Clinical Roundtable Monograph

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Clinical and Pathological Diagnosis of Peripheral T-cell Lymphoma and Emerging Treatment Options: A Case-based Discussion

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Abstract

The diverse group of peripheral T-cell lymphomas (PTCLs) present clinical and pathologic challenges. Proper recognition and diagnosis can be difficult even for experienced pathologists because these entities tend to vary in morphologic appearance from case to case within the same subtype and often mimic other diseases in appearance. This makes the use of immunologic markers an essential tool. Clinically, PTCLs are difficult to treat because they often present in an advanced stage and are resistant to traditional first-line chemotherapeutic regimens. Five-year overall survival rates are dismal, ranging from 20–50%, depending upon subtype. Although high-dose sequential chemotherapy followed by autologous hematopoietic stem cell transplantation has been reported to improve overall survival in patients with PTCL, this therapy is only feasible for the small minority of patients who experience a durable complete response to induction therapy. Therefore, there is much interest in the field in developing novel first-line approaches that will improve response rates and duration. In this monograph, 2 case studies of different subtypes of PTCL will be presented, and the clinical and pathologic features will be discussed. In addition, data on emerging therapies for PTCLs will be reviewed with an emphasis on novel and investigational agents.

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Target Audience
This activity has been designed to meet the educational needs of hematologists and oncologists involved in the management of patients with T-cell lymphoma.

Statement of Need/Program Overview
Data are emerging on novel agents as well as new combination regimens for the treatment of lymphoma. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

Educational Objectives
After completing this activity, the participant should be better able to:

- Describe new study findings from recent presentations abstracts/poster summaries in the natural history of peripheral T-cell lymphoma
- Explain how pathological diagnosis impacts clinical treatment of peripheral T-cell lymphoma.
- Describe how to integrate the latest knowledge on methods for diagnosing and treating patients with peripheral T-cell lymphoma.
- Identify future research directions for all therapies in peripheral T-cell lymphoma.

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Table of Contents

Peripheral T-cell Lymphoma: Diagnosis and Pathology

Jonathan Said, MD

Peripheral T-cell lymphomas (PTCLs) are a group of heterogeneous lymphoproliferative disorders arising from immunologically mature T-cells, as opposed to pre-T-cells or thymic T-cells.[1] The most recent World Health Organization (WHO) classification of the hematopoietic and lymphoid neoplasms groups PTCL into subtypes that are predominantly leukemic, those that are predominantly nodal, and those that are predominantly extranodal.[2] The predominantly nodal subtypes consist of angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS; Figure 1).

PTCL-NOS is the most common subtype of PTCLs. In the past, a number of definite entities corresponding to recognizable subtypes of T-cell neoplasm, such as Lennert lymphoma, T-zone lymphoma, pleomorphic T-cell lymphoma, small and medium-sized T-cell lymphoma, large-cell T-cell lymphoma, and T-immunoblastic lymphoma, have been described.[3] Yet, there is still no definitive evidence that these subtypes correspond to distinctive clinicopathologic entities.[4-7] Therefore, the WHO classification system has gathered many of these subtypes into the diagnosis of PTCL-NOS. Morphologically, these malignancies have a broad spectrum of appearances; therefore, in fact, PTCL-NOS can be thought of as a diagnosis of exclusion.

The case that follows exemplifies the typical disease course of a patient with advanced PTCL-NOS. In this section, we will focus on the distinct pathological features of the disease and diagnosis.

Case 1

The patient was a 72-year-old man who presented with a bilateral lower extremity rash of unknown etiology, night sweats for the past 2 years, and a 40-pound weight loss over the past 2 years. Upon examination, he had diffuse lymphadenopathy in the left neck, bilateral axilla, and inguinal area, the largest of which was a left axillary node of 3.2 centimeters. He also had splenomegaly. A left inguinal node biopsy revealed PTCL-NOS. His bone marrow at that time had less than 1% involvement, but abnormal cells were present in the peripheral blood. Computed tomography (CT) imaging revealed a retroperitoneal lymphadenopathy of 3 centimeters and a left iliac node of 4.2 centimeters. The patient's only comorbidity was a slight dementia or slight Parkinson's disease; it was unclear exactly which.

