Intracerebral hogkin´s lymphoma in a patient with human immunodeficiency virus

Central nervous system (CNS) involvement by Hodgkin Lymphoma (HL) is rarely reported. Retrospective and prospective cohort studies suggest an incidence of 0.2-0.5%, mostly in relapsed disease. In spite of a 3 to 18-fold increased risk of HL in patients with human immunodeficiency virus (HIV), only two cases have been reported so far. In this paper, we now report a third case of HIV patient with HL who progressed with isolated CNS infiltration after a standard chemotherapy induced clinical remission. In 1991, when the first case of intracerebral involvement in HIV+ HL was reported an increase of this type of cases would have been expected, but only one more case has been reported since then.

Haematologica 2007; 92:(6)e72-e73

Case Report

A 41 year old HIV positive male with B symptoms, starting one month before, was admitted for surgery after an intestinal perforation due to ulceration of the intestinal wall. In the pathologic study the ulcer was infiltrated by atypical lymphocytes, frequent eosinophils and Reed-Stenberg cells. By immunohistochemistry, tumour cells were positive for CD30, CD 15 and EBV and, negative for CD20, CD79a. Classic HL EVB+ with depletion lymphoid areas was diagnosed. A whole body computed tomography (CT) scan showed multiple and small (<1 cm) supra and infradiaphragmatic adenopathies and bone marrow biopsy was positive. The disease was classified as stage IV-B and IPS (International Prognosis Score) of 5.

HIV infection was detected four years before. $CD4^+$ T lymphocyte cell count remained >200/μL (median 363/μL) and treatment with Efavirenz, Emtricitabine and Tenofovir were initiated when HL was diagnosed. Chemotherapy with ABVD regimen was administered with complete resolution of all symptoms and disappearance of previously involved areas after the first four cycles of therapy. Just before the fifth cycle of chemotherapy, the patient presented acute urinary retention which required the insertion of an urethral catheter and loss of anal sphincter control. In addition, he related proximal legs weakness with paresthesias, headache and photophobia in the last week. The patient was hospitalised with the clinical suspect of spinal cord compression by infiltration versus infectious myelitis. Magnetic resonance (MR) studies showed peripheral meningeal enhancement, nodular areas in lower spinal cord and conus medullaris, supratentorial nodular lesions with a ring pattern and contrast linear enhancement around V and left II cranial nerve. Spinal fluid showed 18 WBC/per mm^3, increased proteins with decreased glucose, normal adenosine deaminase (ADA) levels and 95% lymphocytes with mature CD3+ phenotype. Screening for infections included bacterial and fungal cultures, cryptococcal latex agglutination, PCR to detect mycobacterium tuberculosis, toxoplasma gondii and neurotrophic virus (HSV, HZV HV6, CMV, EBV). All tests except for EBV, were negative. A stereotaxic guided biopsy of the lesions yielded negative results so a new stereotaxic guided open biopsy was indicated. Pathologic examination revealed CNS tissue infiltrated by HL EBV+. (Figure 1-4). Five lumbar punctures with intrathecal chemotherapy were performed in a period of six weeks. In the first three punctures methotrexate, hydrocortisone and cytarabine were administered, and in the others liposomal cytarabine was used. In spite of improvement of the cauda equine syndrome, the patient developed anisocoria, left blindness by retrobulbar neuritis and neural pain in the left upper member. A new MRI showed progression of the supratentorial lesions. Systemic chemotherapy with high dose methotrexate and citarabine was started without success after a short initial period of symptoms relief. The patient died 8 months from initial diagnoses and 3 months after CNS involvement symptoms appeared with progressive worsening of neurologic symptoms (tonic-clonic seizures, coma).

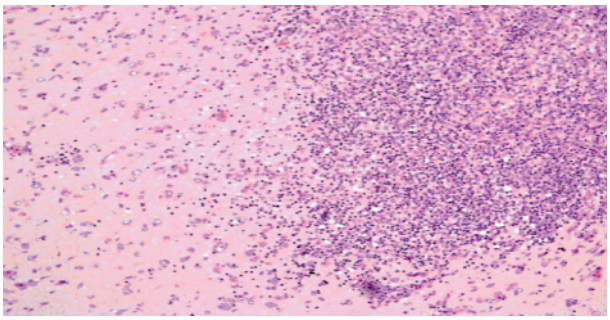

Figure 1. Brain biopsy: Paraffin sections, stained with hematoxylin and eosin, showing neuropil infiltration by lymphocytes.

