Utility of Ancillary Techniques in Cytopathology to Detect Relapse in a Known Case of T Cell Acute Lymphoblastic Leukemia in Hematological Remission

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ABSTRACT

Introduction: Fine-needle aspiration offers a suitable alternative to biopsy in a variety of clinical settings, and there are many studies demonstrating the possibility of using it not only for diagnosis but also to assess therapy response.

Case report: Here we describe a case of T cell acute lymphoblastic leukemia who although was in hematological remission but had central nervous system, testicular and skin involvement which was detected using cytology and ancillary techniques thereby altering the therapy.

Conclusion: Use of FNA and ancillary techniques are reliable non invasive modalities that can establish not only the diagnosis but also should be used to accurately monitor.

Keywords: acute lymphoblastic leukemia, cytology, relapse

INTRODUCTION

Fine-needle aspiration (FNA) offers a suitable alternative to biopsy in a variety of clinical settings.[1] However, not all cytology specimens of suspected lymphoreticular neoplasms can be diagnosed with certainty, especially if the cells lack characteristic morphologic features of malignancy. For example, differentiation of benign lymphocytes from cells of acute lymphoblastic leukemia of the FAB-L1 type in the CSF may not be possible.[2] Similarly, the distinction of small cell lymphomas, small cleaved cell lymphomas, or peripheral T-cell lymphomas from normal lymphocytes in CSF or pleural fluid can be extremely difficult on morphologic grounds alone. These same problems also apply to the interpretation of FNA of suspected lymphoid neoplasms.[3]

Flow cytometric analysis has become the standard method of immunophenotyping blood and bone marrows of patients with leukemia or lymphoma and is easily adapted to the evaluation of body fluids and lymph node aspirates.[3,4] Immunocytochemistry and recently, molecular techniques like flow cytometry (FC) are ancillary tools that contribute not only to the diagnosis but also to assess prognosis and prediction of tumor behavior. Therapies are now being directed towards molecular targets; therefore, the use of ancillary techniques in cytology is a challenge, demanding strict standardization.[1]

CASE REPORT

16 years old male presented in Dept of Cytopathology with bilateral testicular swelling and left cervical lymphadenopathy. The FNA smears from left cervical lymph node were markedly cellular comprising predominantly of monotonous population of atypical lymphoid cells arranged in sheets as well as scattered singly. They had high N: C ratio, coarse chromatin with cleaved and clefted nuclei and scant cytoplasm (Fig 1). FNA from left testicular swelling revealed adequate cellularity predominantly composed of atypical lymphoid cells with morphology as described above. On enquiring it was revealed that patient was a known case of T cell acute lymphoblastic leukemia (T-ALL) who was diagnosed three months back. Flow cytometry of bone marrow sample had shown that blasts were positive for cyCD3, CD7, and co-positive for CD4 and CD8 and were negative for CD34 and other myeloid markers (Fig 2). He had received preinduction protocol with dexamethasone 6 mg/m^2, prednisolone 60 mg/m^2, methotextrate IT stat; Induction with vincristine 1.5 mg/m^2, Danorubicin30 mg/m2, Asparaginase 105000 U/m^2 in divided doses. Post induction bone marrow examination revealed remission and patient was planned for Ph II induction therapy. He did not harbour any cytogenetic abnormality and his karyotype was 46 X, Y. However, the patient had presented with VII cranial nerve

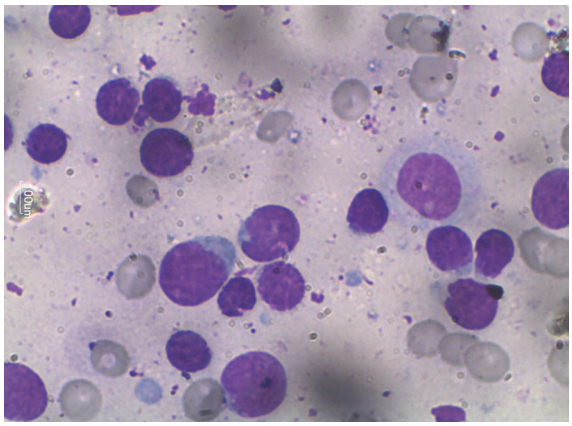

Figure-1: Fnac of cervical lymph node

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How to cite this article: Shiv Pankaj Khanna, Rigvardhan, Prabal Deb. Utility of ancillary techniques in cytopathology to detect relapse in a known case of T cell acute lymphoblastic leukemia in hematological remission. International Journal of Contemporary Medical Research 2018;5(9):I1-I4.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.9.8

