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Diagnostic Dilemmas That Impact Treatment Decisions in Lymphoma

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Abstract: Prognosis in lymphoma varies widely according to the particular subtype, as does the treatment approach. Expert hematopathology review, incorporating current immunohistochemistry, genetic analysis, and fluorescent in situ hybridization (FISH), may be required to ensure an accurate diagnosis and optimal treatment. CD30 expression can be seen in a wide range of lymphomas, including Hodgkin lymphoma, anaplastic large cell lymphomas, cutaneous T-cell lymphomas, and B-cell lymphomas. The introduction of targeted therapies, such as brentuximab vedotin, makes it imperative to establish robust CD30 immunohistochemical assays in the laboratory and should encourage the judicious use of CD30 testing in order to identify potential candidates for novel therapy. Diagnosis of these patients requires close collaboration between hematopathologists and clinicians. This monograph presents 2 case studies in which immunohistochemistry changed a lymphoma diagnosis and provides a commentary on the importance of accurate diagnosis of lymphoma subtypes.

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Diagnosis of ALK-Positive Anaplastic Large Cell Lymphoma Based on CD30 Testing

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The patient was a 35-year-old man who presented with systemic symptoms and lymphadenopathy involving the neck, axilla, and groin. His systemic symptoms included weight loss, fever, and night sweats. His general practitioner referred him to a surgeon. Because a diagnosis of lymphoma was suspected clinically, the surgeon did not perform a fine needle aspirate, but went straight to an open biopsy. The biopsy was performed at a hospital in British Columbia that had the ability to perform routine tissue processing (hematoxylin and eosin [H&E] sections) and a limited immunohistochemical panel. A portion of the fresh lymph node was sent for flow cytometry at the Vancouver Cancer Center (VCC). In the days following the biopsy, the VCC received the report, a complete set of slides, and a representative paraffin block. The slide set included several H&E sections, as well as CD20 and CD3 immunostains. CD30 testing was not performed, an omission that will prove to be important in this case.

Because all suspected cases of lymphoid cancer in British Columbia are centrally reviewed, this case was referred to the lymphoma pathology group at the VCC. The submitting diagnosis was peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) based on absence of CD20 staining and membranous CD3 expression. Central review of the morphology revealed a diffuse infiltrate of large, neoplastic cells with frequent mitoses (Figure 1). Some hallmark cells were also identified, as was a moderate degree of sinusoidal infiltration. Additional immunohistochemistry testing found some pan–T-cell antigen loss, including CD2 and CD5, which is not uncommon. The fresh material that was sent for flow cytometry similarly showed an abnormal phenotype with loss of the same pan–T-cell markers as seen by immunohistochemistry. Molecular genetic studies performed at the VCC showed the presence of a T-cell clone. No *IGH* rearrangements were detected. Flow cytometric studies and molecular genetic tests were also performed at the VCC. Following initial review of all the submitted material, the favored diagnosis was anaplastic large cell lymphoma (ALCL). Additional immunohistochemistry testing was performed, including for CD30, anaplastic lymphoma kinase (ALK), EMA, Ki67, TIA-1, Granzyme B, and perforin. The results of these tests led to a diagnosis of ALK-positive ALCL with strong and uniform membranous and Golgi CD30 staining (Figure 2).

Based on the revised diagnosis, the patient was enrolled in a clinical trial testing brentuximab vedotin, a targeted agent for CD30. It is used in the treatment of CD30-positive lymphomas—Hodgkin lymphoma, in particular, but also ALCL (Figure 3).[1-3] Brentuximab

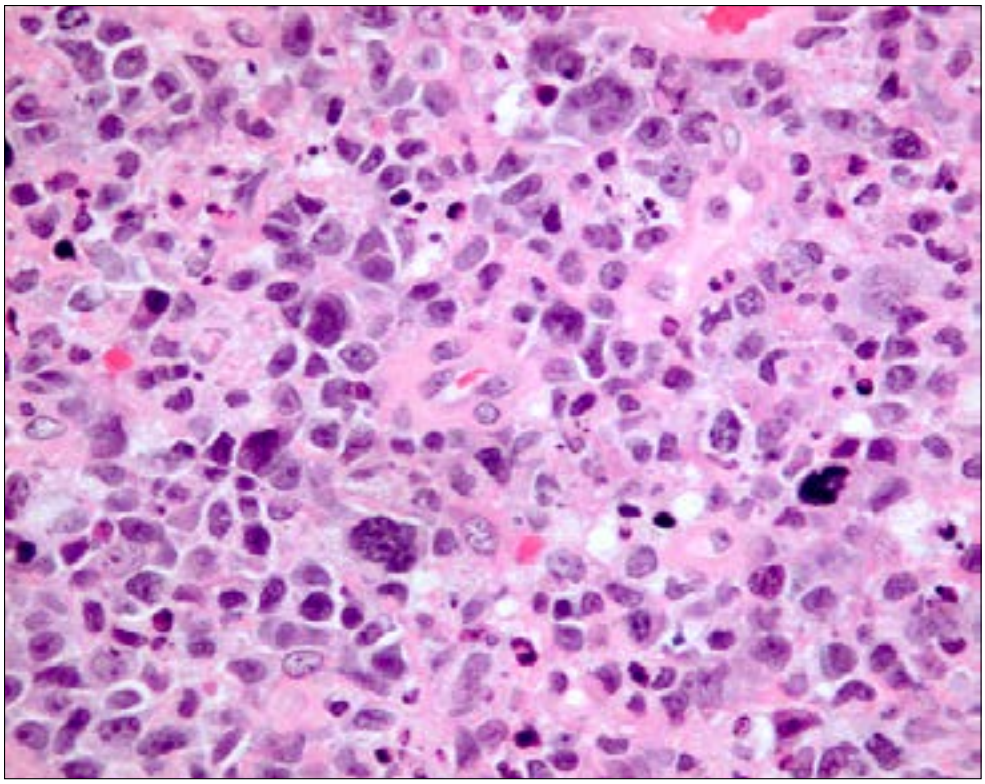

Figure 1. Central review of the morphology revealed a diffuse infiltrate of large, neoplastic cells with frequent mitoses.

