



Langerhans cell histiocytosis with spinal cord involvement in HIV-positive children: a case report

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Abstract

Langerhans cell histiocytosis (HCL) is a mainly pediatric disease whose severity is highly variable and clinical presentation depends on the site affected. Excluding craniofacial lesions, the spine is the most frequently involved bone site. A 5-year-old male, admitted to a tertiary hospital with a history of three weeks of low back pain, with irradiation of lower limb pain, which made walking difficult, with partial improvement after the use of anti-inflammatories. He denied traumas, fever or other symptoms during the period. On physical examination, he presented pain on palpation of the lumbar region, absence of skin lesions or other alterations. Previous HIV diagnosis by vertical transmission, in irregular use of antiretroviral therapy (zidovudine, lamivudine, lopinavir, and ritonavir), with CD4+ cell count of 314/mm³ (12%) and viral load of 28,937 copies (log 4.46). Upon admission, he had normal blood count and high inflammatory activity tests. Computed tomography of the thoracolumbar spine showed destructive lesions of vertebral bodies of T4, T8, and L1. Patient was then submitted to vertebral biopsy, with anatomopathological examination of the tissue, receiving the diagnosis of HCL. In the isolated sample of bone tissue, culture for bacteria and fungi and PCR for tuberculosis were negative. HCL is a disease of difficult suspicion and diagnosis, since its low incidence and nonspecific symptoms, common to many pathologies. For the described patient, HIV infection with high viral load and low concentration of CD4+ lymphocytes made the diagnosis even more challenging.

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INTRODUCTION

As the immune status of people infected with HIV (human immunodeficiency virus) has improved, non-AIDS-defining malignancies (acquired immunodeficiency syndrome) have proportionally become much more important as a cause of morbidity and mortality in this population¹. Children with HIV have an increased risk of cancer^{2,3}, and the reasons associated with this relationship are diverse. Infiltrative lesions must always be considered in the differential diagnosis of bone pain and edema in these children². There is controversy over whether HIV would have a direct effect on cancer risk or whether the relationship is indirect¹.

The first pediatric cases were reported in hemophiliac patients, in which cancer was the first manifestation of THE HIV infection. Although the prevalence of cancer is lower in children than in infected adults^{2,3}. Pediatric patients have at least a 100-fold increased risk of developing cancer, when compared to uninfected children. The incidence of malignant tumors in children with HIV is 1 to 2.5%; and HIV-infected children with cancer have a shorter survival than uninfected ones^{2,3}. There is still insufficient data to determine whether early therapy would reduce the risk of cancer¹; but children with less than 2 years of therapy or with severe immunosuppression are at increased risk of developing proliferative diseases². North American estimates indicate an incidence ranging from 9.4 per 1,000 to 20 per 1,000, before starting ART³.

Langerhans Cell histiocytosis (HCL) is characterized by an abnormal and polyclonal proliferation of dendritic cells^{4,5}, which has the phenotypic characteristics of Langerhans cells, bone marrow-derived cells of monocytic origin that normally they reside in the skin and lymph nodes and function in the presentation of antigens^{4,6}, but they end up being restricted at an early stage of maturation, becoming functionally deficient⁷. Pathogenic cells can spread to almost all organs^{2,4}, and are often accompanied by infiltrates of lymphocytes, eosinophils, macrophages, and multinucleated giant cells⁶.

HCL is mainly a pediatric disease, but it can affect any age group^{4,6}. There is a predominance in males (1.7:1)⁴. The incidence is from 4.1 to 5.4 per million per year in the population^{4,10}. In children, the annual incidence is 3 to 9 cases per million, which makes it a rare disease⁶.

We report a case of Langerhans cell histiocytosis in a pediatric patient with a previous diagnosis of HIV.

CASE REPORT

A 5-year-old male child was admitted to a tertiary care hospital with a three-week history of low back pain, with pain radiating to the lower limbs, which made walking difficult, with partial improvement after the use of common anti-inflammatory drugs. He had had no trauma, fever, or other symptoms during the period. Upon physical examination, he had pain on palpation of the lower back, no skin lesions, or other changes. He had a previous diagnosis of HIV due to

vertical transmission, was in irregular use of antiretroviral therapy (zidovudine, lamivudine, lopinavir and ritonavir), with a CD4+ cell count of 314/mm³ (12%) and a viral load of 28,937 copies (log 4.46). Upon admission, he had a normal blood count and evidence of elevated inflammatory activity. Spine radiography was performed, which showed nonspecific lesion in T4 and T8 vertebrae, and computed tomography of the thoracolumbar spine, which showed destructive lesions of T4, T8 and L1 vertebral bodies.

