

Linfoma primário das cavidades em doente com infecção VIH

Primary effusion lymphoma in a HIV infected patient

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Resumo

O linfoma primário das cavidades é um subtipo de linfoma não-Hodgkin (LNH), de ocorrência rara, prognóstico muito reservado, mais frequentemente descrito em indivíduos imunodeprimidos, em particular no contexto de infecção pelo vírus da imunodeficiência humana (VIH), no qual as células malignas proliferam exclusivamente nas cavidades serosas e que está associado ao vírus herpes humano tipo 8 (VHH8).

Os autores apresentam o caso de um doente com infecção VIH, internado por febre e queixas constitucionais e que desenvolveu, enquanto decorria estudo etiológico da síndrome febril, ascite volumosa e, ainda, derrame pleural direito e derrame pericárdico. O líquido ascítico mostrou a presença de células grandes linfóides com fenótipo não B e não T. Não foram evidenciadas massas tumorais, linfadenopatias ou envolvimento da medula óssea. O doente morreu 41 dias após o diagnóstico, sem ter iniciado quimioterapia. Ainda que não tenha sido possível a demonstração de infecção pelo VHH-8 nas células linfóides, os dados clínicos, citológicos e imunofenotípicos apontam para um diagnóstico altamente provável de linfoma primário das cavidades.

Palavras-chave: linfoma primário das cavidades, infecção VIH, síndrome febril.

Abstract

The primary lymphoma of cavities is a rare subtype of non-Hodgkin (NHL) with reserved prognosis, characterized by the proliferation of malignant cells exclusively in serosal cavities and is associated with infection by type 8 human herpes virus. It is more often described in immunosuppressed patients, particularly in the context of Acquired Immunodeficiency Syndrome (AIDS).

We present a case of a patient diagnosed with AIDS, admitted in hospital for fever and systemic complaints. During the hospitalization he developed insidiously ascites, right pleural effusion and pericardial effusion. The ascitic fluid presented large lymphoid cells with non-B non-T phenotype. The study performed did not detect solid tumors, lymphadenopathies or bone marrow involvement. It was not possible to demonstrate lymphoid cells infection by HHV-8; clinical, cytologic and immunophenotypic data strongly suggest the diagnosis of primary lymphoma of cavities. The patient died 41 days after the diagnosis, before chemotherapy had been attempted.

Key words: pleural effusion lymphoma, HIV infection, fever of unknown origin.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a neoplasm often associated with acquired immunodeficiency syndrome (AIDS) – the NHL risk, in the context of the infection by the human immunodeficiency virus (HIV) is around 60 times higher than the general population. According to the anatomical distribution, the systemic lymphoma can be distinguished (in around of 80% of cases), the primary lymphoma of the central nervous system (around 20% of cases) and the primary lymphoma of cavities (less of 3% of cases).²

This rare form of presentation is characterized by the formation of lymphomatous effusions in the body cavities, pleura, peritoneum and/or pericardium, without evidence of contiguous tumoral masses, lymph node involvement or bone marrow involvement.^{3,4} The analysis of the effusions shows cells of wide dimensions, atypical, with the particularity of having an undetermined phenotype, being its B origin revealed by genotype studies.¹⁻⁴ From a pathogenic point of view, the primary lymphoma of cavities has been related with the infection by the human herpes virus type 8 (HHV-8), as demonstrated identifying the techniques of molecular biology;^{1-4,6} in around half of the cases is isolated simultaneously with genetic material of the Epstein Barr virus (EBV).^{1,2,5} This type of lymphoma has a very aggressive behavior, with a difficult response to chemotherapy, being usually fatal in a short period of time.^{3,5,7}

Although most often associated to the HIV infec-

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tion, the primary lymphoma of cavities can emerge in other stages of immunodepression, as for instances, after a transplant of solid organs; although very rarely, it has been also described in individuals theoretically immunocompetent – they are in general elderly or have co-morbidities conditioning a likely fragility of its immune system.^{8,9,10}

CASE REPORT

50 years old, male patient, Caucasian, worker in the building industry, admitted by fever and constitutional complaints.