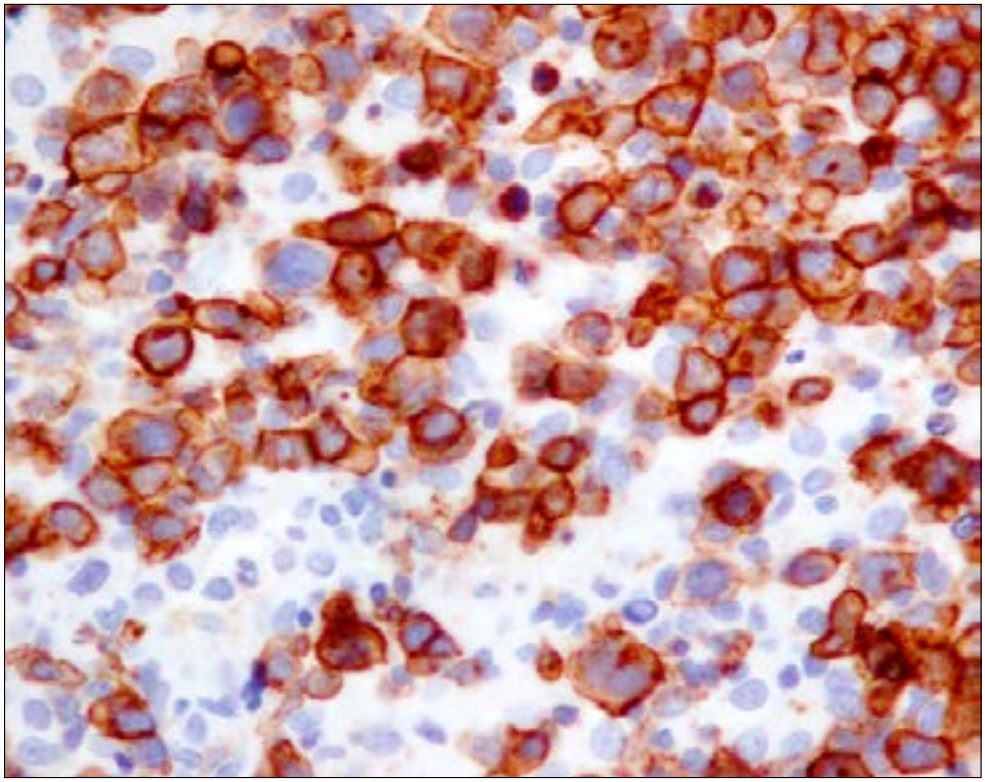

Figure 2. The patient was diagnosed with anaplastic lymphoma kinase–positive anaplastic large cell lymphoma with strong and uniform membranous and Golgi CD30 staining.

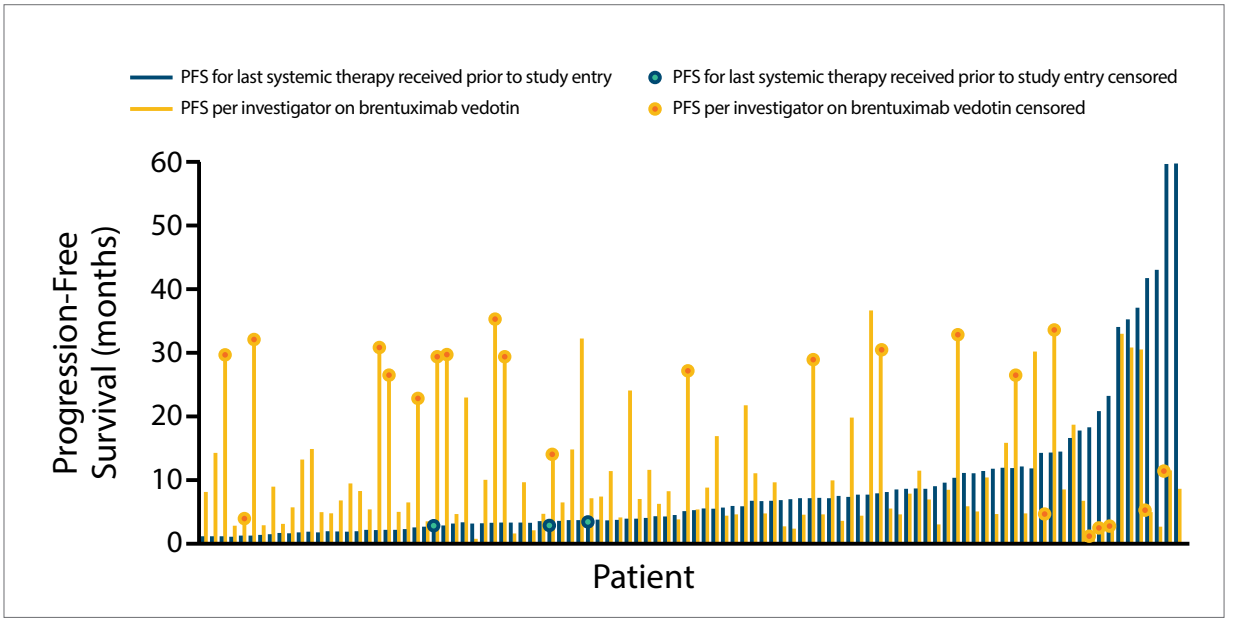

Figure 3. PFS in 2 pivotal phase 2 studies of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma. The median PFS was 9.3 months with brentuximab vedotin and 6.1 months with the previous systemic therapy. PFS, progression-free survival. Adapted from Radford J et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 303.[3]

vedotin was administered with chemotherapy, and the patient achieved a complete response and has maintained it. This case highlights the value of central review for complex hematolymphoid pathology as well as the need for expanded panels of immunohistochemistry with other ancillary tests in order to establish a definite diagnosis and an accurate subclassification of all lymphoid cancers.

