Adult T Lymphoblastic Leukemia (Pro-T ALL) with Reactive Monocytosis: A Case Report

Rachna Khera · Parul Gautam · Sanjeev Gupta ·
Prerna Arora · Tejinder Singh · Naresh Gupta

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Introduction

Malignant lymphoid neoplasms of precursor T cell origin have been designated as T-lymphoblastic leukemia/lymphoma in the recently published world health organization classification for hematologic neoplasms [1]. T-acute lymphoblastic leukemia, T-ALL is a neoplasm of lymphoblasts committed to T-lineage, involving bone marrow and blood. T-ALL comprises of about 15 % of childhood and 25 % of adult ALL. Owing to its relative rarity, T-ALL arising in adults, has not been studied extensively. It typically presents with a high leukocyte count, often a large mediastinal mass of tissue with hepatosplenomegaly and lymphadenopathy. T-ALL can be stratified into different stages of intrathymic differentiation according to antigens expressed: Pro-T, Pre-T, Cortical-T and Medullary-T. Some studies have shown a correlation between the stages of T cell differentiation and survival. Compared to B-ALL, T-ALL patients have increased risk for induction failure, early relapse and isolated CNS relapse. We present a case of adult T-ALL with reactive monocytosis and rapidly fatal outcome, an association which has not yet been described in the literature but when present might cause diagnostic confusion with monocytic leukemias both morphologically

as well as immunophenotypically and may possibly point towards a biologically more aggressive disease.

Case Report

21 year old man presented to the hospital with 1 month history of fever, diarrhea, painless progressive swellings in the neck region, weight loss. General physical examination revealed lymphadenopathy in bilateral submandibular, axillary, inguinal and left epitrochlear region along with presence of bony tenderness. Abdominal examination and USG revealed hepatosplenomegaly and enlargement of retroperitoneal group of lymphnodes (aortocaval and para-aortic region), largest measuring 2.4 cm × 1.2 cm. Chest X-ray and CT scan revealed superior mediastinal widening due to a lymphoid mass (Fig. 1a, b) and axillary, abdominal and inguinal lymphadenopathies (Fig. 2). Complete blood counts were: total leukocyte count $23 \times 10^9 \text{ l}^{-1}$, hemoglobin 11.7 %, platelet count $60 \times 10^9 \text{ l}^{-1}$. Differential leukocyte count performed on peripheral blood smear showed presence of 8 % blast cells with 35 % monocytoid cells while polymorphs and lymphocytes comprised 42 and 15 % of the DLC. In view of the presence of monocytoid cells in the peripheral smear (>20 %), and blast cells (8 %), bone marrow examination was advised to rule out acute leukemia possibly of monocytic lineage. Bone marrow aspirate smears, however, diluted with peripheral blood revealed blast cells constituting 60 % of marrow nucleated cells which were variable in size with opened up nuclear chromatin, inconspicuous nucleolus and high N:C ratio, few blasts also demonstrated nuclear irregularity and notching. Cytochemistry performed on peripheral blood smears as well as on BMA smears demonstrated blast cells to be negative for both MPO and NSE

R. Khera · P. Gautam · S. Gupta · P. Arora · T. Singh ·
N. Gupta

Department of Pathology, Maulana Azad Medical College and
Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi
110002, India

R. Khera (✉)

Department of Pathology, Maulana Azad Medical College and
Lok Nayak Hospital, Room No. 62, Bahadur Shah Zafar Marg,
New Delhi 110002, India

e-mail: rachnakhera@yahoo.com; wadhwa.rachna@gmail.com

Fig. 1 **a** Chest X-ray: superior mediastinal mass likely lymph node enlargement. **b** CT scan coronal image showing mediastinal mass

Fig. 2 CT scan transverse section showing lymphadenopathy in the abdomen

while showing polar positivity with acid phosphatase (Fig. 3). Monocytic component was positive for NSE. Immunophenotyping was performed on peripheral blood as well on bone marrow sample using flow cytometry. There were two distinct populations of cells corresponding to blast cells and larger monocytoid cells. Blast cells expressed CyCD3, CD7, CD10 and CD13, however, were negative for CD2, sCD3, CD19, CD20, CD34, HLA-DR, CD33, CD117 and CD5 (Fig. 4). The monocytoid cells

were negative for cyCD3, sCD3, CD2, CD7, CD10, CD19, CD117, CD34 and expressed CD33, HLA-DR and CD11c (Fig. 5). The patient expired just after the diagnosis before treatment could be started.