This is about a patient with a history of endogenous drug addiction (heroin and cocaine) until five years ago, a chronic infection by the hepatitis C virus and marked alcohol habits.

Three months previously a condition of asthenia, anorexia, weight loss estimated in around five kilos and fever, predominantly in the afternoon, reaching 39°C had started and hardly responding to antipyretic drugs. He denied complaints focusing organs or systems, namely respiratory, genitourinary, gastrointestinal or muscular-skeletal. Two weeks previously he had undergone, in the context of an investigation of the mentioned table, a screening for HIV which was positive.

In the initial observation, the patient was very thin, with a bad general condition, dehydrated, colorless and febrile. Without jaundice, stigma of hepatic disease, changes of the skin and /or mucosa, palpable adenomegalia or oropharynx lesions. The pulmonary exam did not show any changes. The cardiac auscultation had shown a reduction of the cardiac sounds, without murmurs or other anomalous sounds. In the abdominal evaluation there was hepatomegaly, of elastic consistency, smooth surface, blunt edge, painless, around 2 cm below the right costal frame on the midclavicular line, without splenomegaly or other changes. The neurological exam was normal.

In the lab tests carried out on admission it should be highlighted: pancytopenia, (Hemoglobin: 8.2 g/dL, red blood cells -2.670.000/mm³, with the normal constant blood cells; leucocytes -2.560/mm³, neutrophils: 64.4%; platelets: 29.000/mm³), preserved clotting endpoints, normal biochemistry.

The thorax X-ray has shown a slight increase on the cardiothoracic ratio, but there are no evident aspects suggesting an active pleural parenchymatous lesion. The electrocardiogram has shown sinus

rhythm with low voltage QRS complexes, without other changes.

The HIV1 infection was confirmed by Western Blot, and it should be highlighted in the study of the lymphocytary populations a CD4 cell count of 61 /mm³ (8%) with a ratio CD4/CD8 of 0.10.

It was also confirmed by the hepatitis C virus. Markers for hepatitis B were negative, except total anti – HBc antibody, the serology for cytomegalovirus and toxoplasma work compatible with an old infection with a negative VDRL.

The peripheral blood, bone marrow, urine, gastric fluid and CSF microbiologic tests were negative.

The CSF studies by molecular biology techniques/CRP was negative, namely for mycobacteria, herpes group virus and toxoplasma.

The myelogram was inconclusive, with scarce and partially destroyed cellularity, whilst the bone biopsy has shown lesions compatible with myelodysplasia associated with HIV.

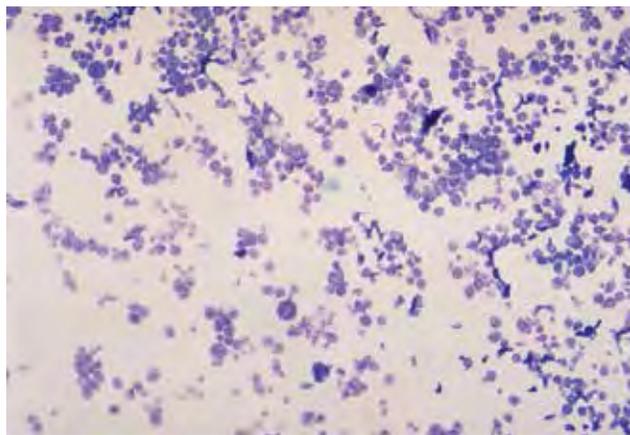
Liver biopsy was not performed regarding the unfavorable hematology endpoints for a percutaneous approach not available in useful time for the transjugular route exam.

The echocardiogram has shown an interior and posterior pericardial effusion, with 6-9 mm of variation without evidence of vegetation.

The abdominal ultrasound has revealed hepatosplenomegaly and ascites in the different abdominal quadrant. The thorax – abdominal – pelvic CT scan has confirmed the presence of hepatosplenomegaly and ascites, and yet a thin layer of right pleural effusion, which would equally become perceptible in the conventional radiology evaluation. None of these image tests has identified adenomegalies or masses of other nature.