Discussion

CD30 expression is characteristic of a number of lymphoid cancers, with the 2 prototypical examples being classical Hodgkin lymphoma and ALCL.[4,5] In ALCL, strong and uniform expression of CD30 is a characteristic finding.[5] This staining pattern should prompt one to then perform the ALK immunostains required to distinguish ALK-positive ALCL from ALK-negative ALCL. Importantly, a number of other non-Hodgkin lymphomas also express CD30, including both B-cell and T-cell subtypes.[6,7] Some degree of CD30 expression can be seen across the spectrum of T-cell lymphomas. Typically, this expression is heterogeneous and thus can be distinguished from the strong and uniform CD30 expression seen in ALCL. Distinguishing between some PTCLs with high CD30 expression and ALCL can be a challenge. A review of the pathology by an expert in the field can be beneficial in such cases. More recently, CD30 expression has been examined in large cohorts of diffuse large B-cell lymphoma (DLBCL).[8] It is heterogeneously expressed in approximately 15% to 20% of cases and seems to be associated with a favorable outcome. It can be seen in both cell-of-origin subtypes (germinal center B cell and activated B cell). CD30 expression is enriched in patients with DLBCL who show concomitant expression of the Epstein-Barr virus; the prognosis for these patients is markedly inferior to that associated with typical DLBCL.[9] The introduction of targeted therapies, such as brentuximab vedotin, now makes it imperative to establish robust CD30 immunohistochemical assays in the laboratory and should encourage the judicious use of CD30 testing in order to identify potential candidates for novel therapy.

Conclusion

The accurate diagnosis and reliable classification of lymphoid malignancies requires an open biopsy for adequate assessment of the tumor. In cases where there is a high index of clinical suspicion of an underlying lymphoid cancer, fine needle aspirates are not acceptable for initial diagnosis and should be passed over in favor of an open biopsy that includes complete lymphoma protocol studies. This approach results in a net savings for the healthcare system and helps to avoid duplicate testing. In a small subset of cases, the distinction between PTCL-NOS with CD30 high expression and systemic ALCL can be challenging, and these difficult cases benefit from secondary review and an expanded immunohistochemical panel.

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Undiagnosed Mycosis Fungoides With Transformation to Large Cell Peripheral T-Cell Lymphoma

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A 42-year-old woman with a remote history of Hodgkin lymphoma (HL) diagnosed in 1988 presented to a surgeon with adenopathy. The patient had been well until 6 months prior, when she developed axillary lymphadenopathy. She had experienced night sweats for the previous month, and she also reported pruritus. Other than the previous diagnosis of lymphoma, her medical history was not significant. Physical examination showed axillary, cervical, and supraclavicular lymphadenopathy. A cervical lymph node was biopsied. H&E staining for CD3, CD20, CD15, and CD30 was performed (Figures 1-3). A diagnosis of classical HL was considered.

The lymph node biopsy was followed by a forearm skin biopsy. A more detailed review of systems revealed a pruritic skin rash, predominantly in the axillae, that had persisted for 20 years. The patient also had a dry cough. Physical examination showed the previously mentioned lymphadenopathy as well as erythematous plaques on the forearms and legs. A complete blood count showed mild thrombocytosis (460×10^9/L), but was otherwise normal.

The skin biopsy revealed a dense upper dermal lymphoid infiltrate composed of small and intermediate-sized lymphocytes, some of which demonstrated nuclear irregularity and deep clefts. The infiltrate was band-like, but infiltration of the epidermis was present. Some of these lymphocytes displayed a cytoplasmic clearing or "halo" effect along the dermal-epidermal junction, and collections of several lymphocytes in the epidermis were present. Immunophenotyping showed that the vast majority of lymphocytes expressed CD3 and CD4, but lacked CD20, CD8, and CD7 (Figures 4 and 5). Polymerase chain reaction (PCR) studies for the T-cell receptor γ gene rearrangement showed 2 dominant peaks by capillary electrophoresis at the 230 and 241 base pairs. These pathologic features were believed to be compatible with cutaneous T-cell lymphoma (mycosis fungoides).

The same molecular analysis was then performed on the lymph node biopsy, and an identical pattern was seen in the capillary gel electropherogram. Given this information, it was thought that the patient likely had a long history of undiagnosed mycosis fungoides with

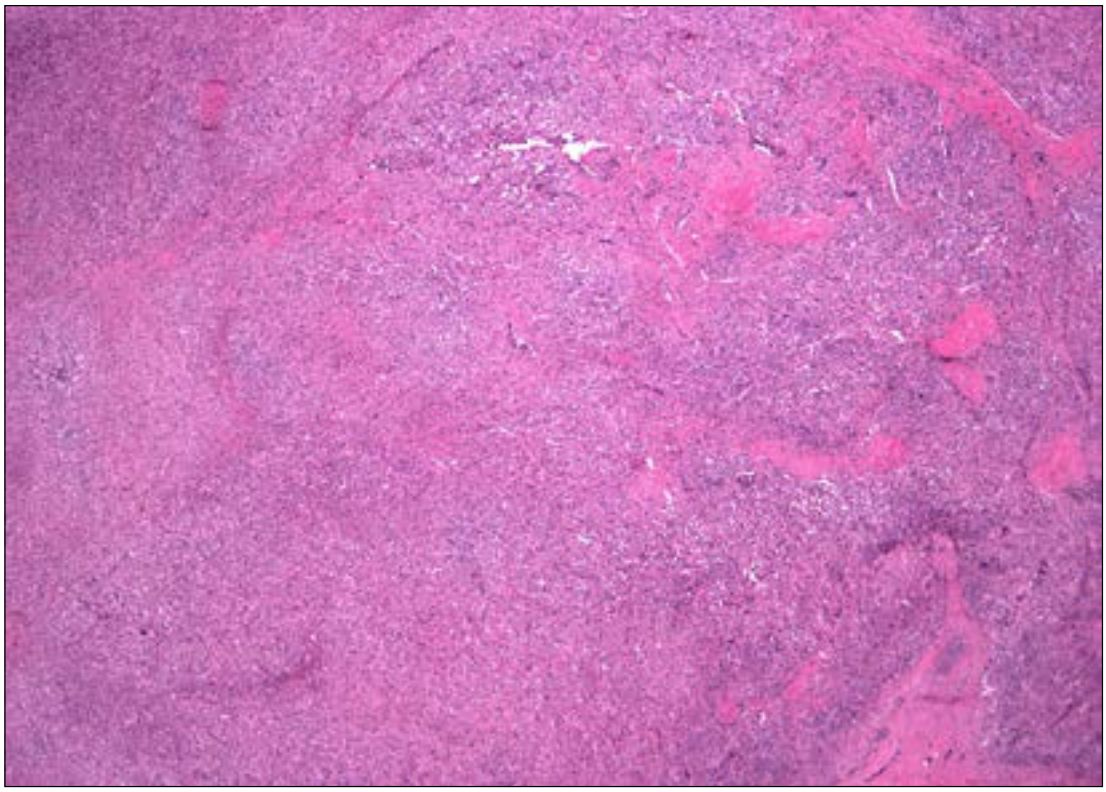

Figure 1. Lymph node biopsy showing effacement of the normal lymph node architecture. There are some fibrous bands present. Hematoxylin and eosin stain (4×).