The patient was treated with standard cyclophosphamide, doxorubicin hydrochloride, vincristine, and oral prednisolone (CHOP) chemotherapy. After the first 2 cycles, his response was sluggish, so the cyclophosphamide

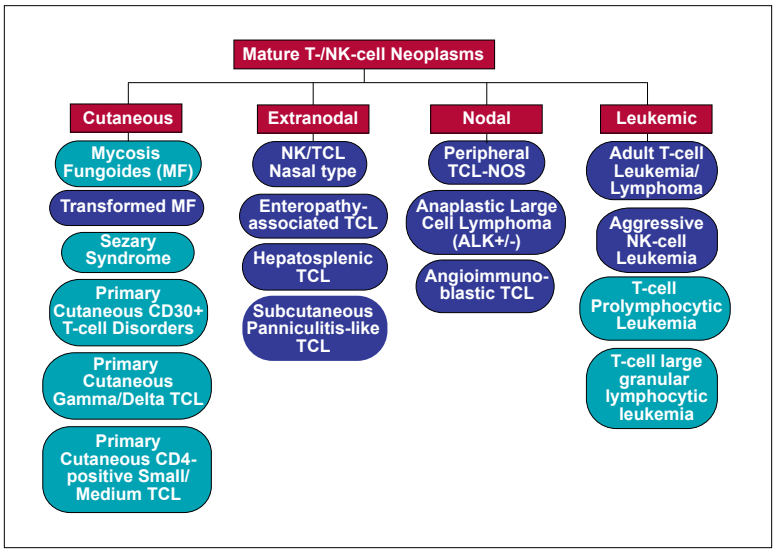

Figure 1. Subtypes of peripheral T-cell lymphoma.

Adapted from Rodriguez J et al. *Crit Rev Oncol Hematol.* 2009;71:181-198.

NK=Natural killer; TCL=T-cell lymphoma.

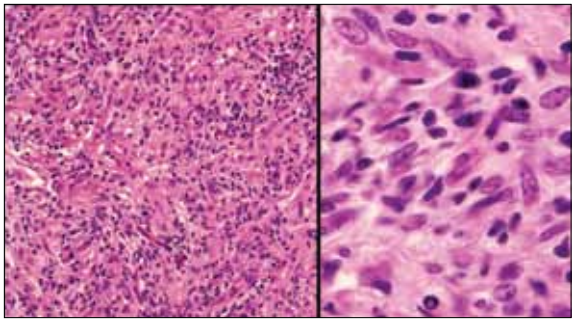

Figure 2. Peripheral T-cell lymphoma with granulomatous appearance.

dose was increased from the usual 750 mg/m^2 to 1 g/m^2. He received a total of 7 cycles and was seen to have a complete response (CR) on positron emission tomography (PET) imaging after the 5th cycle. The patient and his family were, at that point, considering high-dose sequential (HDS) chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT).

Unfortunately, the patient had a recurrence of his lymphadenopathy with a right groin lymph node, swelling of the right leg, and skin rash 2 months after CHOP chemotherapy. He then underwent therapy with gemcitabine and oxaliplatin, which initially produced an excellent response. However, 6 months after treatment, the disease again progressed with a minimally positive bone marrow. At that time, the patient was enrolled in a clinical trial and received treatment with pralatrexate. He did experience complications from the pralatrexate: an oral herpes simplex virus inflammation as well as a peri-rectal inflammation, which may have been due to herpes simplex but was culture negative. He achieved an excellent partial response (PR) with single agent pralatrexate in almost all lymph node areas and maintained that response for 6 months, at which time the disease progressed with positive bone marrow. The patient then was enrolled in a second clinical trial and received romidepsin; however, he had only a mixed response and expired shortly thereafter.