Bronchofiberscopy collecting biologic products was also carried out, after what was carried out a therapeutical proof against tuberculosis, with a combination of four antibacillary drugs of first choice. However there was no reaction to such approach and the mycobacteria tests (direct, cultural and CPR technique) would reveal all as negative. Also the pneumocystis and fungi research was negative without evidence of neoplastic cells.

Meanwhile and in simultaneous with the deterioration of the patient's general condition, the ascites detected in the image tests became clinically evident and gradually bulkier. Its etiology was construed in



Pathoanatomical test of the ascitic fluid.

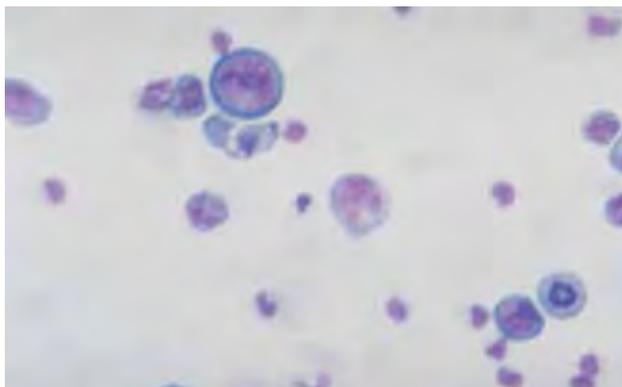
FIG. 1

the context of a likely chronic liver disease, for which there was a contribution by alcohol habits and an infection by the C hepatitis virus, a hypothesis that seemed to be corroborated by the fact the ascitic fluid presented characteristics of a transudate (proteins of 1.3 g/dL, LDH of 52 U/L), with a ADA lower than 1 U/L and negative bacterial and mycobacterial tests. It was not possible, for the reasons already mentioned, and now by the important volume of ascites, to perform a liver biopsy to get a histologic confirmation of this diagnosis.

The pathoanatomical test of the ascitic fluid described a hypercellular sediment made up by big dimensions cells – Fig. 1, with nuclear atypia (an increase of the relationship nuclei/cytoplasm, cellular hyperchromatism and small cytoplasm border) – Fig. 2. The immunocytochemical test has shown that these cells were marking positively with monoclonal antibodies CD45 and CD30, being negative for CK7, CK20 and calretinin – Fig. 3.

The presence of big lymphoid cells with non B and non T phenotype in the ascitic fluid, associated to a non evidence of contiguous tumoral mass, lymphadenopathies or bone marrow involvement, led us to the primary lymphoma of cavities as the most likely diagnostic hypothesis. It was not possible to make a HHV-8 and EBV research in neoplastic cells, due to a non timely availability of the necessary technology.

The patient was then referred to hematology assessment in order to schedule an eventual chemotherapy and started anti-retroviral therapy of high strength (HAART - *Highly Active Antiretroviral Therapy*-)



Pathoanatomical test of the ascitic fluid.

FIG. 2

with a combination of tenofovir, emtricitabine and lopinavir/ritonavir.

Meanwhile, the clinical situation, already in overt deterioration, was worsened by an intercurring nosocomial pneumonia a pneumothorax complication – the evolution is kept unfavorable and the patient ended up dying on the 41st day of admission. Autopsy was not carried out.

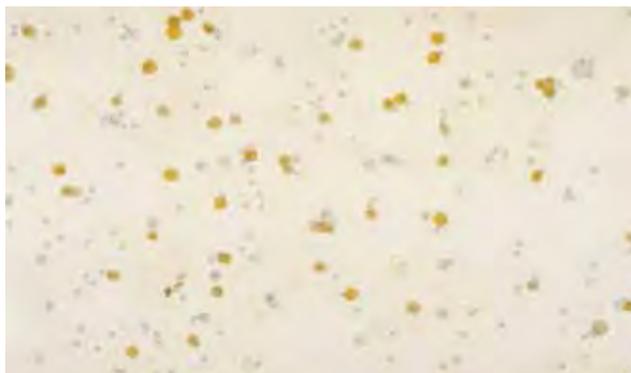
DISCUSSION

In the clinical practice, the physician is often confronted with situations that challenge its expertise and scientific knowledge. This is particularly true for fever of undetermined origin which is still a common clinical issue and an important cause for hospitalization. In the presence of HIV infection, fever is one the main reasons for admission, corresponding to 5-21% of admission causes, as shown in some studies.¹¹

The clinical case presented refers to a patient with a recent knowledge of seropositivity for HIV1, but in an already advanced stage of the infection, with marked immunodepression, admitted in hospital to clarify a condition of prolonged fever.