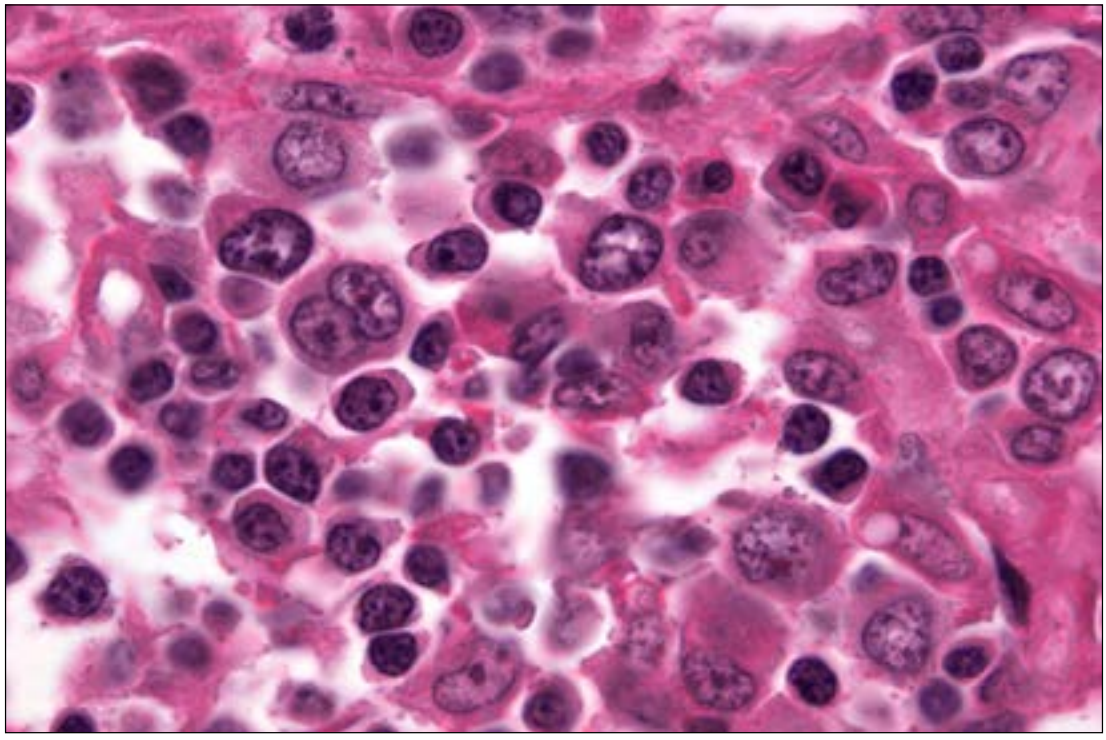

Figure 2. High magnification showing an atypical lymphoid infiltrate with occasional binucleated Reed-Sternberg–like cells. Hematoxylin and eosin stain (100×).

transformation to a large cell peripheral T-cell lymphoma expressing CD15 and CD30.

Discussion

This case illustrates some interesting clinical and histopathologic points that can serve to confound the pathologist. From a histopathologic standpoint, the CD15 and CD30 expression was misleading, particularly within the context of a history of Hodgkin lymphoma. CD15/CD30 coexpression in Reed-Sternberg–like cells is characteristic of classical Hodgkin lymphoma. A twist was added with the subsequent skin biopsy findings and long-standing skin rash, which made it possible to postulate a pre-existing cutaneous T-cell lymphoma. The addition of the molecular genetic information, indicating that the 2 processes are related, highlighted the fact that cutaneous T-cell lymphomas, such as mycosis fungoides, can have a prolonged and indolent course (often with nonspecific pathologic findings), followed by transformation to a CD30-positive large T-cell lymphoma.

The lymph node biopsy showed numerous large transformed cells with vesicular chromatin and variably prominent nucleoli. In some sections, a vague nodularity with some sclerosis was seen. Scattered Hodgkin and Reed-Sternberg–like cells were present but in the minority. There was a background of small lymphocytes, neutrophils, and eosinophils. Immunophenotyping showed that these large atypical cells were CD15-positive and CD30-positive. At first, these larger cells appeared to lack expression of CD45RB and CD3. Close examination, however, showed some intermediate-to-large mononuclear cells that were positive for CD3 and CD45RB. Given the patient's history of Hodgkin lymphoma, consideration of recurrent Hodgkin lymphoma was not unreasonable. Although we now know that classical Hodgkin lymphoma originates from B cells, unusual cases of T-cell origin have been reported.[1,2]

At this point, the possibility of coexistent/pre-existent mycosis fungoides was not considered. The skin biopsy, however, showed fairly typical pathologic features of mycosis fungoides. The immunophenotype (CD3-positive, CD4-positive, CD7-negative, and CD8-negative) and T-cell receptor gamma PCR results all supported mycosis fungoides. The clinical features of long-standing rash on the trunk, pruritus, and lesions on the extremities were consistent with a cutaneous T-cell lymphoma, such as mycosis fungoides.

