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Behçet's syndrome / AIDS / Cerebral toxoplasmosis: an unusual association

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Few cases of AIDS associated to manifestations suggesting Behçet's syndrome have been reported. This case is of a young married woman who presented, during a period of 7 years, clinical manifestations consistent with the late diagnosis of Behçet's syndrome, when she developed recurrent lymphomonocytic meningoencephalitis. At this time, she was found to be infected by HIV-1. Immunosuppressive doses of glucocorticoid produced an unsatisfactory response and she evolved to death due to CNS toxoplasmosis. The latter diagnosis was presumed on the basis of magnetic resonance imaging findings and proved by necropsy after her third hospital stay. One of the factors hindering the appropriate diagnosis was the low level of CD4 and the CD4/CD8 ratio, sometimes observed in active Behçet's syndrome and higher than those observed in patients with this severe opportunistic infection. No information about the exact period of time she had been infected with HIV-1 is available. So, we do not know whether both diseases were overlapped, if the patient, infected by HIV-1, developed an unusual clinical feature consistent with Behçet's syndrome, and subsequently evolved to AIDS.

UNITERMS: Aids Behçet's Syndrome Cerebral toxoplasmosis

As the different forms of presentation AIDS (acquired human immunodeficiency syndrome) have been elucidated, some of them have been shown to simulate defined rheumatic syndromes, occasionally with exuberant clinical phenotype (3,7,8). Such clinical forms may hinder early diagnosis, delay and impair therapeutic management, as well as favor the appearance of severe complications that are difficult to be identified. This is specially true for the differential diagnosis with seronegative spondyloarthritis and, in particular, Reiter's syndrome and psoriatic arthropathy.

Associations between AIDS and Behçet's syndrome have been recently described (2,13,16). Although these

findings may be regarded as concomitant diseases, accidental manifestations, or nonspecific secondary complications, they still represent a challenge: to find a common denominator explaining the pathogenic sensitivity. We report the case of a young female patient who developed multisystemic clinical manifestations suggesting Behçet's syndrome, and was found infected with HIV-1. She eventually died of CNS toxoplasmosis, which was first considered as a vasculitic manifestation due to CD4 level being higher than expectations. The difficulty in making an accurate diagnosis of the primary pathology and its complications underscores the need of continuous and careful clinical evaluation.

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CASE REPORT

A 31-year-old Caucasian woman was admitted on October 22, 1992, with frontal and occipital headache, as

well as progressive mental confusion.

She had been admitted two months before that with lymphomonocytic meningitis, and at this period it was made the Behçet's syndrome diagnostic. On this occasion, it was found that she had been infected with HIV-1, as shown by positive ELISA test. CNS abnormalities were not shown by computerized cerebral tomography.

She reported that she had been presenting recurrent painful oral and genital ulcers and arthralgias affecting small and large joints since she was 24 years old. She developed deep venous thrombosis in the right leg in March 1991. She had lost 4 kg in the last two months and complained of anorexia, asthenia, blurring of vision and photophobia. She had presented thrombocytopenia six years before that, which failed to respond to several therapeutic approaches and was finally treated with splenectomy and blood transfusion. On this occasion, she presented lung tuberculosis for which she received specific treatment and was considered cured; in 1990, she was submitted to sclerotherapy sessions (for the treatment of small varicose veins) which were withdrawn due to the appearance of pustules in the sites of puncture (pathergy?).

The physical examination showed that she was in poor health, characterized by fever (38.0 C), dehydration, dyspnea, disorientation, and oral moniliasis. No cardiovascular and abdominal abnormalities were found. She did not present any abnormality in the arms and legs, but a questionable stiffness in the neck was found. Bullous lesions were observed on the scalp. Gynecological examination detected leukorrhea and three painful vulvar ulcers (diameter: 4 mm, each) with well-defined borders and clean bottom.