Pathology and Diagnosis

The histology of PTCL is characterized by nodal effacement by a diffuse growth of neoplastic T-cells, which is often accompanied by reactive histiocytes and high endothelial venules. The malignant cells can range in size, but they all tend to have clear cytoplasm and irregular nuclei. Multinucleated tumor giant cells and Hodgkin-like cells may be seen. There is generally a marked inflammatory component of histiocytes, eosinophils, plasma cells, and B-lymphocytes.

There are some histologic variants worth noting. One is lymphoepithelioid (Lennert) lymphoma, which has characteristic small 'squiggly' lymphocytes with evenly dispersed granulomatous clusters of epithelioid histiocytes (Figure 2).[8] It is important not to confuse these clusters with infectious granulomas. A second variant is follicular T-cell lymphoma, in which intrafollicular aggregates of irregular T-cells with clear cytoplasm can be seen.[9] These may mimic follicular B-cell lymphoma.

Diagnosing PTCL-NOS on the basis of morphology alone can be quite difficult for the pathologist, due to the variations in appearance of the malignant cells as well as the existence of similar "look-alike" conditions. Therefore, we often need to look at genotypic and phenotypic features to confirm the diagnosis (Figure 3). On the phenotypic side, the expression of T-cell markers can be very helpful.[10] The most common T-cell marker that pathologists use is CD3, which is called a pan T-cell marker because it is generally present on all types of T-cells. The next subset of T-cell markers includes CD2, CD5, and CD7. Normal, nonmalignant T-cells will express all 4 markers: CD3, CD2, CD5, and CD7. However, the most common genotypic abnormality in T-cell lymphomas is the loss of some of the normal T-cell markers. CD7 is most commonly lost first, followed by CD5 and then CD2. Thus, in diagnosing a T-cell lymphoma, we look for a tumor that expresses CD3 but has a variable loss of CD2 and CD5, and usually CD7 as well.

The next step is to determine if the malignant cells are helper T-cells (T_H) or cytotoxic T-cells (T_C). CD4 is a marker for T_H cells and CD8 is a marker for T_C cells, although it is also expressed by suppressor or regulatory T-cells. Most PTCL-NOS cells are CD4-positive, although a subset is positive for CD8; in one study the breakdown was 46% CD4-positive and 15% CD8-positive.[9] We also need to determine if the malignant cells are alpha/beta (□□) or gamma/delta (□□) T-cells. About 97% of PTCL-NOS cells have □□ T-cell receptors and stain positive for T-cell receptor □F1 when they are exposed to an anti-□F1 antibody.[9] This finding is helpful in distinguishing PTCL from □□ T-cell lymphomas and natural killer (NK) cell lymphomas, both of which would be negative for □□ T-cell receptors.

Although most PTCL-NOS cells are CD4-positive, other abnormal CD4/CD8 phenotypes can be seen as well and can be helpful for making a diagnosis. For example, normal mature T-cells express either CD4 or CD8, but they do not express both CD4 and CD8 together. Therefore, if mature T-cells that express both CD4 and CD8 are found, then we can be sure that they are abnormal. Another example might be cells that are clearly T-cells because they stain positive for T-cell receptor □F1, but which are negative for both CD4 and CD8. Again, we know that this is an abnormal T-cell phenotype.

