Precursor NK Cell Lymphoblastic Leukemia/Lymphoma— Report of a Case with Literature Review

Sonal Jain · Rajiv Kumar · Abhishek Purohit ·
Hara Prasad Pati

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Abstract Precursor Natural Killer (NK) cell lymphoblastic leukemia/lymphoma is a rare entity defined clearly by WHO (2008 WHO classification). However, the pathobiology of this subset of neoplasms is not clearly defined. There is wide disparity in the literature regarding the nomenclature and diagnostic criteria used to diagnose and characterize acute leukemias of presumed NK cell origin. In the present article we report a case of Precursor NK cell lymphoblastic leukemia/lymphoma and review the cases reported after 2008 WHO classification came into vogue, as acute leukemias of NK cell origin.

Keywords Natural killer · Leukemia · Precursor

Introduction

There is considerable confusion in the literature with respect to terminology used as well as the treatment protocol used for Precursor Natural Killer (NK) cell leukemia/lymphoma. WHO 2008 classification has defined this entity

and separated it from previously reported Myeloid/NK cell Precursor acute leukemia, Blastic Plasmacytoid Dendritic Cell tumor and Acute lymphoblastic leukemia (ALL) expressing NK cell markers. On review of cases reported after 2008, the different terminologies used include Myeloid/NK cell precursor acute leukemia (MNKPL), Myeloid/NK acute leukemia (MNKL), Blastic NK cell leukemia/lymphoma and Precursor NK cell lymphoblastic leukemia/lymphoma. In the present article we describe a case of NK cell Lymphoblastic leukemia/lymphoma and review the cases reported as NK cell acute leukemia after WHO 2008 classification came into vogue [1].

Case Report

23 year old male presented with history of intermittent fever, body ache, fatigue and weakness of 1 month duration. On examination, he was pale and afebrile. There were bilateral, discrete, non-tender, cervical and axillary lymphadenopathy of 0.5–1.0 cm, liver was palpable 2 cm below costal margin and spleen was palpable 3 cm below costal margin. He also had sternal tenderness. Testicular examination was normal and there were no skin nodules or rash.

CT scan chest showed multiple mediastinal lymphadenopathy (largest being 2×2 cm in size) with normal lung parenchyma and mild bilateral pleural effusion. Hemogram showed a hemoglobin of 6.5 gm/dl, TLC of $75 \times 10^3/\mu\text{l}$ and platelet count of $45 \times 10^3/\mu\text{l}$. Peripheral blood smear showed 91 % blasts which were large with abundant agranular pale basophilic cytoplasm, fine nuclear chromatin with inconspicuous to single nucleolus. Bone marrow smears showed near total replacement with blasts showing similar morphology. Flow cytometry was done on bone

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S. Jain (✉) · R. Kumar · A. Purohit · H. P. Pati
Department of Hematology, All India Institute of Medical
Sciences, New Delhi, India
e-mail: sonalmalhotra80@gmail.com

R. Kumar
e-mail: k_rajiv76@yahoo.com

A. Purohit
e-mail: garcon007@yahoo.com

H. P. Pati
e-mail: harappati@yahoo.co.in

Fig. 1 Bone marrow aspirate showing large cells with moderate to abundant amount of agranular cytoplasm showing inconspicuous to single nucleolus

marrow aspirate using BD FACS Canto II and analysed using BD FACS Diva software. The blasts were positive for CD2, CD5, CD7, CD56, TdT, HLADR, and negative for cMPO, cCD3, cCD79a, CD13, CD33, CD117, CD10, CD19, CD22, CD64, CD11c and CD34. Bone marrow cytogenetics was inconclusive. CSF examination showed no blasts. Based on these findings and absence of skin lesions, a diagnosis of NK cell lymphoblastic leukemia/lymphoma (Provisional, WHO 2008) was made. The patient was treated using the Augmented BFM chemotherapeutic protocol with prednisolone and 4 weekly cycles of Daunorubicin with Vincristine along with L-Asparaginase. The day 7 marrow was M1 (<5 % blasts). The induction chemotherapy course was uncomplicated and day 31 marrow was in remission with no clinical evidence of hepatosplenomegaly or lymphadenopathy (Fig. 1).

On D34 he was started on consolidation chemotherapy. Post induction, the patient received consolidation chemotherapy and prophylactic cranial radiotherapy. In view of the aggressive nature of the disease, he was given interim maintenance-II and delayed intensification-II as per protocol, although he had a M1 marrow on D7 of initial induction chemotherapy. CSF analysis for CNS disease remained negative throughout and he received all his intrathecal methotrexate doses as per protocol. On completion of DI-2, he has been started on maintenance chemotherapy, which he has been tolerating well for the last 2 months and continues to be in remission.