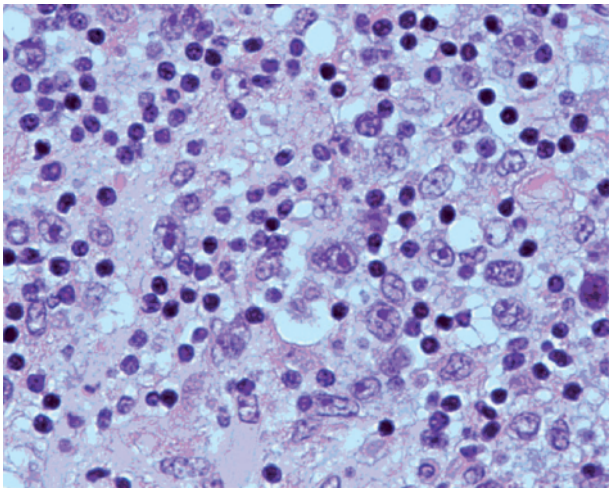

Figure 2. Uninucleated Hodgkin´s cell within a diffused background of pleomorphic lymphocytes.

Discussion

HL is the most common non AIDS defining cancer occurring in patients with HIV infection who have a 3 to 18 fold increased risk of disease when compared to non HIV patients.[1,2] These patients also have a more advanced stage disease at presentation with up to 60% extranodal involvement,[2] clinical features associated with an increased risk of refractory or progressive disease. Although CNS involvement is infrequent in immunocompetent patients with advanced HL (0.2-0.5%), one would expect more than two case reports in the HIV positive population since 1991.[3,4] Furthermore, diagnosis of CNS involvement in HL may not be easy. In the cases reported, as in ours, spinal fluid studies were not explanatory, and diagnosis required brain biopsies or was an autopsy finding.[5,6,7,8] Perhaps, the high risk of infection in these patients (including CNS), the use of empirical treatment,

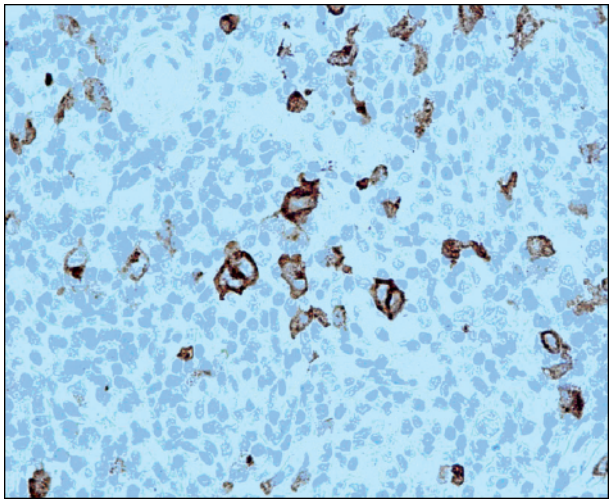

Figure 3. Immunohistochemical staining with CD15 and CD30 showed expression in tumour cells.

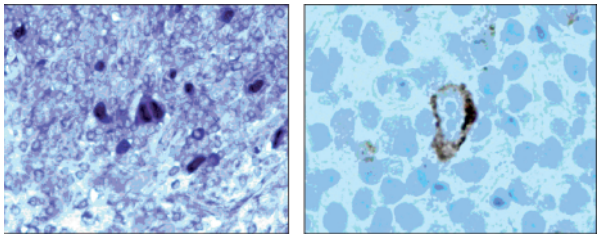

Figure 4. Typical Reed-Sternberg cell with nuclear staining using an *in situ* probe for EBV-encoded small ribonucleic acid (EBER). Uninucleated Hodgkin´s cell with citoplasmic staining showed EVB-latent membrane protein 1 (LPM-1).

