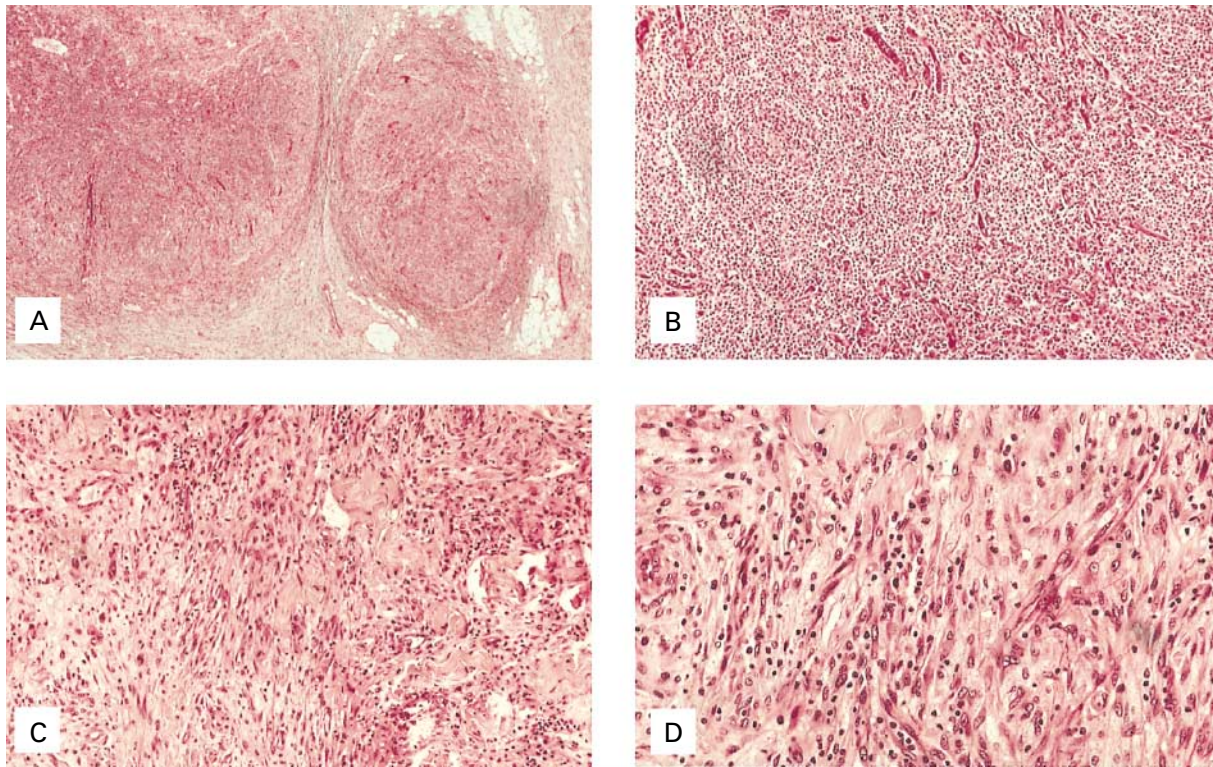


Figure 1. Histopathological Findings in the Cervical Lymph Node and Cervical Mass.

Panel A shows intense hypodermal nodular lymphoid hyperplasia (hematoxylin and eosin, $\times 25$). Panel B shows a hypocellular germinal center surrounded by marked paracortical lymphoid and vascular hyperplasia (hematoxylin and eosin, $\times 100$). Panel C (hematoxylin and eosin, $\times 100$) and Panel D (hematoxylin and eosin, $\times 200$) show a Kaposi's sarcoma with proliferation of long, spindle-shaped cells associated with slit-like blood vessels and inflammatory cells.

RESULTS

The architecture of the cervical lymph node was still recognizable. The most striking feature was an intense lymphoid and vascular hyperplasia associated with large sheets of plasma cells in the interfollicular area and hypocellular germinal centers. The second biopsy revealed similar lesions associated with foci of Kaposi's sarcoma (Fig. 1). Bone marrow biopsy disclosed moderate plasmacytosis. Polytypic cytoplasmic immunoglobulins were present in the lymph-node specimen, with the expression of both kappa and lambda light chains, suggesting polyclonal plasmacytosis. T cells were located in both T-cell zones and follicular zones, and the levels of CD4+ and CD8+ T cells were similar. Neither EBV latent membrane protein 1 nor EBV-encoded RNA transcripts were detected in these specimens. PCR analysis of the clonality of the B-cell population revealed a heterogeneous pattern of the immunoglobulin heavy-chain V-D-J sequence, with no individualized band, corresponding to polyclonal B-cell populations. Similarly, PCR analysis of the recombinations of V-J of T-cell-receptor γ genes showed the poly-

clonal nature of the T-cell populations (data not shown).

