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Fine-Needle Aspiration Cytology of T-Lymphoblastic Lymphoma Associated FGFR1 Rearrangement Myeloproliferative Neoplasm

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Keywords

8p11 myeloproliferative syndrome; 8p11 myeloproliferative neoplasm (MPN); T-lymphoblastic lymphoma (T-LBL); Fibroblast growth factor receptor 1 (FGFR1); t(8;13)(p11;q12); fine needle aspiration (FNA)

Myeloid and lymphoid neoplasms with *FGFR1* abnormalities, also known as the 8p11 myeloproliferative syndrome (EMS),^{1,2} represent a recently recognized entity described in the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues,³ and have been recently reviewed by Jackson et al.⁴ EMS is a heterogeneous group of hematological neoplasms carrying a chromosomal abnormality involving the fibroblast growth factor receptor 1 (*FGFR1*), commonly presenting as chronic myeloproliferative neoplasms with eosinophilia and an aggressive course, with frequent occurrence of T-cell lymphoblastic lymphoma (LBL) and progression to acute myeloid leukemia, which usually has a poor prognosis.^{1,2,4–6} In many cases, lymphadenopathy and/or neck mass is the presenting symptom, for which fine-needle aspiration (FNA) with cytologic examination, a popular alternative to lymph node biopsy, may be requested. Certain cytomorphologic findings on FNA specimens from lymph nodes diagnosed as precursor T-LBL may suggest the presence of the EMS, which would warrant further investigation including, but not limited to, cytogenetic and molecular testing. We report a case of an FNA of an axillary lymph node performed in a patient with EMS. To the best of our knowledge, this is the first case describing FNA cytology of this entity.

Case Report

A 50-year-old man from Nigeria presented with generalized lymphadenopathy, and subjective fevers. Physical examination showed diffuse cervical, axillary, and groin lymphadenopathy. Complete blood count showed elevated hemoglobin and hematocrit,

leukocytosis with absolute neutrophilia and absolute eosinophilia, and mild thrombocytopenia. A superficial FNA of a 3 cm left axillary lymph node was performed with a 23-gauge needle. Air-dried and alcohol-fixed smears were prepared for Diff-Quik and Papanicolaou stains, respectively. A portion of the FNA sample was also submitted for flow cytometric analysis. The FNA material showed cellular smears with a monomorphic lymphoid population and increased intermixed eosinophils (Fig. C-1A). Medium-sized neoplastic lymphoid cells showed high N:C ratio, dispersed chromatin, indistinct nucleoli, and scant cytoplasm (Fig. C-1B). Eosinophils were increased (Figs. C-1C and D) with occasional eosinophilic precursors (Figs. C-1E and F) and eosinophilic abnormalities including nuclear hyposegmentation and sparse granulation with clear cytoplasmic areas (Figs. C-1G and H). The corresponding flow cytometric analysis identified an aberrant T-cell population comprising 36% of the total population with loss of surface CD3, and expression of dim CD5, CD7, and CD4 with a sub-population double positive for CD4 and CD8. The case was finalized as a T-cell lymphoproliferative disorder. Staging bone marrow biopsy was performed and showed hypercellularity (95% cellularity) with trilineage hyperplasia and mild marrow eosinophilia. No increased blasts were identified; however, a minute population of T-lymphoblasts (0.42%) that were double positive for CD4 and CD8 was also identified by flow cytometry analysis of the bone marrow aspirate. The above features were suggestive of a myeloproliferative disorder. The corresponding peripheral blood smear showed mild left shift with eosinophilia. Subsequent excisional biopsy of a left axillary lymph node showed diffuse infiltration by a population of medium-sized and occasionally large neoplastic lymphoid cells with dispersed chromatin and inconspicuous nucleoli admixed with eosinophils (Fig. C-2A). Immunohistochemical stains showed the neoplastic lymphoid cells were positive for cytoplasmic CD3, CD1a, and TdT (Figs. C-2B–D). The case was diagnosed as T-cell LBL. Corresponding cytogenetic studies of the bone marrow subsequently revealed a t(8;13)(p11;q12) translocation. The paraffin-embedded tissue of lymph node was submitted for reverse transcription polymerase chain reaction (RT-PCR) testing for the *ZNF198-FGFR1* fusion transcript and was positive (Figs. C-3A and 3B). The combination of FNA and histologic findings of the lymph node with bone marrow, flow cytometric analysis, cytogenetics, and molecular findings supported a diagnosis of T-LBL associated with *FGFR1* rearrangement myeloproliferative neoplasm.