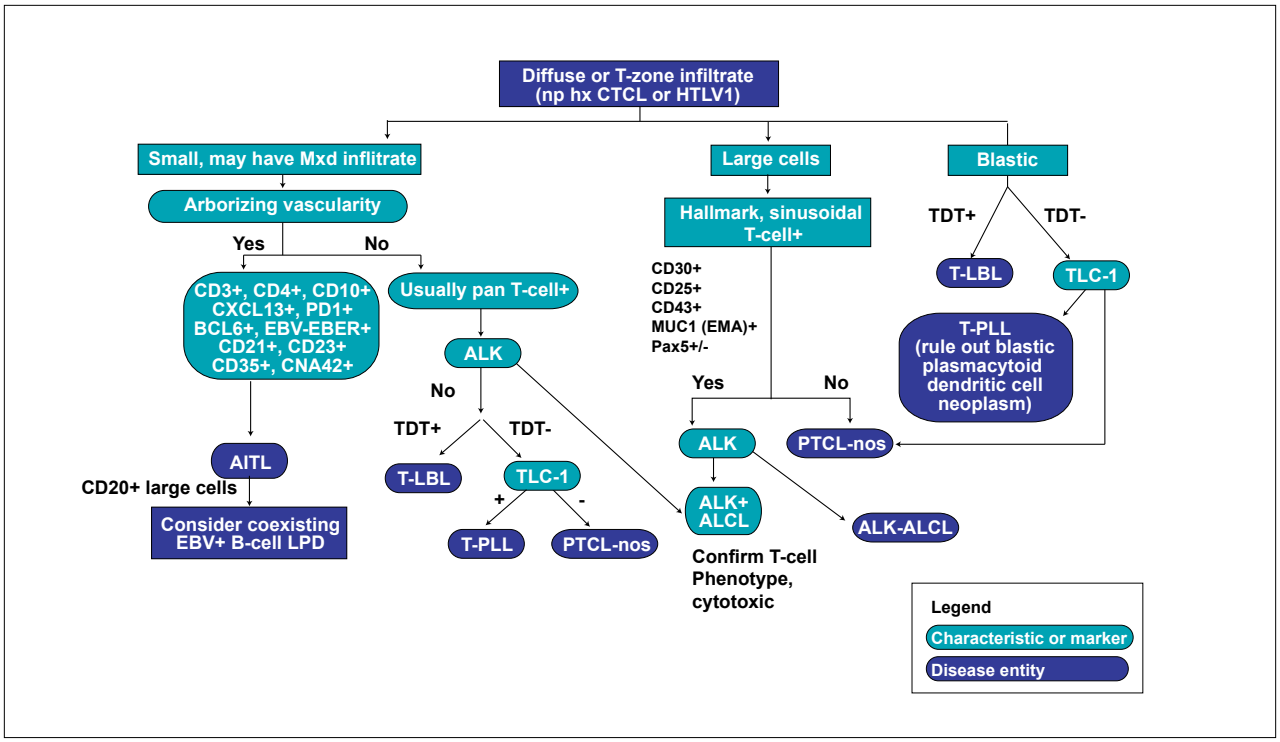

Figure 3. Nodal peripheral T-cell lymphoma flow chart.

Because PTCL-NOS is a diagnosis of exclusion, there are other markers that are useful for ruling out alternate diagnoses. One is CD30, which is uniformly expressed by anaplastic large-cell lymphomas.[11] Although PTCL-NOS may involve a subset of CD30-positive large cells, the expression is not uniform.[9] Rare cases of PTCL-NOS are CD15-positive and CD30-positive[12,13]; these must be distinguished from Hodgkin lymphoma. Another set of useful markers is the combination of CD10, BCL6, PD-1, and CXCL13. This combination, when positive, points to the diagnosis of angioimmunoblastic T-cell lymphoma, as it is not seen in PTCL-NOS.[14,15]

Some pathologic features are prognostically useful. For example, cases with cytotoxic activity (TIA1-positive, granzyme-positive, or perforin-positive) may be more aggressive.[16] Patients with T-cell lymphomas that are positive for the Epstein-Barr virus (EBV) tend to have a worse prognosis, particularly among the elderly.[17] High proliferation rates and Ki-67 scores have also been associated with an adverse prognosis.[9]