PCR amplification revealed HHV-8 DNA sequences in the cervical-mass specimen. A positive control was obtained from a patient with HIV-associated multicentric Castleman's disease,⁵ and peripheral-blood mononuclear cells from healthy donors and lymph nodes from subjects with benign lymphoid hyperplasia were used as negative controls.⁵ The specificity of the reaction was demonstrated by hybridization with an internal oligoprobe (Fig. 2). The biopsy specimen of the lymphoma that developed six months after the resolution of the angiolymphoid hyperplasia was not examined for the presence of HHV-8 DNA. However, the morphologic and phenotypic characteristics of the tumor were not suggestive of HHV-8-associated lymphoma.

Serum obtained from the patient 14, 7, and 4 months before the onset of symptoms was negative for HHV-8 in four serologic assays, including the immunofluorescence assay that measures antibodies to lytic structural HHV-8 antigens. Assays of this kind are thought to have high sensitivity but un-

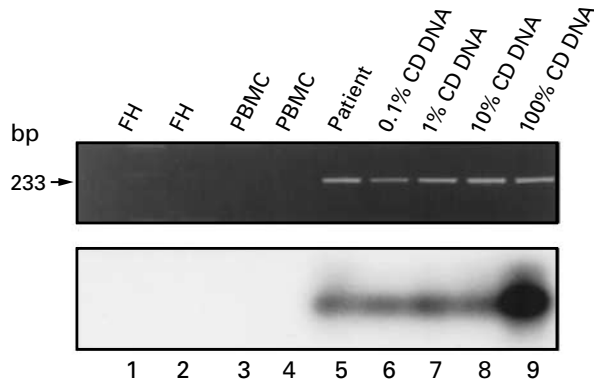


Figure 2. Detection of HHV-8 DNA Sequences in the Cervical Mass by PCR (Upper Blot) and Southern Blotting (Lower Blot). Biopsy specimens from two patients with follicular hyperplasia (FH) (lanes 1 and 2), and peripheral-blood mononuclear cells (PBMC) from healthy donors (lanes 3 and 4) were used as negative controls. Lane 5 shows the cervical mass from the patient. A lymph-node–biopsy specimen from a patient with HIV-associated multicentric Castleman's disease (CD) was used as a positive control. DNA from this control patient was examined undiluted (lane 9) and after serial dilution with DNA from PBMC from normal subjects (lanes 6, 7, and 8). The specificity of the PCR was demonstrated by Southern blotting with an internal oligoprobe.

certain specificity. Seroconversion was evident in the serum collected five weeks before the onset of symptoms; immunofluorescence assay showed that this sample reacted with both undefined lytic HHV-8 antigens (Fig. 3) and the latent nuclear antigen.^{8,9,11} A latent nuclear protein encoded by open reading frame 73 of HHV-8 is the main component of latent nuclear antigen, and serum samples collected five weeks before the onset of symptoms as well as two weeks, eight months, and seven years afterward all reacted with a recombinant fragment of this protein (Table 2). Antibodies to another recombinant HHV-8 protein, encoded by open reading frame 65, were present only in the last serum sample obtained, at seven years.

DISCUSSION

HHV-8, a newly identified herpesvirus, is closely associated in HIV-infected patients with three proliferative disorders: Kaposi's sarcoma,¹⁻³ primary effusion lymphoma,⁴ and HIV-associated multicentric Castleman's disease.⁵ The consistent detection of the virus in these lesions suggests that HHV-8 is necessary in the pathogenic process of these diseases. Although some viral genes are homologues of cellular genes involved in cell proliferation (viral interleukin-6 and G-protein–coupled receptor)^{17,18} and transformation (viral *Bcl-2* and viral cyclin),^{16,19,20} the direct transforming capacity of this virus remains uncertain.²¹