The following laboratorial data were found: hemoglobin = 11.2 g; Htc = 34%, leucocyte count = 11,500 / mm³; 340,000 thrombocytes/mm³; erythrocyte sedimentation rate = 50 mm in the first hour (Westergren); total lymphocytes = 4,227/mm³ with 709 CD4 and 3451 CD8; and a ratio CD4/CD8 = 0.2. The Western-Blot for HIV-1 was positive for gp 160, gp 120, gp 41, p 24, p 66, and p 31. Antinuclear antibodies including anti-DNA, anti-Sm, antiRNP, anti-SSA, anti-SSB, LE cell, and other ANAs, were negative. Total hemolytic complement (CH50) and the fractions C3 and C4 were normal. CSF collected on October 27, 1992, showed 133 cells/mm³ (lymphocytes = 90%; monocytes = 8%; and plasma cells = 2%), protein level = 100 mg/dl.

Laboratorial tests and cultures (bacteria and fungi) were negative. Serologic tests for toxoplasmosis (immunofluorescence technique) revealed IgG antibodies (1/256), but negative IgM; serological tests for cytomegalovirus were negative.

Scalp bullous lesions spread, leading to a clinical

picture similar to that of herpes zoster.

At this moment, the presumed diagnosis was Behçet's syndrome, and she received prednisone (60 mg/day) and acyclovir (daily oral dose of 1.5 g. for 10 days).

She improved and was referred to outpatient follow-up on November, 5, 1992. CSF collected at this date showed 28 cells/mm³ (lymphocytes = 88%; monocytes = 11%, and plasma cells = 1%) and protein level of 148 mg/dl.

One week later, on November 13, 1992, the patient presented a marked worsening of her neurological picture with disorder of consciousness (stupor). The family reported that she had developed deep venous thrombosis in the left leg three days before that and was given heparin. Her physical examination revealed stiff neck, positive Kernig's and Brudzinski's signs, with no localizing manifestations. The left leg was swollen and warmer than normal and Doppler examination confirmed the diagnosis. CSF revealed 86 cells/mm³ (lymphomononuclear cells = 93% and polymorphonuclear neutrophils = 7%), and a protein level of 172 mg/dl. Microbiological investigation was negative. The ratio of the peripheral levels of CD4 and CD8 was shown to be 0.4 (CD4 = 546 cells/mm³, or 21%, and CD8 = 1534 cells/mm³, or 59%). Her level of awareness deteriorated progressively and she presented high fever. *Staphylococcus aureus* was isolated from blood culture.

Magnetic resonance imaging revealed lesions consistent with granulomatous reactions due to CNS toxoplasmosis (figure 1).

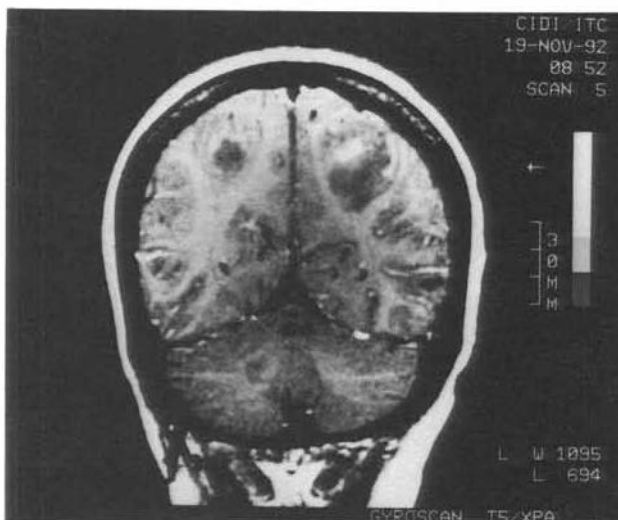


Fig. 1 - T1 weighted.MRI (after the administration of gadolinium contrast) showing diffuse cerebral involvement and an extensive lesion in the left parietal tissue characterized by a central hyperdense region surrounded by a hypodense area (ring aspect). The findings are consistent with the hypothesis of CNS toxoplasmosis.

Despite the intensive care, she evolved to death. Multiple cerebral lesions due to toxoplasmosis, staphylococcal bronchopneumonia, and deep venous thrombosis in the left leg were confirmed by necropsy. It was not found any other vascular involvement suggesting Behçet's syndrome; there was no evidence of active or dormant tuberculosis.