In regard to genotypic features, gene rearrangement studies can be helpful as adjunct tests in making a diagnosis of PTCL-NOS. Most T-cell lymphomas have clonal T-cell receptor gene rearrangements. Unfortunately, it is not always possible to detect the T-cell gene arrangement. It is also possible to get false-positive T-cell clones because T-cell clones can occur in benign conditions as well as lymphomas, so care should be taken when interpreting gene rearrangement studies. Cytogenetic studies are another avenue to pursue, if there is access to fresh tissue. Most PTCLs have quite complex karyotypes, and there is not a single specific chromosomal abnormality that delineates PTCL-NOS, but it is helpful to demonstrate an abnormal karyotype.

Case 1: Question and Answer Forum

What were the most important morphologic, genotypic, and phenotypic features of the patient's disease that enabled you to make the diagnosis of PTCL-NOS?

Dr. Jonathan Said: This case was difficult to diagnose. The main problem was that we had only a very small fragment of tissue—a needle core biopsy taken from the retroperitoneal area—to work with. The current tendency is for clinicians to take smaller and smaller biopsies, particularly in patients with invasive disease or sites that are difficult to access. Pathologists are therefore constantly having to struggle with less and less tissue, which can make it very hard to make a diagnosis.

Nonetheless, the biopsy showed a diffuse effacement of the nodal architecture. The cells were very atypical, consisting of mainly medium-sized lymphoid cells with convoluted or irregular nuclei and vesicular open chromatin and distinct nucleoli. These are abnormal features that indicate cellular transformation. There were also a few very large, irregular cells. An inflammatory background of epithelioid histiocytes and plasma cells was seen, which is often the case in PTCL-NOS. Flow cytometry revealed an aberrant T-cell population making up approximately 53% of the total. These aberrant cells were positive for CD2, CD4, and CD5 and had partial exhibition of CD25.

A bone marrow biopsy was obtained, which showed a paratrabecular aggregate consisting of CD4-positive, abnormal, irregular peripheral T-cells mixed with histiocytes, which looked very similar to what was seen in the lymph node. Flow cytometry of the bone marrow again showed an abnormal T-cell population, which constituted about 4% of the marrow cells. This population was CD4-positive and CD7-negative, which again is an abnormal phenotypic feature. So, putting everything together, we were confident in making a diagnosis of PTCL-NOS with bone marrow involvement.

Was this patient's case representative of the disease course seen in PTCL-NOS?

Dr. Lauren Pinter-Brown: Clinically, this case is very typical of PTCL-NOS. Here we have a patient that presented in stage IVB with advanced disease and many constitutional symptoms. The patient was given CHOP chemotherapy, which is the same therapy we would use for aggressive B-cell lymphomas; unfortunately, unlike cases of aggressive B-cell lymphomas, this patient truly exemplifies the difficulty of treating patients with PTCL. Although he experienced a CR after first-line treatment, he quickly relapsed. The patient was an older man who had neurologic problems, and he and his family had a great deal of difficulty deciding whether they wanted to consolidate any of his remissions with HDS chemotherapy followed by ASCT. With such a brief period of remission, no decision was made before his relapse. This exemplifies a common problem; the solution would be a more sustained remission after first-line therapy, which will only come with different medications or a different platform than what is currently available.

The patient was then treated with gemcitabine, which is a very active agent in T-cell lymphoma, though not extensively studied, with a platinum agent. Again, the disease showed a very nice response, but it was not sustained long enough to achieve the transplantation. And at that point, the patient was becoming more debilitated, and he and his family decided that the transplantation probably was not a good option, leading him to participate in clinical trials. This is the course of action recommended by the NCCN guidelines.[18] In the end, the patient expired 2 years after his diagnosis. This is in keeping with the dismal statistics on PTCL-NOS which indicate that, at 5 years post-diagnosis, only 20–25% of patients survive.[19]

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Peripheral T-cell Lymphoma: Clinical Features and Treatment Options

Lauren Pinter-Brown, MD

PTCLs are notoriously difficult to treat. They are less responsive to standard chemotherapeutic regimens than are diffuse large cell B lymphomas, and therefore PTCLs have a poorer prognosis. Furthermore, there have been no randomized, controlled studies of the standard regimens conducted solely in patients with PTCL, so there is no standard treatment for these diseases.