difficult diagnosis and poor outcome might have contributed to fewer cases being reported. A treatment strategy has not yet been defined in these patients. Results of retrospective and prospective studies with standard chemotherapy were poor in the pre highly antirretroviral period, with survivals ranging from 12 to 18 months due to proggressive disease, an increased risk of opportunistic infections and treatment related toxicities.[1,2,9,10] Since 2002, significantly better outcomes have been communicated using a more intensive upfront chemotherapy such as BEACOPP or Stanford V regimens with G-CSF (granulocyte colony-stimulating factor) support.[11,12] However, these intensive regimens have been used combined with HAART (highly active antiretroviral therapy) and therefore we cannot know what the contribution of these regimens is on the improved outcome. Surprisingly, there is scarce information on the results of ABVD (considering the standard therapy for HL) combined with HAART. Recently, a retrospective study was published analyzing the results of the ABVD regimen plus HAART in a series of 62 patients with advanced stage HIV-relates HL (13) and the results are similar to those reported by Spina et al [11] and Hartmann *et al.*[12] Our patient progressed on a standard chemotherapy treatment, but the risk of treatment failure due to IPS score was high, regardless of the HIV infection. The potential prognostic impact of the IPS in HIV patients has not been evaluated. We do not know what the patient´s evolution would have been if a more intensive treatment had been used. In summary, it is important to rule out CNS infiltration in HIV + patients with HL, neurologic symptoms and not explanatory spinal fluid. In these cases a cerebral biopsy is necessary because it is the best method available at the moment to obtain a reliable diagnosis, and the means to know the real incidence of this event. If a higher incidence of CNS involvement in HL were to be reported in the future, another approach could be to administer prophylactic intrathecal chemotherapy when bone marrow is infiltrated, just as recommended for aggressive NHL. More studies are, therefore, necessary to define the optimal monitoring and therapy for these patients.

A. García-Noblejas,[1] S. Nieto,[2] R. Liberal,[3] J. Cannata,[1] J.L. Steegmann,[1] J.M. Fernández- Rañada,[1] R. Arranz[1]
Departments of [1]Hematology, [2]Pathology and [3]Neurosurgery, La Princesa Hospital, Spain

References

1. Levine A. Hodgkin´s Disease in the setting of human immunodeficiency virus infection. Monogr Natl Cancer Inst 1998;23: 37-42.
2. Tirelli U. et al. Hodgkin´s disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Groups on AIDS and Tumors. J Clin Oncol 1995 13 (7): 1758-67.
3. L.S. Hair et al. Intracerebral Hodgkin´s Disease in a Human Immunodeficiency Virus-Seropositive Patient. Cancer 1991. 67: 2931-4.
4. Suleiman Massaeweh et al. HIV-related Hodgkin´s disease with central nervous system involvement and association with Epstein-Barr Virus. Am. J. Hematol. 2003. 72:216-219.
5. Hirmiz K, et al. Intracraneal presentation of systemic Hodgkin´s disease. Leuk Lymphoma. 2004. Aug; 45 (8): 1667-71.
6. Sheehan T, et al. Central nervous system involvement in haematological malignancies. Clin Lab Haematol 1989;11 (4): 331-8.
7. Dujovny M, et al. Intracranial manifestations of Hodgkin´s disease. Surg Neurol 1980;13 (4), 258-65.
8. Sapozink MD, et al. Intracranial Hodgkin´s Disease. A report of 12 cases and review of the literature. Cancer 1983;52 (7): 1301-7.
9. Errante D et al. Combined antineoplastic and antiretroviral therapy for patients with Hodgkin´s disease and human immunodeficiency virus infection. A prospective study of 17 patients. The italian cooperative group on AIDS and tumors. Cancer 1994;73: 437-44.
10. Levine AM et al. Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multi-institutional AIDS clinical trials group study (ACTG 149). J Acquir Immune Defic Syndr 2000 24 (5): 444-50.
11. Spina M t al. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. Blood. 2002. Sep; 100 (6): 1984-1988.
12. Hartmann P et al. BEACOPP therapeutic regimen for patients with Hodgkin´s disease and HIV infection. Annals of Oncology 2003;14: 1562-9.
13. Xicoy B, Ribera JM et al. Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus-related Hodgkin´s lymphoma. Haematologica 2007;92 (02): 191-8.