Mycosis fungoides is the most common primary cutaneous T-cell lymphoma. It presents most commonly in adults who are middle-aged or older (median age, 57 years; 1.7:1 male:female ratio), with patches and plaques in a "bathing trunk" distribution. The natural history is long, with an indolent clinical course. The median overall survival is 11.4 years, with a disease-specific survival at 10 years of 74%. Important prognostic factors include age, T-cell classification, and presence of extracutaneous disease.[3] The clinical and histopathologic features can mimic other inflammatory lesions, and diagnosis may take years.[3-5] The difficulty of diagnosis is well-known, and the clinical conundrums have recently been highlighted by the description of a clinically inapparent form ("invisible mycosis fungoides").[6]

There are reported cases of patients with Hodgkin lymphoma and mycosis fungoides that manifest sequentially or simultaneously.[7-20] Most of these cases, however, were reported before it was possible to perform detailed immunophenotyping and molecular genetic studies, such as T-cell receptor gene rearrangement studies, in fixed tissues. More recent studies suggest different cells of origin when the 2 diseases occur in the same patient.[12,14,18] The molecular studies in this case strongly support a common clonal origin for these 2 histopathologically disparate cases. One cannot help but wonder whether some of the previously reported cases of Hodgkin lymphoma and mycosis fungoides were, in fact, similar to this case.

Transformation of mycosis fungoides to lesions of a higher cytologic grade has been well-described. In a recent series, transformation was estimated to occur in approximately 10% of cases, when it was defined as large cells that compose at least 25% of the infiltrate or the presence of nodules with large cells.[21] The transformed lesions first occurred in the skin a median of 6.5 years after diagnosis. Other series provide somewhat different figures, perhaps due to selection bias. For example, Salhany and colleagues reported a transformation rate of 18%, with a median time to transformation of 12 months.[22] Of note in this analysis, 7 of 17 cases showed transformation at the time of diagnosis, similar to the current case. Extracutaneous areas were the initial site of transformation in 41% of patients. Histologic features varied, but the cells were usually large (8-35 μm) with oval nuclei, prominent nucleoli, and moderate amounts of cytoplasm, and could be classified as PTCL-NOS. Occasionally, the transformed cells have nuclear irregularity or can resemble ALCL. Although Reed-Sternberg–like cells may be seen, they are in the minority.[21,22] Histologic grouping into pleomorphic medium and large T-cell lymphoma, immunoblastic T-cell lymphoma, and ALCL has been described.[23] When disease occurs in the skin, tumors are often present and lack epidermotropism.[21] All series describe a poor prognosis associated with transformation, particularly with extracutaneous disease.[21,22,24]

Immunophenotypically, the transformed lymphoma cells are usually CD4-positive T cells and express pan–T-cell antigens, such as CD3. A pretransformation phenotype can be maintained, but phenotypic drift occurs with loss of some T-cell–associated antigens, and even changes in the CD4 or CD8 expression pattern can occur.[21] CD30

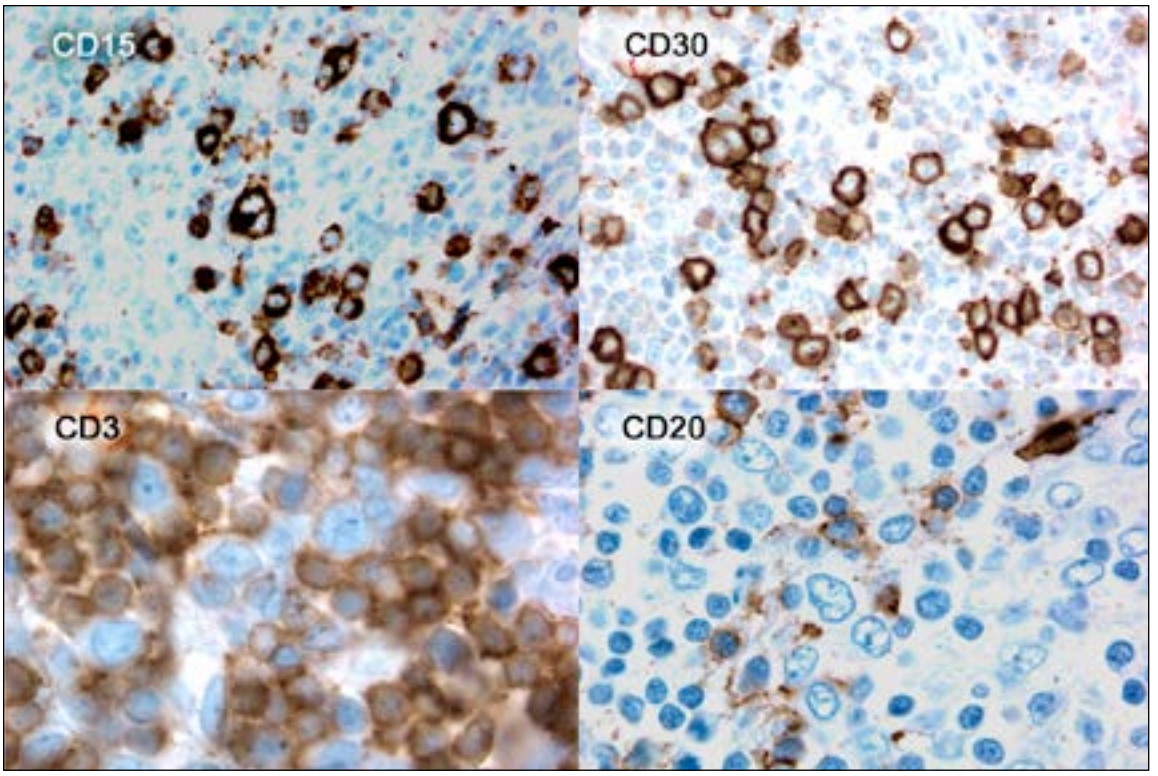

Figure 3. Composite immunohistochemistry for CD15, CD30, CD3, and CD20.