Fig. 3 Acid phosphatase stain showing polar positivity in the blast cells

Fig. 4 **a** CD45/SS plot showing two populations A CD45 moderate, blast population (21.1 %) and CD45 bright, monocytoid population (20.8 %). Blast population is positive for cyCD3 and CD7 as shown above. Blast cells also expressed CD10 and CD13 and were negative

for CD2, sCD3, CD19, CD20, CD34, HLA-DR, CD33, CD117 and CD5 (not shown). **b** Blast cells expressing positivity for cyCD3. **c** Blast cells expressing positivity for CD7

Fig. 5 Monocytoid population expressing CD33, HLA DR and CD11c

Discussion

T-ALL is an aggressive neoplasm derived from malignant transformation of lymphoblasts committed to T cell lineage. The results of therapy of adult ALL remain unsatisfactory [2]. Despite complete remission rates up to 80–90 %, similar to those obtained in children, the prognosis in adults is less favourable, mainly because of high rates of relapse. The relative rarity of T cell ALL in adults has made it difficult to describe clinical and biologic factors determining outcome [3]. Our case was diagnosed as Pro-T ALL based on cyCD3+/CD7+/CD2–/CD5–/sCD3–/CD34– immunophenotype. Pro-T ALL, also called T-I ALL, is extremely rare disease where cells at the

earliest defined stage of T-lineage maturation proliferate in the bone marrow. They are characterized by the absence of all T-lineage differentiation markers except intracytoplasmic CD3 and surface CD7 [4]. In a study by Garand et al. [5], on T-ALL, Pro-T immunophenotype was observed more often in adults and showed lower incidence of hyperleukocytosis than more mature T-ALL, which was also seen in our case, adult age group with WBC count was $<30 \times 10^9$. There have been doubts regarding the clinical relevance of subgrouping T-lineage ALL according to thymocyte maturational stages (Pro-T, Pre-T, Cortical and Medullary) since the early days of immunophenotyping [6]. Recently, Pro-T ALL has been reported to have unfavourable outcome by CALBG and German study

group [7]. Babusikove et al. [8] confirmed Pro-T ALL to have unfavourable prognosis because of being either completely responsive to the therapy or having persistent MRD during continuation phase. Garand et al. [5] also suggested a poorer outcome for Pro-T ALL in adult patients similar to our case who also had aggressive clinical course and fatal outcome. While in a study done by Marks et al. [9] with the exception of the CD1a cortical stage, the maturation level of T lymphoblasts was not associated with prognostic significance. Our case showed an aberrant expression of myeloid antigen (MyAg) CD13; moderate in 74 % of the gated cells. Few studies have evaluated the clinical significance of immunophenotyping in childhood acute lymphoblastic leukemia [10] but the prognostic value of MyAg expression in adult ALL is a controversial issue [11]. Lack of expression of CD13 was associated with better survival in cases of acute T-ALL in a study by Marks et al. Vitale et al., documented MyAg expression in 35 % of the adult ALL cases analyzed; more frequently associated with B-lineage ALL (38 %) than with T-ALL (24 %) and there was no impact of CD13 antigen expression on prognosis in cases of adult ALL. Similar findings were documented by Iwamoto et al. [12]. Garand et al. demonstrated My Ag expression more frequently in Pro T-ALL than in late T-ALL. Our case showed a dim expression of CD10 in 74 % of the blast cells. A review of the literature shows that immunodetection of CD10 in T-lymphoblastic leukemia/lymphoma (LBL/L) using fresh tissue (flow cytometric suspensions or frozen sections) varies from 15 to 40 % [13–16]. CD10 is expressed in lymphoid progenitor cells and has been found to play a specific role in promoting early T cell development [17–19]. Although the absence of CD10 expression in B-ALL is reportedly associated with poor outcome [20], its expression in T-ALL in relation to the clinical outcome is more uncertain. Coexpression of a T cell marker and CD10 is highly indicative of immature T cells, making CD10 a valuable tool in the assessment of T cell lesions. A review by Pui et al. [21] showed that CD10 expression is not an independent prognostic factor in B- or T-ALL. Consolini et al. [22] in their study also stressed upon the lack of its independent significance either in B-lineage or T cell lineage ALL.

Presence of monocytic component in our case raised a suspicion of acute monocytic leukemia. But the immunophenotype was unequivocally in favor of T ALL with characteristic lymphoid blast morphology and MPO and NSE negativity in blast cells so monocytosis in this case was labeled as reactive. Causes of reactive monocytosis are myriad and include infections, inflammation, hematological disorders such as chronic myeloproliferative neoplasms, myelodysplastic syndromes, acute monocytic leukemia and Hodgkin's disease. Association of monocytosis with ALL

has rarely been reported, Braham et al. [23]. reported a case of T ALL with Ph+ monocytosis with presence of signs of dysplasia and monocytic contingent evoked a confusion with myeloid acute leukemia which was resolved by immunophenotype characteristic of T-ALL. The karyotype showed the presence of Philadelphia chromosome in all the mitotic figures. Though karyotyping could not be done in our case, we suggest that such cases should be looked for the presence of Ph chromosome as it portends a poor prognosis in adult ALL cases and though rare in T-ALL, may be one of the underlying factors for the biologically aggressive behavior in this case.

Conclusion

Recognition of T-lineage acute lymphoblastic leukemia is important as historically unfavourable outcome has now been improved by effective treatment protocols. Stratification into stages of intrathymic differentiation can be helpful as poor outcome is suggested for early T cell immunophenotype, i.e. Pro-T stage. We propose that cases with peripheral blood monocytosis should be looked for the presence of Ph chromosome as it can help in identifying biologically aggressive group of T ALL and thus outcome of such cases may further be improved.

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