DISCUSSION

Although manifestations suggesting Behçet's syndrome associated to HIV infection are rare, they have been previously reported. These findings suggest the possibility that this virus might account for this form of presentation in susceptible individuals, yet the pathogenic mechanisms are unknown.

In the present case, the patient did not belong to any high-risk group for AIDS. Despite a blood transfusion in 1987, one can not establish the exact period of HIV contamination. The overall impression was that she had developed primary Behçet's syndrome (recurrent oral and genital ulcers accompanied by arthralgias) although the criteria for this diagnosis were incompletely fulfilled at this time. She eventually developed other clinical manifestations that met O'Duffy's criteria as well as those of the International Study Group for Behçet's syndrome or disease (pathergy, vascular thrombosis, and meningoencephalitis) (5,9). In spite of being infected with HIV-1 and presenting slightly decreased levels of CD4, she was regarded, clinically, as having active vasculitic manifestations of Behçet's syndrome. The latter were considered responsible for the recurrent episodes of lymphomonocytic meningoencephalitis (1). This kind of CNS involvement may also be observed in the early phases of HIV-1 infection or in the late phases of AIDS, when there is a marked decrease in the circulating levels of CD4 (10).

The levels of CD4 and the CD4 / CD8 ratio found in this case were not consistent with those usually found in the presence of severe opportunistic infections associated to AIDS, when they are usually much lower (14). Meanwhile, the low level of CD4 and the inversion of the CD4/CD8 ratio has been previously described in patients with active Behçet's syndrome (1,6).

On the other hand, herpes zoster is known that may occur in the early phases of immune abnormalities of AIDS, with normal or slightly decreased levels of CD4.

These facts made us believe that the clinical picture was not primarily related to AIDS and, for this reason, we maintained the high doses of corticosteroids. It is noteworthy that, although acyclovir has been used in the treat-

ment of herpetic lesions, its use in the treatment of meningoencephalitis in Behçet's syndrome has been previously described based upon some indirect evidence, though controversial, suggesting that persisting infection with Herpes simplex plays a role in the etiopathogeny of this disease (11,12,15).

Also, it is noticeable the demonstration of CNS toxoplasmosis in the late phase of her disease; this was the main culprit of her death and was probably aggravated by the immunodepressor therapy. Such complications, when observed in patients with AIDS, is generally associated with markedly decreased levels of circulating CD4 and CD4/CD8 ratios. These abnormalities were not observed in the present case, disturbing clinical reasoning.

Toxoplasmosis as an opportunistic infection in patients with AIDS is generally associated with values lower than 200 CD4 cells/mm³ (4).

It is necessary to warn general physicians, as well as specialists, to be aware to the differential diagnosis of rheumatic pathologies and their clinical complications, on patients infected with HIV-1. One should try to detect opportunistic infections that present themselves atypically, misleading the diagnosis of superimposed diseases, and be careful on the interpretation of the CD4 levels as marker of definite pathology.

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RESUMO

Há raras descrições da AIDS associadas a manifestações sugestivas de síndrome de Behçet. Apresentamos o caso de uma jovem senhora que apresentou progressivamente no período de sete anos, critérios clínicos para o diagnóstico de síndrome de Behçet e que ao desenvolver meningoencefalite linfomonocitária recidivante, observou-se estar infectada com o vírus HIV-1. A terapêutica imunodepressora com glicocorticóides em altas doses não foi satisfatória e a paciente veio a falecer por toxoplasmose cerebral, suspeita por ressonância magnética e confirmada por necrópsia, após sua terceira internação. Níveis baixos de CD4 e da relação CD4/CD8, algumas vezes observadas na síndrome de Behçet ativa, no entanto, mais altos do que comumente se observa na presença desta complicação oportunística grave, foram outros elementos que nos levaram a dificuldade diagnóstica, alertando o clínico para a necessidade de interpretar com restrições os achados laboratoriais. A falta de conhecimento definitivo do período no qual se infectou pelo HIV-1 possibilita as seguintes considerações: ou estamos diante de síndrome de superposição de distintas enfermidades; ou, então, de uma forma inusitada de apresentação evolutiva, mimetizando a síndrome de Behçet, numa enferma infectada por este vírus, que, posteriormente, desenvolveu AIDS.