Patients who have abnormalities involving 8p11 may develop a myeloproliferative neoplasm and/or acute myeloid leukemia after a diagnosis of LBL, and usually have poor prognosis.^{1,2,4–6} Treatment regimens used to treat patients with EMS have been varied and usually resulted in inadequate treatment, and bone marrow or stem cell transplant has been used in a subset of patients and appear to improve outcome.⁴ Our patient was treated with eight rounds of hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD). Despite aggressive treatment, he had relapsed disease at 7 months after initial presentation, and he expired 11 months after initial diagnosis.

Discussion

Among patients with EMS who have lymph node biopsies for lymphadenopathy, T-LBL is the most common finding, with the remaining cases showing myeloid sarcoma or rarely bilineal T-cell/myeloid lineage, with a single case of concurrent B- and T-cell LBL

described.^{2,4} Although a variety of translocations have been described, the most common translocation in EMS is t(8;13)(p11;q12), as demonstrated in our patient.^{2,4} Moreover, lymphadenopathy and T-LBL occur more often in patients with t(8;13) than in those with variant translocations.^{3,4} The histological features of LBL in EMS are essentially similar to those without associated *FGFR1* abnormalities, although characteristic eosinophilic infiltration admixed with the lymphoblasts are more common in EMS.^{3,4} FNA cytology of T-LBL associated with EMS has never been reported previously. In addition to typical cytomorphology of LBL, we observed increased eosinophils and occasional eosinophilic precursors with eosinophilic abnormalities including nuclear hyposegmentation, sparse granulation with clear cytoplasmic areas, the features of which have been described in bone marrow and peripheral blood smear associated with clonal causes of eosinophilia.^{7,8} The above features of abnormal eosinophils are usually seen on Romanowsky stained peripheral blood smears or bone marrow aspirate smears; Diff-Quik stained FNA cytology smears allow assessment of those findings, which is not possible on the histologic sections of biopsy sample alone. The presence of increased eosinophils and abnormal eosinophils in FNA cytology smears that otherwise demonstrate features of LBL may provide a clue to the diagnosis of T-LBL associated with EMS. Of note, the degree of eosinophilic infiltration varies, and in some cases, eosinophilic infiltration may be focal, limited, or not identified.⁴ In cases with bilineal T-cell/myeloid lineage lymphoma, identification of myeloid components in FNA cytological smears in addition to lymphoblastic population may also raise the possibility of this entity. In such cases, ancillary studies, including flow cytometry to confirm a diagnosis of T-LBL or mixed T-cell/myeloid lineage lymphoma, as well as cytogenetic and molecular studies to identify translocation involving *FGFR1* may help confirm a diagnosis of this entity.

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Fig. C-1.

A, –H: FNA cytology of a left axillary lymph node: Cellular smears with a monomorphic lymphoid population and increased intermixed eosinophils (arrows) (C-1A, Diff-Quik, 600×). Medium-sized lymphoma cells showed high N:C ratio, dispersed chromatin with indistinct nucleoli, and scant cytoplasm (C-1B, Papanicolaou, 600×). Eosinophils are easily identified on Diff-Quik stain by brightly eosinophilic granules (C-1C, Diff-Quik, 1,000×). Eosinophils characteristically have bi-lobed nuclei identified on Papanicolaou stain, but granules are not readily identified (C-1D, Papanicolaou, 1,000×). Occasional eosinophilic precursors (eosinophilic myelocytes) characterized by unilobation and mixed eosinophilic and basophilic granules (C-1E and 1F, Diff-Quik, 1,000×). Features of eosinophilic abnormalities including nuclear hyposegmentation (C-1G, Diff-Quik, 1,000×) and sparse granulation with clear cytoplasmic areas (C-1G and 1H, Diff-Quik, 1,000×).

Fig. C-2.

A: –D: Subsequent corresponding excisional biopsy of a left axillary lymph node demonstrated diffuse infiltration by a population of medium-sized to large neoplastic lymphoid cells with dispersed chromatin and inconspicuous nucleoli admixed with eosinophils (arrows) (C-2A, H&E, 400×). Immunohistochemical stains showed the neoplastic lymphoid cells were positive for membranous CD1a (C-2B), nuclear TdT (C-2C), and cytoplasmic CD3 (C-2D), immunohistochemical stain, 400×.

Fig. C-3.

A: –B: RT-PCR showed amplification product from the *ZNF198-FGFR1* fusion gene in duplicate of patient's lymph node specimen (lower image). The RNA quality was shown to be adequate (top image). Neg ctrl indicates no template control; pos ctrl indicates presence of *ZNF198-FGFR1* chimeric fusion with the same size of patient's amplicons (C-3A). Dideoxynucleotide sequencing analyses of the RT-PCR product demonstrated the presence of a *ZNF198-FGFR1* chimeric transcript (C-3B).