The patient was then submitted to a T8 vertebral biopsy, which pathology exam of the tissue, led to the diagnosis of LCH. In the isolated sample of bone tissue, cultures for bacteria and fungi and PCR for tuberculosis were negative. He then underwent chemotherapy with vinblastine and had his antiretroviral regimen changed to zidovudine, lamivudine, darunavir, ritonavir, raltegravir and enfuvirtide. He responded well to the antiretroviral drugs, with a drop in viral load to 52 copies (log 1.71) in 4 weeks of use, which represented a reduction of 2.75 log. The patient evolved with good HCL control, being discharged after vinblastine infusion, using oral corticosteroids, for outpatient follow-up. Five days after hospital discharge, he suddenly developed nausea, vomiting, cyanosis of the extremities and was taken to a point-of-care unit where he evolved with cardiorespiratory arrest and death.

COMMENTS

The case reported concerns a pediatric patient, 5 years old, male, HIV positive, diagnosed with unifocal HCL in his lumbar spine. Therefore, it falls within the predominant age group for the non-disseminated disease, and it is also the most affected sex, although the location of the lesion is not the most common in this type of patient^{4,5,9}.

HCL is a disease that is difficult to suspect and diagnose, given its low incidence and nonspecific symptoms, common to many pathologies⁶. For the patient described HIV infection with a high viral load and a low concentration of CD4+ T-lymphocytes made the diagnosis even more challenging, since in these patients the association of the pathology with HIV is rare²; and there is an increased incidence of several diseases, benign or malignant, that also need to be considered, such as vertebral tuberculosis, spondylodiscitis, and lymphomas.

Clinical manifestations are widely varied¹⁰ and are related to the site of location, but bone lesions are more characteristic⁸. The most common are unifocal bone lesions in the head and neck⁴, and when the involvement is skeletal, pain and swelling are the most common^{8,9}. Excluding craniofacial lesions, the spine is the most affected bone region in the pediatric population, as in the case described, in which lytic lesions were found in vertebral bodies T4, T8 and L1, leading to vertebral flattening and clinical low back pain with irradiation to lower members.

Imaging exams play a crucial role in diagnosis, especially in the case of bone lesions⁵. Typically, bone involvement is

represented by diffusely destructive lytic lesions with well-defined soft tissue margins without sclerosis^{4,5}. In conventional tomography, it is shown as a destructive bone lesion⁴. Spinal involvement usually appears as a flattening of the vertebral body (flat vertebra), but the pedicle, lamina, and transverse process may be involved.

Radiological findings can also be well-defined with computed tomography (CT), magnetic resonance (MR) and Tc-99 Bone Scan. The diagnosis must include complete blood count, coagulogram, liver function tests and urinary osmolality⁴, and must be confirmed by biopsy to rule out other bone lesions with similar radiological appearance and establish a definitive diagnosis^{5,8}.

Upon examination, the patient had formalin-fixed tissue under optical microscopy, showing reactive infiltration of immature granulocytes, eosinophils, and Langerhans cells. These Langerhans cells have abundant vacuolated cytoplasm, with oval vesicular nuclei^{4,5}.

The diagnosis is confirmed by immunohistochemical detection of S-100 protein from surface antigens, leukocyte adhesion molecules (CD1 antigens) and anti-langerin (CD207)^{5,10,11}. Bone marrow aspiration, liver, spleen and chest imaging, liver and lung biopsy, and immunological studies are reserved for specific patients, to rule out multisystem involvement⁴.

The clinical course is unpredictable and can be rapidly progressive and fatal or evolve with spontaneous resolution. Age at presentation, multisystem involvement and vital organ dysfunction are the main associated prognostic factors. The prognosis is worse in children under two years of age^{4,9}. Neuropsychiatric consequences are the most debilitating, and the orthopedic ones are the most common¹⁰.

The variability in terms of severity, etiology, and pathogenesis, associated with the rarity of the disease leads to a lack of consensus in management and treatment⁵. There are several treatment modalities for bone HCL, including surgery, radiation therapy, chemotherapy, and steroids. Treatment can be done alone or in combination, depending on the extent and severity of the disease⁴. Chemotherapy is preferred by most authors when there is multifocal disease; and different protocols have already been described. Current recommendations for the treatment of multisystem LCH call for the use of prednisone and vinblastine as first-line, intensive weekly treatment regimen for 6 weeks, followed by maintenance therapy for a total of 12 months. There are several options for refractory multisystem LCH, including cytarabine and cladribine or hematopoietic stem cell transplantation⁶.

The treatment of spinal LCH should be as conservative as possible, using symptomatic and supportive measures,

except for aggressive lesions that compromise stability or extend to neural structures⁸. In addition to the diagnostic difficulty that this entity brings, especially when associated with HIV, the need for chemotherapy while on antiretroviral therapy implies a lot of attention and care, both because of the possibility of drug interaction and because of the effects on the patient's immune system, target of both therapies².

Finally, HCL is a disease with heterogeneous, nonspecific manifestations, difficult to diagnose and non-standardized to treat. The increase in its incidence in HIV-infected patients has not been described; however, when this association is present, diagnosis and treatment become even more challenging, due to the numerous differential diagnoses and the difficulty in associating treatment for both conditions without harm to the patient.

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