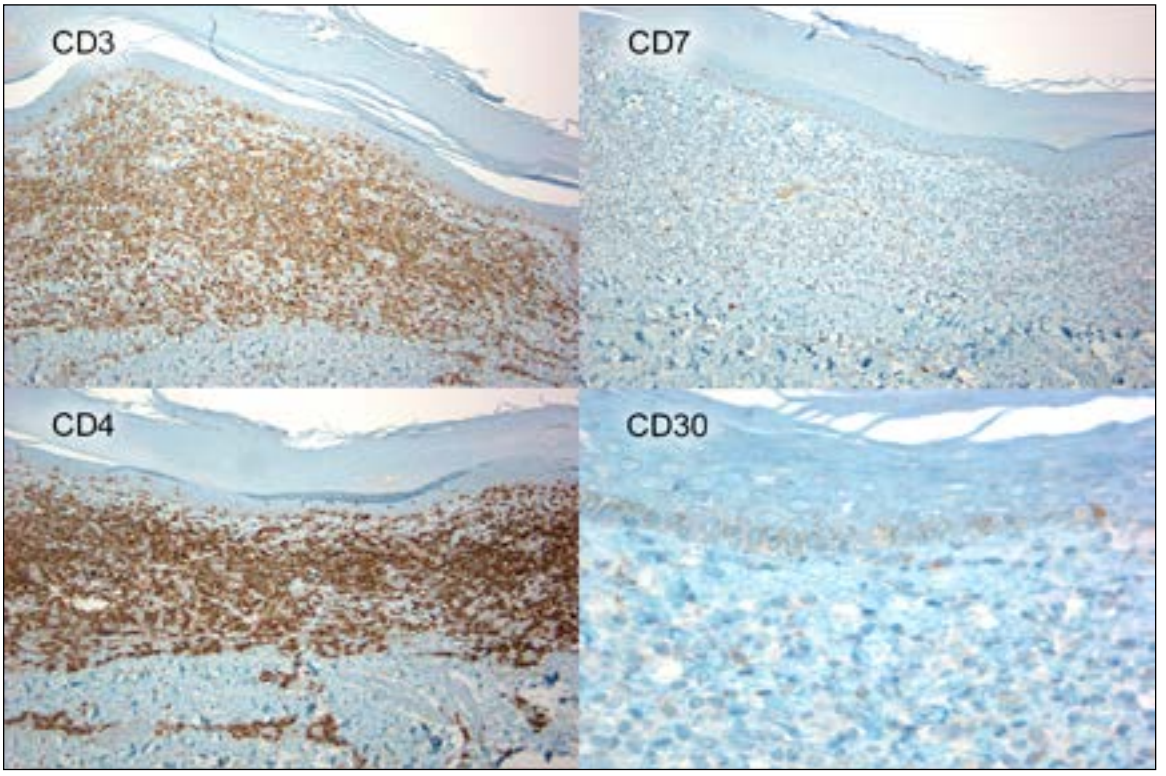

Figure 4. Skin biopsy showing a dermal lymphoid infiltrate of small lymphocytes with epidermotropism. Hematoxylin and eosin stain (40×)

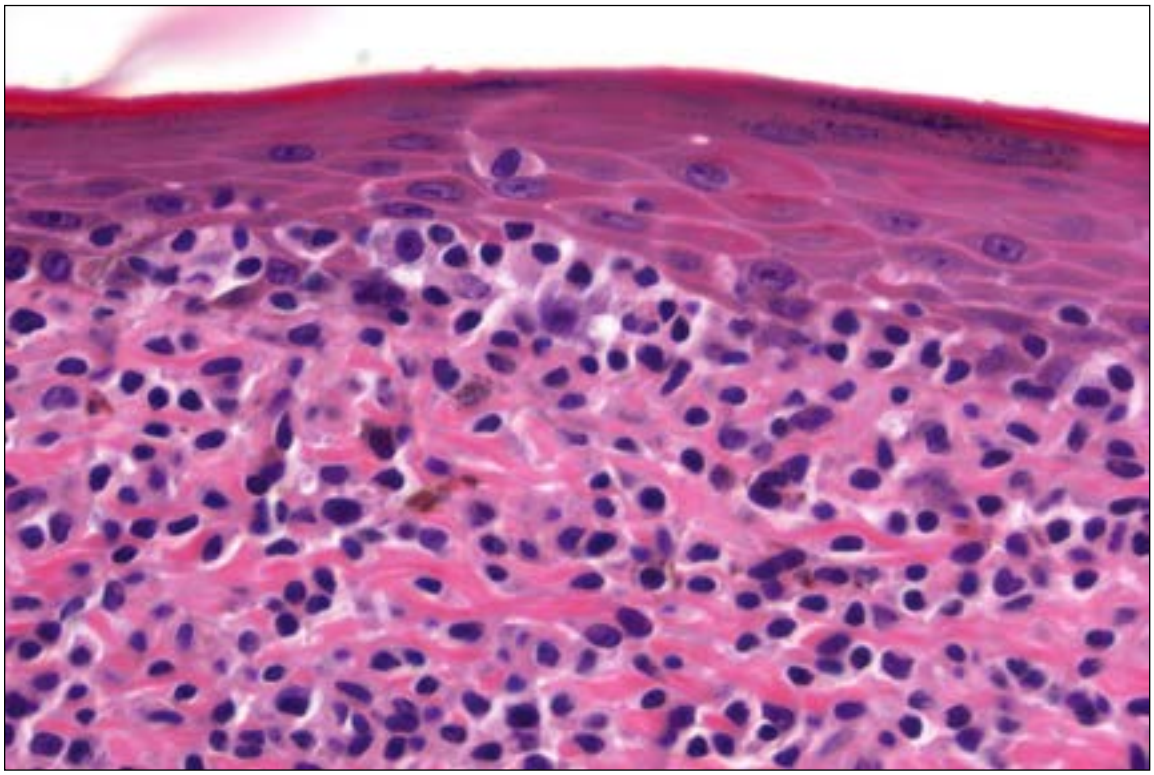

Figure 5. Skin biopsy immunohistochemistry for CD3, CD7, CD4, and CD30. The cells are CD4-positive T cells that lack CD7 and CD30.

expression is seen in a substantial proportion of cases (30%-45%).[21,22] Strong expression (>75%) can be seen in 15% of cases. The expression of CD30, particularly in the majority of large cells, raises the potential diagnosis of ALCL. Expression of ALK has not been reported in this setting. When CD30-positive large cell transformation occurs in the skin, a simultaneous primary cutaneous ALCL is also a consideration. Distinction is important given the excellent prognosis of primary cutaneous ALCL.[25] Ultimately, the clinical history and appearance may be most helpful in resolving the issue.