The list of causes of an undetermined febrile syndrome is vast and tending to increase when clinical cases referring to rare entities are published regularly. They can be divided in three big etiologic groups: infections, neoplasms and connective tissue inflammatory diseases.

The infectious etiology is more common in the general population and also in patients with seropositivity for HIV. In a study¹² performed in 70 patients with HIV infections hospitalized to clarify a fever



Pathoanatomical test of the ascitic fluid.

FIG. 3

condition, it was verified that the infectious cause has contributed to 88% of cases, neoplasms for 8% and the fever induced by drugs to 3%.

The important immunodepression of our patient (CD4 lower than 100/mm³) made him susceptible to a wide range of opportunistic infections. Among the infectious causes, mycobacteria have a particular relevance – in a Spanish study¹¹ involving 54 patients with HIV infection, hospitalized by undetermined febrile syndrome makes in 41% of cases the cause, followed by the infection by atypical mycobacteria in 22% of patients. For such reason and even because the tuberculosis still has a high prevalence, it seems to us justified the approach taken in the current clinical case, with a comprehensive research of this agent in the different biologic products and performing a therapeutic proof.

Another great nosology group responsible for clinical conditions of prolonged fever is of neoplastic diseases, with particular emphasis for the patient infected by HIV to the NHL. Our patient did not show any neoformations, adenopathies or any other evidence of lymphomatous infiltration, reason why this hypothesis of diagnosis seemed less likely.

The connective tissue inflammatory pathology, in the absence of articular complaints, cutaneous changes or ophthalmologic, as well as other possible entities causing febrile syndrome, seemed to us, in this patient, not very likely.

In a standby stage, where all the research shown was negative, a new datum emerged, with developing ascites. Together with hepatosplenomegaly and in a patient with a history of alcoholism and infection

by hepatitis C virus, the hypothesis that seems more plausible to us was of concomitant chronic hepatic disease. The important thrombocytopenia and bulky ascites have dissuaded the performance of a hepatic biopsy, not allowing to confirm this presumptive diagnosis.

Also the presence of pleural and pericardial effusion – that a small volume did not allow to collect for characterization – could be explained by secondary dysproteinemia to chronic hepatopathy or malnutrition that, concomitantly, the patient had.

Tuberculosis infection, already discussed in relation to the febrile condition, it would also be a very attractive etiology to explain polyserositis development, but as referred, all the study was negative in such sense.

The pathoanatomical test of the ascitic fluid was crucial in the diagnostic orientation, when revealed the presence of many lymphoid cells with a non B and non T immunophenotype.

The HHV-8 identification in tumor cells, a characteristic of the primary lymphoma of cavities was not feasible, due to the impossibility of making available, in time, the necessary molecular biology appropriate technology. For the same reason, it was not possible to evaluate the possible association with EBV, frequent in this kind of lymphoma.

The clinical situation had a quick fatal outcome, being associated, in this case, to the common aggressive behavior to this kind of lymphoma, the unfavorable evolution of a nosocomial infection. It was not possible, to start the chemotherapy that in any way would not improve in a significant way, predictably, the patient's survival – as a matter of fact, and in spite of the HAART concomitant administration had modified significantly the NHL natural history, associated to HIV infection, in the particular case of primary lymphoma of cavities, the optimum treatment remains to be defined and the response ratio is in general very low.³

CONCLUSION

This clinical case shows the difficulty of establishing a diagnosis in certain cases of febrile syndrome in the patient with HIV infection, being necessary to consider a wide range of etiologies, some common in the community, it can assume classical or atypical presentations, other rare, as in the case of our patient.

The diagnosis of primary lymphoma of cavities

would be reinforced by the HHV-8 identification in tumor cells, what, as referred was not possible. However, the cytological and immunophenotypical characteristics, allied to the clinic, are conjugated in a way to make the mentioned diagnosis highly likely. ■

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