Langerhans cell histiocytosis in a pediatric HIV patient

Rachna Seth¹ · Panneer Selvam¹ · Richa Jain¹ · Ranajoy Gosh² · Jenish Arun¹ · Rakesh Lodha¹

Received: 12 May 2015 / Accepted: 25 June 2015 / Published online: 28 July 2015
© Indian Virological Society 2015

Abstract Children infected with human immunodeficiency virus (HIV) have an increased risk of malignancies. Herein, we present a 16 month old HIV infected child receiving antiretroviral therapy who presented with pain and swelling of both knees and ankles. This child was diagnosed as Langerhans cell histiocytosis (LCH) which is an uncommon proliferative disorder rarely reported in a HIV patient. The child was treated with chemotherapy and is well clinically. Infiltrative disorders like LCH should be kept among the differential diagnosis of bony pain and swelling in HIV infected children.

Keywords Malignancy · Histiocytosis · HIV · Chemotherapy

Children with HIV infection have an increased risk of malignancies. [3] HIV-associated malignancies remain an important cause of morbidity and mortality among HIV-infected children. The incidence of malignancies in pediatric HIV cases is less compared to adults [1, 3]. Non hodgkins lymphoma is the commonest malignancy followed by solid tumors. Viral infections like EBV and immunosuppression as defined by low CD4 counts are important risk factors for development of malignancies in such patients [8]. We report an unusual case of LCH occurring in an HIV infected child on combination antiretroviral therapy (ART).

A 16 month old male child, known case of HIV infection on anti-retroviral therapy (stavudine + lamivudine + nevirapine) since 4 months of age presented with the complaints of pain and swelling around both knees and ankles for 1 month duration. There was no history of fever, trauma, similar symptoms involving other joints, bleeding from any site, blood transfusions and contact with tuberculosis. The child was previously diagnosed to have CMV infection based on urine CMV PCR with evidence of CMV retinitis.

On examination there was swelling, tenderness and warmth involving distal 1/3 of the left leg and swelling of both knees. Systemic examination revealed a hepatomegaly of 5 cm below the costal margin. Rest of the systemic examination was normal. The clinical possibilities considered were osteomyelitis or arthritis.

The investigations revealed a normal hemogram (Hb.—9.6gm %, Plt.—1,76,000/cubic mm, TLC-4800/cubic mm). The X-rays of both knees and legs revealed irregular lytic lesions in eccentric locations in metaphyses of right proximal femur, distal femur and lower end of both tibia along with regular solid pattern, and periosteal reaction along the medial aspect of the bilateral tibia—features suggestive of multifocal lytic lesions possibly infective or infiltrative (Fig. 1). Rest of the skeletal survey including chest radiograph was normal. Technetium 99 MDP bone scan showed irregular areas of radiotracer uptake involving upper end of right femur and lower end of left tibia in blood flow and blood pool images—scan findings suggestive of infective/inflammatory/infiltrative pathology. Workup for tuberculosis (Tuberculin skin test, Chest X ray) was not contributory. Core biopsy from left distal tibia showed bony trabeculae with fragment comprising of sheets of cells with nuclear grooves and convolution and lymphocytes, eosinophils and monocytes in background. The cells were immunopositive for CD1a—compatible

✉ Rachna Seth
drrachnaseth@yahoo.co.in

¹ Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

² Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

Fig. 1 X-ray showing lytic lesions at the *lower* end of both tibia

Fig. 2 Bone biopsy showing CD1a positive cells

with LCH (Fig. 2). The liver and renal function tests were normal. Ultrasound examination of the abdomen revealed a normal echotexture, no periportal involvement, no evidence of retroperitoneal mass, adenopathy or free fluid. The absolute value of CD4 count was $1748/\text{mm}^3$. The final diagnosis was langerhans cell histiocytosis—Single

system, multifocal bone disease: no involvement of risk organs. The diagnosis of LCH is clinicopathologic based on clinical findings and histologic/immunohistochemical criteria [10]. The child was started on prednisolone (40 mg/sqm) and vinblastine (6 mg/sqm) chemotherapy. The child also continued on antiretroviral treatment. On follow up after 24 weeks of starting chemotherapy, the child is afebrile with subsidence of symptoms of swelling and pain in lower limbs.

Like in adult HIV patients, malignancies are common also in pediatric cases. Mueller et al. estimated that there was at least a 100-fold increased risk of malignancy in HIV infected children [6]. Aggressive cellular proliferative disorders in children with HIV infection have decreased following the introduction of ART. It is realized that children on ART for less than 2 years and those with profound immune suppression are at increased risk for proliferative disorders. From a US surveillance cohort of 4954 children with AIDS, 124 children (2.5 %) were identified as having a malignancy [3]. In a multicentric case control study, 43 HIV infected children were

diagnosed with malignancies out of those 4 (9.2 %) had B cell acute lymphoblastic leukemia (ALL); 28 (65 %), non-Hodgkin lymphoma (NHL); 1 (2.3 %), Hodgkin disease (HD); 8 (18.6 %), leiomyosarcoma; 1 (2.3 %) hepatoblastoma; and 1 (2.3 %), schwannoma [8].