Discussion

There is considerable confusion in the literature regarding the nomenclature, diagnostic criteria and treatment

protocol used for acute leukemias presumed to be originating from NK cells. According to WHO 2008 classification the diagnosis of precursor NK lymphoblastic leukemia/lymphoma may be considered in a case in which the blasts express CD 56 along with immature T associated markers such as CD7, CD2 and even cCD3, provided that it lacks B cell markers and myeloid markers.

The previously defined entity of myeloid/NK cell acute leukemia which was suggested to be of precursor NK cell origin has a phenotype that is indistinguishable from acute myeloid leukemia with minimal differentiation and should be considered as AML until further evidence emerges [1].

Despite this attempt at clarifying the concept of “Precursor NK cell lymphoblastic leukemia/lymphoma” by WHO 2008, the confusion in the literature persists. Early in development, NK cell progenitors express no specific markers or express markers that overlap with those seen in T cell ALL, including CD7, CD2 and even CD5 and cCD3 (ε), so that distinguishing between T ALL and NK-cell tumors may be difficult.

Guan et al. [2] described 5 pediatric patients with leukemias possibly arising from immature NK cells. Four out of these five cases were diagnosed as Myeloid NK Precursor Leukemia (MNKPL) with blasts being cytochemically MPO (–) and phenotypically CD56 (+), CD3 (–), CD7(+), CD34(+) and myeloid antigens(+). These four patients were treated with a protocol designed for childhood high risk ALL. One case was labeled as Myeloid NK cell Leukemia (MNKL) defined as blasts cytochemically MPO (dim) and phenotypically CD56 (Pos), CD16(Neg), CD3(Neg), CD33(Pos), HLA DR (Neg). This patient (MNKL) abandoned treatment.

On reclassification according to 2008 WHO classification, all of these 5 patients will be labeled as AML (with NK cell markers). All five of these cases although were diagnosed between 2005 and 2008.

Similarly Owatari et al. [3] described 2 cases of immature NK cell neoplasms expressing CD 56 along with different combinations of myeloid antigens. Hashii et al. [4] reported a case of CD13, CD33, CD56 positive leukemia diagnosed as Myeloid NK cell precursor lymphoma/leukemia. Chen et al. [5] reported a case diagnosed as MNKL expressing CD33, CD117, MPO and CD56. Ma et al. [6] reported a case of MNKPL with multiple subcutaneous nodules. According to new WHO classification, all of the above mentioned cases will be diagnosed as AML (expressing NK cell markers).

The treatment protocol used and the outcome in the studies cited is summarized in Table 1.

Acute leukemias (myeloid/lymphoid) expressing NK cell markers have been shown to have poor prognosis. Suzuki et al. [7] analysed 49 patients with CD7(+), CD56(+) AML. Seventeen were AML M0 and 32 were

Table 1 Summary of the treatment protocols used and outcome in the studies quoted

Study	Diagnosis	Treatment	Outcome
Present study	Precursor NK lymphoblastic leukemia/lymphoma	Augmented BFM protocol (ALL)	Complete remission
Guan et al. [2]	4-MNKPL 1 MNKL	MNKPL—childhood high risk ALL MNKL7—abandoned treatment	CR in $\frac{3}{4}$ 1/4 died in CR from pneumonia
Owatari et al. [3]	Blastic NK cell lymphoma with expression of myeloid antigen	3 courses of AML oriented therapy	Multiple relapses
Hashii et al. [4]	MNKPL	ALL oriented t/t at relapse Refractory—PBSCT	Died at D 210 of PBSCT of septic shock
Chen et al. [5]	MNKL	AML oriented therapy	Complete remission
Ma et al. [6]	MNKL	DA skin nodules did not regress F/b FLAG	Complete remission after second course (FLAG)

AMLs other than AML M0. This subset was found to have poor prognosis. Dalmazzo et al. analysed 84 T all case and found that CD 56 and/or CD16 were expressed in 28.5 % (24) of these cases. The mean overall survival and disease free survival were shorter in this subset of patients. CD56/CD16 were found to be independent variables for disease free survival [8].

The disparity in the literature regarding the diagnostic criteria used to diagnose NK cell leukemias reflects how little is our knowledge regarding the pathobiology of precursor NK cell leukemias. The poor prognosis of other leukemias (ALL and AML) expressing NK cell markers is probably a reflection of a missing link which needs to be explored. Whether myeloid or lymphoid leukemias expressing NK cell markers are more akin to NK cell precursor leukemias or myeloid/lymphoid leukemias respectively is still not clear. The problem is compounded by the different treatment protocols and outcome reported in the limited literature available.

Conclusion

Precursor NK cell leukemia/lymphoma is an incompletely understood nomenclature with incomplete diagnostic criteria. There is a wide disparity among cases diagnosed as acute leukemia of presumed NK cell origin. Thus the treatment protocol used and outcome reported is also highly variable. For a better understanding and unified treatment of this rare subset of patients, a better definition

and demarcation from other acute leukemias is still needed.

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