In our patient, the expression of CD15 on many of the atypical cells in the lymph node confounded the issue of whether the lymph node biopsy represented Hodgkin lymphoma. CD15 antibodies recognize the Lewis X antigen. It is expressed in various epithelial and myeloid cells, and it is useful in the diagnosis of classical Hodgkin lymphoma because approximately 85% of cases express CD15 on Hodgkin and Reed-Sternberg cells. However, CD15 is also expressed in other hematolymphoid malignancies, including acute lymphoblastic leukemias (particularly those with mixed-lineage leukemia [*MLL*] rearrangements), acute myeloid leukemias, and rare cases of B-cell non-Hodgkin lymphoma.[26-30] Cytomegalovirus-infected cells mimicking Hodgkin and Reed-Sternberg cells have also been shown to express CD15.[31] More relevant to this case, CD15 has also been reported to be expressed in some post-thymic T-cell lymphomas.[32] In the setting of transformation of mycosis fungoides, strong CD15 expression has been reported in 3 of 17 cases.[22]

This phenomenon has been documented in 2 studies that specifically report cases of peripheral T-cell lymphomas that express both CD30 and CD15.[33,34] These markers are typically coexpressed in classical Hodgkin lymphoma. A study by Gorczyca and coworkers reported 9 cases of T-cell lymphomas that coexpressed these markers, including 2 cases of ALK-positive ALCL.[34] The median age of the patients in this study was 62 years, with a 2:1 male predominance. Barry and associates reported on an additional 11 patients, who had a remarkably similar median age of 62 years and a male predominance.[33] Among these 11 patients, 8 showed nodal disease, and 2 had primarily cutaneous disease. Importantly, 1 group of 5 patients had histologic features that closely mimicked classical Hodgkin lymphoma, with a mixed inflammatory infiltrate and Reed-Sternberg–like cells. The remaining cases had features more in keeping with peripheral T-cell lymphoma, but also had a proportion of neoplastic cells that coexpressed CD15 and CD30. T-cell monoclonality could be demonstrated in the majority of cases (9 of 11), and Epstein-Barr virus was not detected. These 2 reports show that although CD15 is commonly seen in the Reed-Sternberg cells of classical Hodgkin lymphoma, it can also be

expressed in T-cell lymphomas. The histopathologic features in such cases may also mimic Hodgkin lymphoma.

Conclusion

The presented case was interpreted as a CD30-positive/CD15-positive T-cell lymphoma that most likely represents a transformation of an undiagnosed cutaneous T-cell lymphoma (mycosis fungoides). It illustrates several teaching points. First, expression of CD15 is not completely specific for classical Hodgkin lymphoma and can be misleading, particularly with the clinical history (albeit unconfirmed) of Hodgkin lymphoma. Second, CD30 expression is not specific for a lymphoma type and can be seen in a wide range of lymphomas, including Hodgkin lymphoma, anaplastic large cell lymphomas, cutaneous T-cell lymphomas, and even B-cell lymphomas. Finally, evaluation of the entire evolving clinical and pathologic findings combined can help resolve diagnostic difficulties. The combined pathologic findings, clinical features, and application of molecular genetic studies make it possible to render an appropriate diagnosis.

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Commentary: Diagnostic Dilemmas That Impact Treatment Decisions in Lymphoma

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Dr Gascoyne described a young patient, age 35 years, who presented with diffuse lymphadenopathy.[1] The patient underwent a biopsy at an outside institution and was diagnosed with PTCL-NOS based on the staining that was performed. In British Columbia, all suspected cases of lymphoid cancer are centrally reviewed. The central review at VCC involved additional staining and testing of T-cell clonality. Immunohistochemistry showed CD30 positivity, and ALK staining was positive. The diagnosis after central review was changed to ALCL, ALK-positive.

This case raises several important points. Expert hematopathology review, incorporating current immunohistochemistry, is often necessary to determine the subtype of lymphoma. Genetic analysis or fluorescent in situ hybridization (FISH) may be important for the diagnosis. In this case, it was important to identify that the patient was CD30-positive, as this status provided additional treatment options. The patient was enrolled in a clinical trial with brentuximab vedotin. Adequate testing can provide information not only on diagnosis but also prognosis and treatment. In this case, the correct diagnosis of ALCL has a much better prognosis than PTCL-NOS, and it also opened up additional treatment options. It is very important to diagnose the correct subtype of lymphoma in order to develop the optimal treatment plan.

Dr Hsi described a 42-year-old woman with a remote history of Hodgkin disease diagnosed in 1988. In 2003, the patient presented with lymphadenopathy, night sweats, and pruritus. Physical examination revealed diffuse lymphadenopathy present in many different areas. The patient underwent biopsy of a cervical lymph node. Results from H&E stains and immunostains suggested a diagnosis of classical Hodgkin lymphoma. The patient had a rash on her forearm; biopsy demonstrated a dermal infiltrate of lymphocytes, an unusual characteristic for Hodgkin lymphoma. Immunostains performed on the second biopsy, however, demonstrated some T-cell characteristics: CD3, CD4, and lack of CD8. PCR studies performed to test for T-cell gene arrangements were also positive.

Results of the skin biopsy were believed to be compatible with mycosis fungoides, a type of cutaneous T-cell lymphoma. In this case, a skin biopsy offered information that led to reevaluation of the original diagnosis. Reassessment of the lymph node biopsy suggested that the patient had experienced transformation of mycosis fungoides to a CD30-positive peripheral T-cell lymphoma. As Dr Hsi noted, this phenomenon is unusual. We know, however, that a variety of different clinical pathologic entities can occur in patients with CD30-positive lymphomas, including Hodgkin lymphoma, mycosis fungoides, and certain types of peripheral T-cell lymphoma. Some patients exhibit a spectrum of disease that can encompass different types of lymphoma, and they need to be treated differently from patients with a distinct diagnosis. Transformed disease is often a much more aggressive type of lymphoma, and its treatment differs from that for mycosis fungoides or Hodgkin disease. This case again stresses the importance of having the pathology results reviewed by an expert hematopathologist.