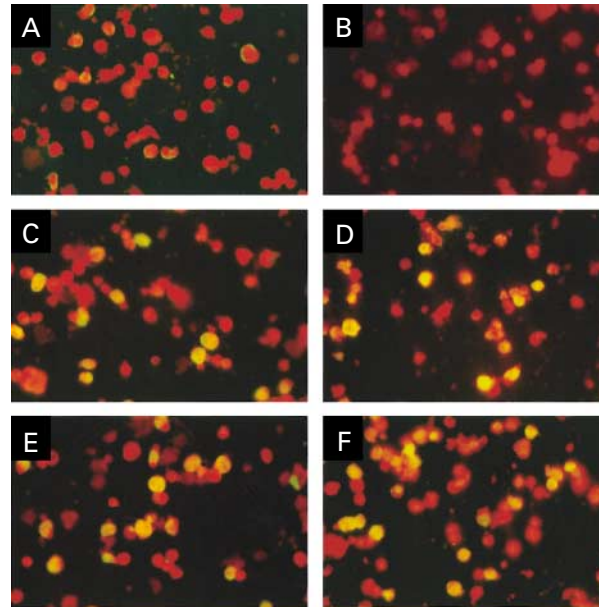


Figure 3. Immunofluorescence Assay for HHV-8 with ISI-1 Cells. Panel A shows a serum sample from a healthy blood donor (dilution, 1:10); Panel C, a serum sample from a patient with AIDS and Kaposi's sarcoma (dilution, 1:200); and Panel E a serum sample from the patient with AIDS and primary effusion lymphoma whose cells were used to establish the ISI-1 cell line (dilution, 1:200). Serum samples from the patient are shown four months (Panel B) and five weeks (Panel D) before the onset of symptoms and two weeks afterward (Panel F) (dilution, 1:10, 1:50, and 1:200, respectively). Only the serum samples from the patient with AIDS and Kaposi's sarcoma and the patient with AIDS and primary effusion lymphoma and both the second and third serum samples from the case patient have nuclear and cytoplasmic staining at dilutions of more than 1:10.

Serologic studies have shown that HHV-8 is probably not ubiquitous. A low seroprevalence was found in the general population in the United States and United Kingdom, contrasting with the higher prevalence in Mediterranean and East African populations. Seroconversion has been retrospectively documented in cohorts of homosexual men, and epidemiologic studies have suggested that HHV-8 infection could be sexually transmitted. However, whether primary infection with HHV-8 causes a self-limited disease remains unknown. A few cases of benign lymphadenopathy with germinal-center hyperplasia and increased vascularity in which HHV-8 DNA sequences were detected have been reported in HIV-negative young adults^{5,7} and HIV-positive young adults.^{1,7} In these cases, an association with primary HHV-8 infection could not be demonstrated in the absence of serologic data.

In our patient, the sudden onset of a clinical syndrome of fever, arthralgia, cervical lymphadenopathy, and splenomegaly suggested an acute infectious

TABLE 2. SEROLOGIC FINDINGS IN A PATIENT WITH HIV INFECTION AND HHV-8 SEROCONVERSION.*

TIME OF ASSESSMENT	ELISA†			IMMUNOFLUORESCENCE ASSAY‡	
	OPEN READING FRAME 65	OPEN READING FRAME 73	CONTROL ANTIGEN	LYTIC ANTIGENS	LATENT NUCLEAR ANTIGEN
	optical density			titer	
Before onset of symptoms					
14 mo	–	–	–	<1:10	<1:50
7 mo	–	–	–	<1:10	<1:50
4 mo	–	–	–	<1:10	<1:50
5 wk	–	(+)	–	1:50	1:2000
After onset of symptoms					
2 wk	–	3+	–	1:200	1:6000
8 mo	–	3+	–	1:200	1:6000
7 yr	3+	3+	–	1:100	1:800
Negative control	–	–	–	<1:10	<1:50
Negative control	–	–	–	<1:10	<1:50
Positive control	3+	3+	–	1:200	1:8000

*Serum from healthy blood donors was used as a negative control, and serum from a patient with AIDS, primary effusion lymphoma, and HHV-8 was used as a positive control.

†Minus signs indicate an optical density that is less than the mean (+3 SD) value for 10 negative blood donors, the plus sign in parentheses an optical density that is more than the mean +3 SD but less than the mean +5 SD, and 3+ an optical density more than the mean +10 SD. The control antigen was recombinant dihydrofolate reductase protein, the fusion partner of the two recombinant HHV-8 proteins.

‡The reactions were estimated visually with serial serum dilutions with the use of the ISI-1 cell line after butyrate activation for the detection of the lytic antigens and with the use of the BCP-1 cell line for the detection of latent nuclear antigen.

disease. Unusual features were the prolonged duration of the fever, the secondary development of leukopenia and anemia, and the pseudotumoral aspect of the cervical mass. Retrospective analysis of stored serum revealed seroconversion to HHV-8 within the four months preceding the onset of the clinical symptoms. These data support the hypothesis of a recent primary infection with HHV-8. Pathological examination of the cervical mass and lymph nodes revealed angiolymphoid hyperplasia, intense plasmacytosis, and foci of Kaposi's sarcoma. All these features have previously been reported in association with HHV-8 infection in HIV-infected patients.²² However, in our patient, these lesions as well as all clinical symptoms resolved spontaneously within two months and had not recurred after eight years.

In this patient, primary infection with HHV-8 was associated with transient fever, arthralgia, cervical lymphadenopathy, splenomegaly, and cytopenia. However, the severity of the illness was most likely related to the associated HIV infection and is not what might be expected in a primary infection in the absence of HIV infection. The pathological features of the lymph node suggest that HHV-8 can induce vascular hyperplasia and intense activation and proliferation of B cells. The spontaneous resolution of the lesion suggests that persistent dysreg-

ulation of cellular cytokines, continued activation of some HHV-8 viral genes, or an oncogenic event is necessary for the development of HHV-8-associated tumors.

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