Clonal Relationships Between Malignant Lymphomas and Histiocytic/Dendritic Cell Tumors

Andrew L. Feldman, MD

KEYWORDS

• Transdifferentiation • Histiocytic sarcoma • Dendritic cell tumor • Langerhans cell histiocytosis • Transformation • Lineage plasticity • Clonality

KEY POINTS

- Some histiocytic/dendritic cell (H/DC) tumors in patients with lymphoma are clonally related to the underlying lymphoma; these H/DC tumor may arise synchronously or metachronously.
- The mechanism for this clonal relationship appears to be transdifferentiation of the lymphoma clone in most cases.
- The most commonly reported lymphomas are low-grade B-cell lymphomas, particularly follicular lymphomas and cases of chronic lymphocytic leukemia/small lymphocytic lymphoma.
- The most commonly reported H/DC tumor is histiocytic sarcoma.
- Diagnosis requires awareness of the entity, thorough immunophenotypic evaluation, and supporting evidence from comparative molecular studies.

ABSTRACT

Tumors of histiocytic or dendritic cell origin appear to occur with increased frequency in patients with lymphoma. Recent molecular data have demonstrated clonal relationships between the lymphoma and the histiocytic/dendritic cell tumor in some of these cases. Clinical, pathologic, and experimental data suggest that this phenomenon probably represents transdifferentiation of the lymphoma clone to a histiocytic/dendritic cell lineage in most cases. Awareness of this entity is necessary to prompt comparative molecular studies in appropriate cases.

INTRODUCTION

Tumors of histiocytic or dendritic cell (H/DC) origin appear to occur with increased frequency in patients with lymphoma.[1–3] Recent molecular data have demonstrated clonal relationships between the lymphoma and the H/DC tumor in some of these cases (**Table 1**). Most early data focused on clonal relationships between B or T lymphoblastic leukemias/lymphomas and H/DC tumors.[4–7] Because lymphoblastic neoplasms are tumors of precursor lymphoid cells, such tumors might retain some degree of lineage plasticity inherent to hematopoietic precursors in general. However, more recent data have established that clonal relationships also can be seen between lymphomas derived from mature lymphoid cells and H/DC tumors.[8] Experimental data also have demonstrated reprogramming of mature lymphocytes into H/DC cells.[9] These findings challenge the concept of lineage commitment in the traditional model of hematopoietic cell differentiation, and suggest mature lymphoid cells have more lineage plasticity than previously thought.

Clinical, pathologic, and experimental data suggest that this phenomenon probably represents transdifferentiation of the lymphoma clone to an

Disclosures: None.

Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
E-mail address: feldman.andrew@mayo.edu

Surgical Pathology 6 (2013) 619–629
http://dx.doi.org/10.1016/j.path.2013.08.003
1875-9181/13/$ – see front matter

surgpath.theclinics.com

Table 1
Reported examples of clonal relationships between lymphomas and H/DC tumors

	H/DC Tumor (No. of Reported Cases)				
Lymphoma	**HS**	**IDCS**	**LCH**	**LCS**	**References**
Precursor lymphoid neoplasms:					
B-LBL	6	—	—	1	5,6,25,33–36
T-LBL	2	—	3	—	4,7,25,27
Mature lymphoid neoplasms:					
CLL/SLL	3	5	—	1	28,37,38
SMZL	1	—	—	—	39
HCL	—	—	—	2	40,41
FL	12	1	2	1	8,13,14,24,26,39,42,43
MCL	1	—	—	—	44
DLBCL	1	—	—	—	42

Abbreviations: B-LBL, B lymphoblastic leukemia/lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; H/DC, histiocytic/dendritic cell; HS, histiocytic sarcoma; IDCS, interdigitating cell sarcoma; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; MCL, mantle cell lymphoma; SMZL, splenic marginal zone lymphoma; T-LBL, T lymphoblastic leukemia/lymphoma.

H/DC lineage in most cases.[8,10] Transdifferentiation refers to the reprogramming of a cell of one lineage to another lineage, as assessed by a combination of morphologic, phenotypic, and in some cases functional characteristics (**Fig. 1**). Outside the laboratory setting, it is difficult to distinguish transdifferentiation from the alternate mechanism of dedifferentiation to a pluripotent precursor cell and redifferentiation to a different lineage.[11] Here, we use the term transdifferentiation for lack of clinical evidence of an intermediate, dedifferentiated component in the cases reported.[8,10]

MICROSCOPIC FEATURES

Microscopic features of reported cases of clonal relationships between lymphomas and H/DC tumors have not differed from those seen in each of the entities alone according to standard World Health Organization (WHO) criteria.[12] The classifications of the lymphoma and H/DC components in previous reports are shown in **Table 1**. The 2 components may occur metachronously or synchronously, and when synchronous may occur in the same or different anatomic sites.

Among precursor lymphoid neoplasms, both B and T precursor lymphoblastic leukemia/lymphoma have been seen (**Fig. 2**). These may have either a leukemic or lymphomatous presentation. Among mature lymphoid neoplasms, B-cell lymphomas have represented all the well-documented cases (see **Fig. 2**; **Figs. 3** and **4**). The most common reported subtypes have been follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Cases with diffuse large B-cell lymphoma, hairy cell leukemia, splenic marginal zone lymphoma, and mantle cell lymphoma also have been reported. Most reported H/DC tumors have been histiocytic sarcomas, followed by Langerhans cell tumors (either Langerhans cell histiocytosis or Langerhans cell sarcoma) and interdigitating dendritic cell sarcomas.

DIFFERENTIAL DIAGNOSIS

Clonal relationships between lymphomas and H/DC tumors must be differentiated from sporadic occurrence of clonally unrelated neoplasms in the same patient. An apparent increase in the appearance of H/DC tumors among patients with lymphoma has been reported regardless of clonal relationship.[1–3] This may be due to increased tissue sampling in patients with cancer, treatment effects (including immunosuppression), genetic predisposition to both neoplasms, effects of lymphoma-derived cytokines, and reporting bias.[1,3]

H/DC tumors arising in patients with lymphoma also must be differentiated from conventional transformation of a low-grade (typically B-cell) lymphoma to a higher-grade process (usually diffuse large B-cell lymphoma). Morphologic similarities between some large-cell lymphomas and histiocytic proliferations are reflected in the older "histiocytic lymphoma" nomenclature. Although this differential diagnosis probably applies more to cases reported in the preimmunohistochemistry