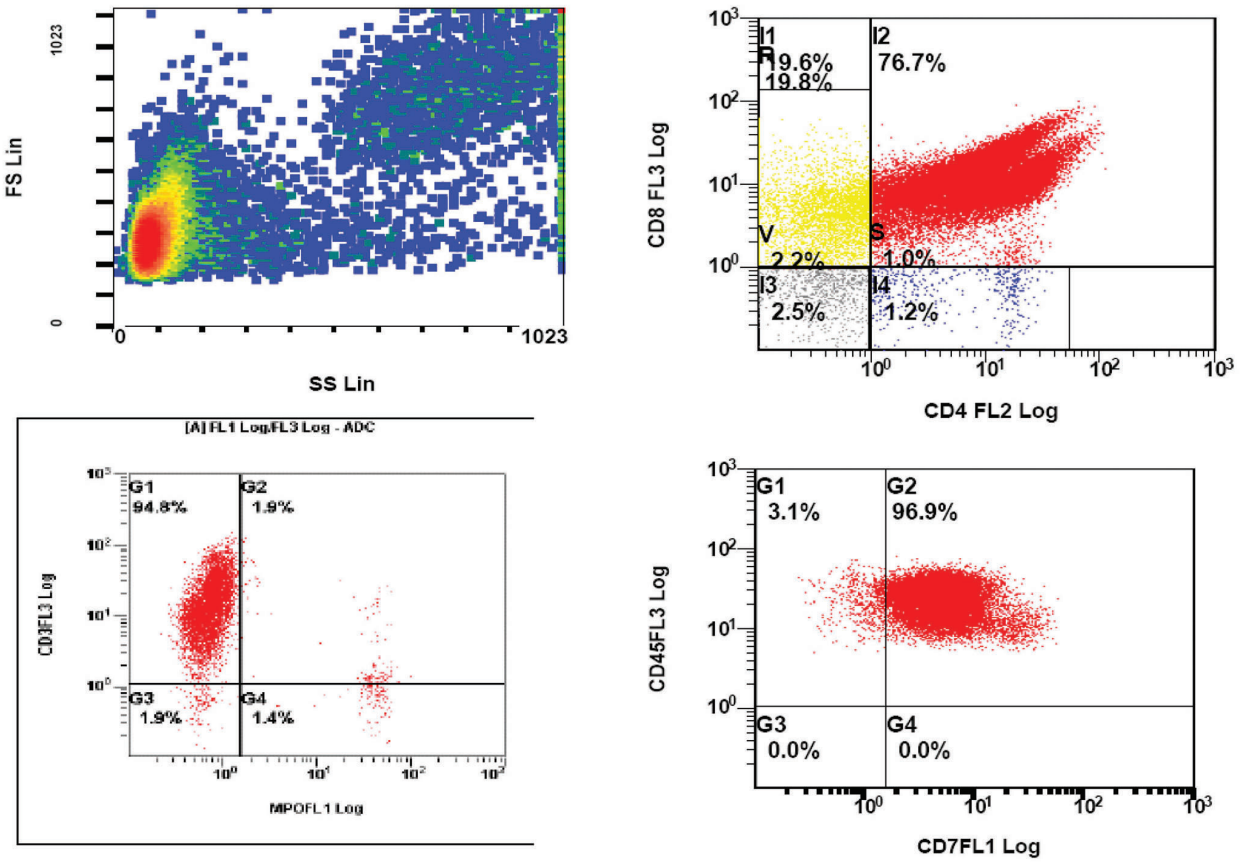

Figure-2: Flow cytometry of bone marrow

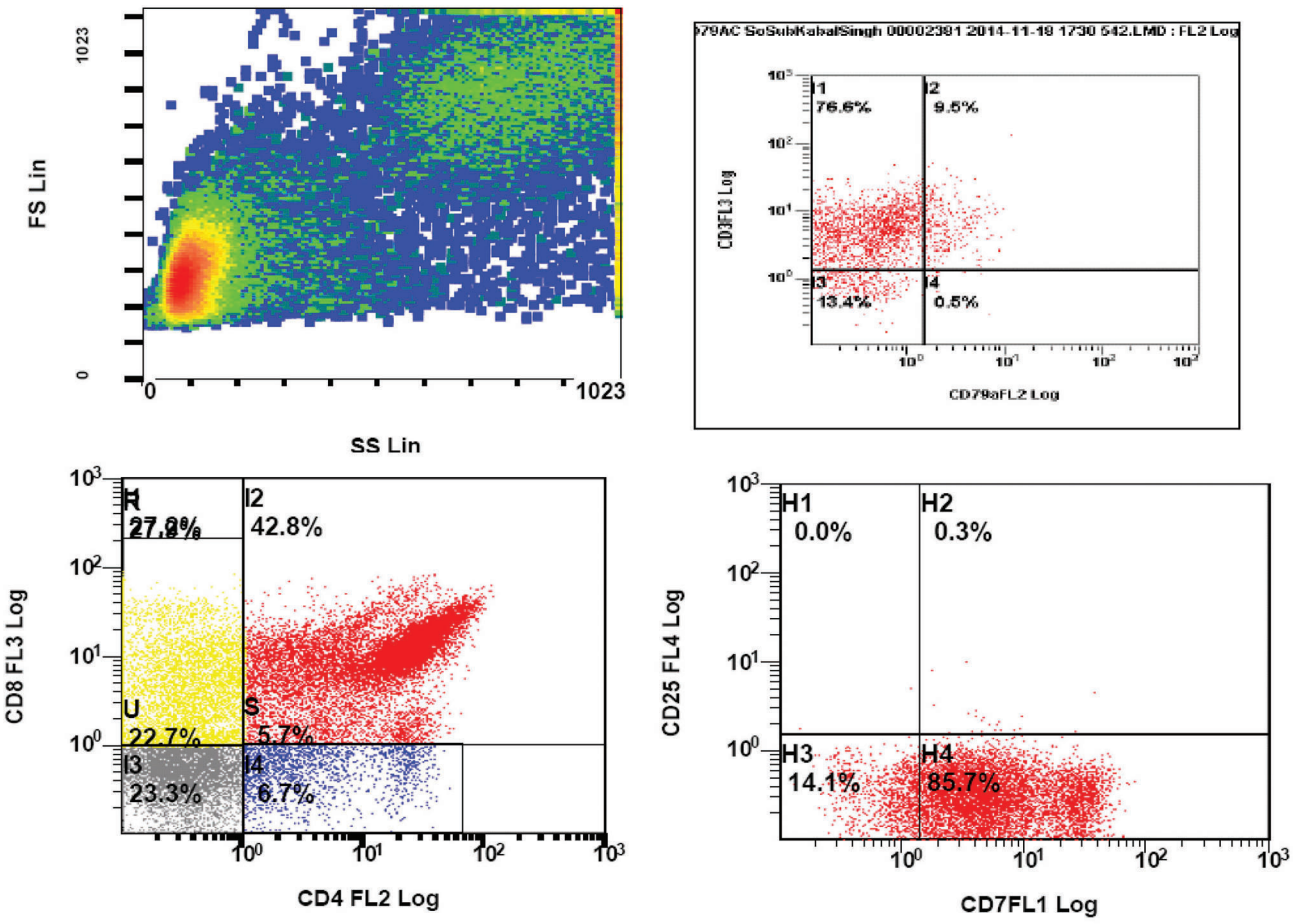

Figure-3: Flow cytometry of lymph node

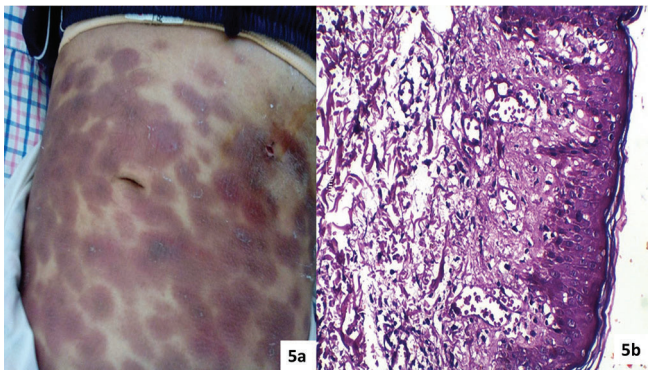

Figure-4:

palsy which had persisted despite adequate chemotherapy.

Considering the history, flow cytometry was performed on lymph node aspirate which revealed blasts whose immunophenotypic profile was same as described above (Fig 3**).** Patient now also started developing rash on abdomen and trunk which spread to all parts of body. These started to coalesce and became nodules measuring 1.5-2 cm (Fig 4a**).** Skin biopsy was done which showed dermal invasion by blasts **(**Fig 4b**)** with immunohistochemical profile same as that of blasts.

Due to cytological evaluation along with other ancillary techniques it was proved that although the patient was in hematological remission as shown by bone marrow and peripheral blood smear examination, he was not in remission due to involvement of lymph node, testes and skin. Thus his treatment protocol had to be changed. Patient now also developed tooth infection due to which appropriate chemotherapy could not be instituted. His tooth extraction was performed. At present patient is on aggressive antibiotic therapy and hyper-CVAD is planned once infection subsides.