Conclusion

Both of these cases illustrate the fact that it is very important to have the correct diagnosis. Oftentimes, it can be difficult to make the correct diagnosis without all of the necessary immunohistochemical stains and a central pathology review. Prognoses vary among the different types of lymphoma. Treatments used for Hodgkin disease are very different from those for peripheral T-cell lymphoma; there are different types of drugs and different types of regimens. For example, brentuximab vedotin is a targeted agent for CD30 that is used in the treatment of CD30-positive lymphomas.[3,4] It should be noted that the correlation of response to brentuximab vedotin and the expression of CD30 is unclear, with a lack of a direct association in some studies.[5]

The hematopathologist and the clinicians must work closely together. For a correct diagnosis, the hemato-

pathologist requires the clinical history, and the clinicians require the hematopathology review. It is important to work as a clinical team on these types of cases.

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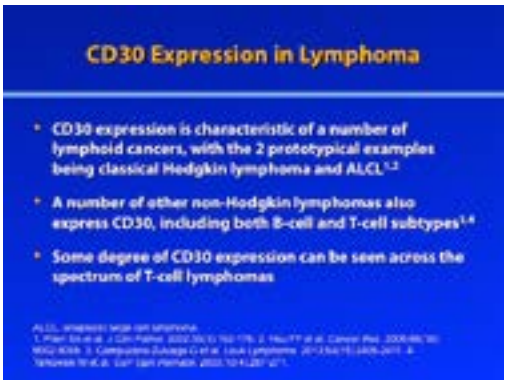

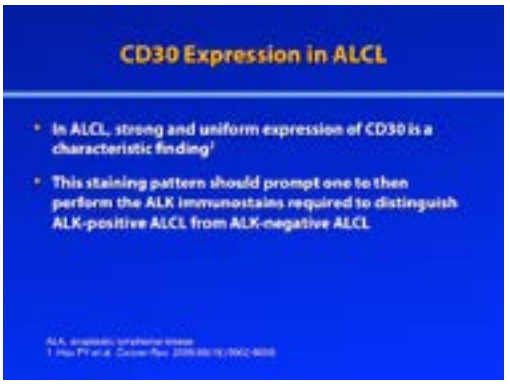

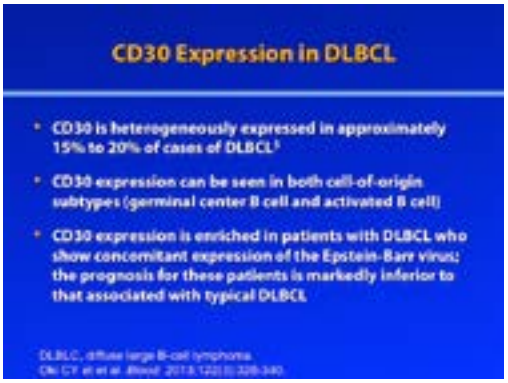

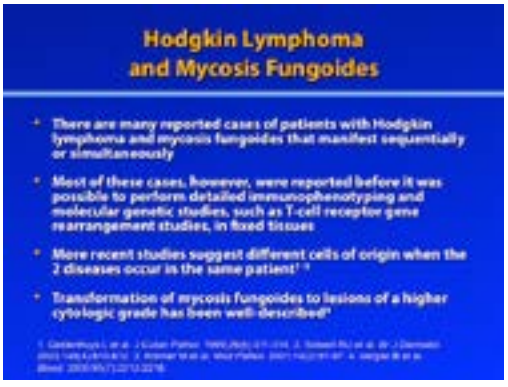

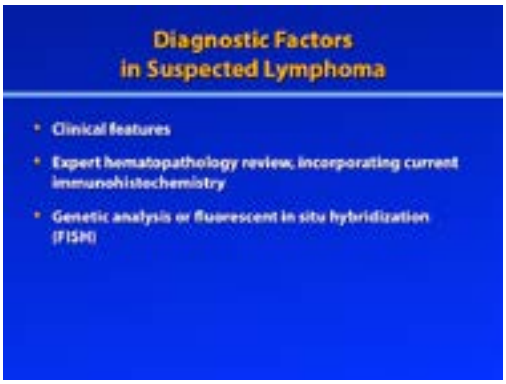

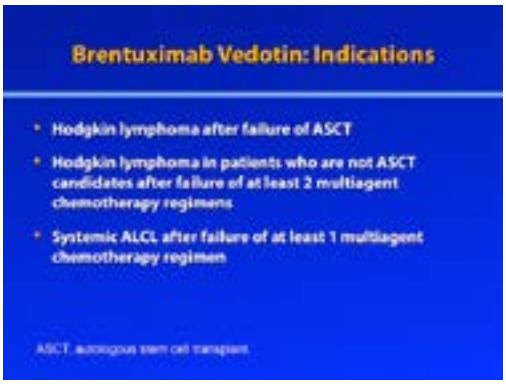

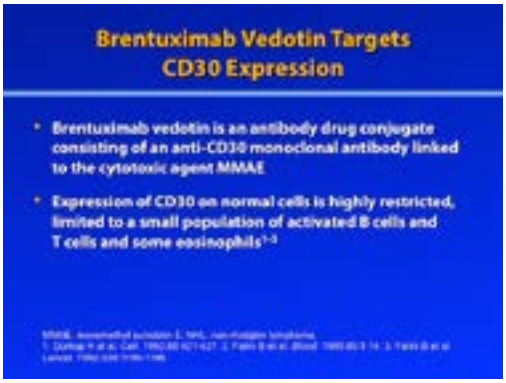

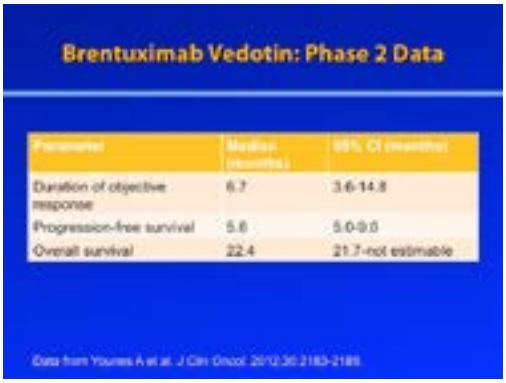

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