There are only a few reports of histiocytosis in HIV infected individuals mostly in adult patients. To our knowledge there are only 2 cases of fatal histiocytic proliferative disorders in pediatric HIV infection with CMV disease; one was an infant with sinus histiocytosis with massive lymphadenopathy (SHML) and the second case was that of hemophagocytic lymphohistiocytosis (HLH). Both were started on therapy with methylprednisolone but one of them succumbed to the disease and in the other therapy was stopped due to complications [7]. To the best of our knowledge LCH in a HIV infected child has not been reported.

LCH is characterized by a clonal proliferation of pathologic cells with the characteristics of Langerhans cells in single or multiple organs. The question about LCH whether it is a reactive or neoplastic disorder still remains unanswered. Clonality, familial clustering, recurrent BRAF mutations, elevated expression of P 53, Ki67, RAS, c-myc, Bcl-2 and LOH on chromosomes 1,4,6,7,9,16,17 and 22 Are indicators of a neoplastic process. the other hypothesis is that LCH is a reactive process wherein immune dysregulation often triggered by viral infections leads to aberrant reaction between T lymphocytes and Langerhans cells [2] Studies were done to relate LCH to viral etiologies but were not able to prove such a relationship. McClain et al. used sensitive in situ hybridization and polymerase chain reaction (PCR) techniques in 56 LCH patients but failed to find evidence of genomes for adenovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpes virus type 6, human immunodeficiency virus, human T-cell leukemia virus types I and II, and parvovirus [7]. HIV infection per se could least likely to be the cause of LCH in our patient. Concomitant HIV and CMV infection could be the cause contributing to the etiology of LCH in this patient. As demonstrated by the previous report of 2 similar cases by Nastouli et al., infections can act synergistically in a myelosuppressive manner and provide antigenic and inflammatory context for the development of histiocytic proliferations [7].

Chemotherapy in AIDS patients can be a double-edged sword since its anti-tumor effects must be balanced against

its possible deleterious effect on the underlying condition. Potential problems include increased risk of infections, worsening of pre-existent hematological deficits, and development of more severe chemotherapy-related toxicity. Most of the reported study series of children with AIDS and malignancies, predominantly NHL, show a short median survival time of about 6 months following initiation of chemotherapy.[4, 5] LCH, a proliferative disorder that mimics cancer, often is less aggressive and requires fewer chemotherapeutic agents which are well tolerated as compared to multiagent chemotherapy used for leukaemia/lymphoma. Patients of LCH who respond to chemotherapy have a 88–91 % survival rate [9].

Infiltrative disorders like LCH should be kept among the differential diagnosis of bony pain and swelling in HIV infected children. A skeletal survey followed by biopsy from appropriate sites would help in diagnosis.

References

1. AlGhamdi A, Beyzael-Arani A, Albarghuthy B, Shwartz A, Jain V. Pulmonary Langerhans cell histiocytosis and HIV infection. *American Journal of Resp and Critical care medicine*. Meeting Abstracts. A 43. Case Reports: Int lung Disaese 2014:189.
2. Abba Q, Egeler RM, Weitzman S. Langerhans cell histiocytosis: current concepts and treatments. *Cancer Treat Rev*. 2010;36:354–9.
3. Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. *JAMA*. 2000;284:205–9.
4. Gonzalez CE, Adde M, Taylor P, Wood LV, Magrath I. Impact of chemotherapy for AIDS related malignancies in pediatric HIV disease. *Ann N Y Acad Sci*. 2000;918:362–6.
5. McClain K, Jin H, Gresik V, Favara B. Langerhans cell histiocytosis: lack of a viral etiology. *Am J Hematol*. 1994;47:16–20.
6. Mueller BU. HIV associated malignancies in children. *AIDS Patient Care STDS*. 1999;13:527–33.
7. Nastouli E, Carrol E, Malone M, Riordan A, Lyall H. Fatal histiocytic proliferative disorders in pediatric HIV infection with cytomegalovirus end-organ disease. *B J Hematol*. 2009;146:580–2.
8. Pollock BH, Jenson HB, Leach CT, Mc Clain KL, Hutchinson RE, Garzarella L, et al. Risk factors for pediatric human immunodeficiency virus-related malignancy. *JAMA*. 2003;289:2393–9.
9. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol*. 2008;25(3):291–5.
10. Weitzman S, Egeler RM. Langerhans cell histiocytosis: update for the pediatrician. *Curr Opin Pediatr*. 2008;20:23–9.