DISCUSSION

T-ALL accounts for 10-15% of newly diagnosed cases of childhood ALL. Historically, T-ALL have worse prognosis than other ALL patients.[5] As first reported by the Berlin Frankfurt Munster (BFM) Group, T cell patients are prone to early initial relapse and inferior outcome after marrow relapse. Outcomes may be somewhat better for combined marrow and extramedullary relapses and late marrow relapse.[6] Our patient had achieved bone marrow remission following induction therapy but his cranial nerve palsy did not respond to treatment. Thus the patient had clinical evidence of CNS disease although his CSF study failed to reveal any blast. This kind of picture is highly suggestive of CNS leukemia.[7]

FNA of cervical lymph node and testes revealed presence of disease which did not respond to therapy. FNA combined with FC has been found to be valuable tool not only in establishing the diagnosis but also to assess response to therapy and residual disease. Barroca et al[8] established that use of FNA and FC may not be able to achieve a precise subclassification in lymphomas but can be used to achieve rapid diagnosis, allowing definitive management of patients with minimal additional invasiveness, thereby reducing the need for tissue biopsy. They were able to establish that combination of FNA and FC may be of great help in the first approach for dealing with lymphoproliferative disorders.

Schmitt et al[1] and Senjug et al[9] established that FNA and FC are complimentary diagnostic procedures which play pivotal role in the process of diagnosis and follow up of lymphoid neoplasms. The advantage of flow cytometry lies in its ability to evaluate a large number of cells over a short time period. Also, the ability of flow cytometry to focus on a group of cells based on cell size and light scatter characteristics allows for the analysis of particular subpopulations of cells with particular light scatter characteristics.[10] This allows the detection of small populations of malignant cells.[3] In doubtful cases in which cytology is found to be either negative or suspicious for malignancy and in which positive flow cytometric findings are found, the cells with a characteristic malignant immunophenotype can be found in subpopulations as small percentage of the total cell number. This capability of flow cytometry is best applied to those specimens in whom the cytologic interpretation is suspicious for malignant cells, but malignancy cannot be determined with certainty due to an insufficient number of cells with an atypical appearance. However, the major limiting factor of using flow cytometry in the evaluation of body fluids and FNA is in obtaining sufficient cells for analysis with the battery of desired monoclonal antibodies. In FNA, multiple needle passes may be required to obtain sufficient cells for both routine morphology and flow cytometric studies.[1,3,11] In cytology, the amount of material is a limiting factor for the use of ancillary techniques thus precise clinical information and proper morphologic workup for interpretation is required to select the correct test.

In our case, the testes were normal at the time of initial clinical presentation but enlarged during hospital stay. Earlier, chemotherapeutic agents used for treatment of ALL in children were deemed to be unable to penetrate the blood-testicular barrier. Hence, the testes were designated as a "drug sanctuary." Relapse of disease in the testis in boys treated for ALL was considered an ominous event, especially if associated with relapse at other sites such as bone marrow and/or CNS.[12] In the current era, with the advent of risk-adapted therapy protocols and high-dose methotextrate therapy, there has been a substantial reduction in the incidence of testicular relapse.[7,12] Relapse was documented in 23.8% (n = 127) of the cases by Kulkarni et al, of whom 111 were documented in boys. Data pertaining to testicular relapse from the Indian subcontinent is scant.[12] In a series of reports over different time periods, Advani *et al.* observed that testicular relapse constituted 4.1%, 8.2% and 14.2% (isolated in 7.1%) of the relapsers.[13]

Overall, testicular relapses are difficult to predict and often manifest at variable interval, months/days, after completion of treatment. Risk factors are difficult to define although a high white blood cell and older age (> 10 years) at presentation have been cited as possible indicators.[12]

Leukemia cutis is defined as cutaneous infiltration by neoplastic leukocytes (myeloid or lymphoid), resulting in

clinically identifiable cutaneous lesions and when they are composed of neoplastic granulocytic precursors, leukemia cutis has been designated as myeloid sarcoma, granulocytic sarcoma, primary extramedullary leukemia, or chloroma.[14] Skin involvement can be seen up to 50% of patients with acute myelomonocytic and monocytic types.[15] Regarding lymphocytic leukemias, skin involvement has been described in 4% to 20% of CLL /small lymphocytic lymphoma cases and in 20% to 70% of mature T-cell leukemias, including adult T-ALL.[16]

CONCLUSION

To conclude, we would like to emphasize that use of FNA and ancillary techniques are reliable non invasive modalities that can establish not only the diagnosis but also should be used to accurately monitor and assess therapy response as was demonstrated in this case where these techniques were able to detect relapse in T-ALL even though the patient was in hematological remission. Also, the aim of presenting this case is to illustrate the entire clinical spectrum of T-ALL where CNS involvement, testicular and skin involvement were also present.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 14-08-2018; **Accepted:** 05-09-2018; **Published:** 16-09-2018