CHOP chemotherapy is the most commonly used first-line regimen for these patients, but responses are often poor. Curative responses are only seen in a small minority of cases with favorable prognostic features.[1] For patients with a favorable response to induction therapy, HDS and ASCT can produce 2-year overall survival (OS) rates of 84% and 2-year progression-free survival (PFS) rates of 63%.[2] Again, however, there are no randomized, controlled trials that have compared standard chemotherapy with HDS and ASCT in patients with PTCL; thus, agents used in clinical trials are the preferred treatment option for these patients.

In this section, we will examine the case study of a patient with extranodal NK/T-cell lymphoma, nasal type, with a focus on the clinical features as well as treatment options, both approved and emerging, in the developmental pipeline.

Case 2

The patient is a 63-year-old man of Greek and Mexican ethnicity who had been in very good health. He presented with nasal congestion on the left side, which had been previously diagnosed as sinusitis. However, an otolaryngologic consult found necrotic and extraneous tissue in the nose. A nasal sinus biopsy showed a marked mixed inflammatory infiltrate as well as neoplastic cells with large, irregular nuclei. Much of the normal sinus tissue had been destroyed. The patient had also developed a fistula between the nose and the soft palate. The diagnosis was extranodal NK/T-cell lymphoma nasal type.

The patient was given radiation therapy to his nose and soft palate. Midway through radiotherapy he developed lymphadenopathy in his left submandibular area. At this point, he was seen at a referral institution and was started on standard ifosfamide, carboplatin, and etoposide (ICE) chemotherapy. He received 2 cycles of ICE with only a minor response and then received radiotherapy to the submandibular node. The patient had foul-smelling skin lesions with central necrosis of approximately 8 or 9 centimeters in length. Imaging studies revealed right inguinal and pelvic adenopathy.

The patient continued to decline, experiencing a 30-pound weight loss, sweats, and fevers. At that time, his private physician prescribed bexarotene, to little effect. The patient was referred to our center at that point, and his chemotherapy was changed to gemcitabine and oxaliplatin. The patient achieved a near-complete response with only a 1-centimeter skin lesion remaining; however, he developed shortness of breath and had pulmonary infiltrates, which were noninfectious in etiology. Because there was concern that gemcitabine might be causing these adverse events, his therapy was switched to asparaginase. He is planning to go forward with allogeneic stem cell transplantation.

Clinical Features and Treatment Options

In general, the most common presentation of extranodal NK/T-cell lymphoma, nasal type in an adult patient is of a destructive nasal and midline lesion.[3] The median age of diagnosis is approximately 50 years. The disease is most common in people with Asian or Central and South American ethnicity. Importantly, the disease does not always present in the nose; common extranodal sites include the skin, the soft tissues, the testis, the upper respiratory tract, and the gastrointestinal tract.[4]

Extranodal NK/T-cell lymphoma is a particularly chemoresistant type of PTCL (Figure 4). Although the disease generally responds well to radiotherapy in the early stages, with reported 5-year overall survival rates of about 83%,[5] radiation in the later stages of the disease is not useful. This situation necessitates the use of chemotherapy in patients with advanced disease; however, as is typical of PTCLs, the disease is aggressive and responds poorly to standard chemotherapeutic regimens. The 5-year OS for patients with advanced disease is only 20–40%.[6,7]

When considering treatment plans for extranodal NK/T-cell lymphoma—indeed, for all of the PTCLs—it is important for the clinician to think carefully about the precise diagnosis and causality when deciding which

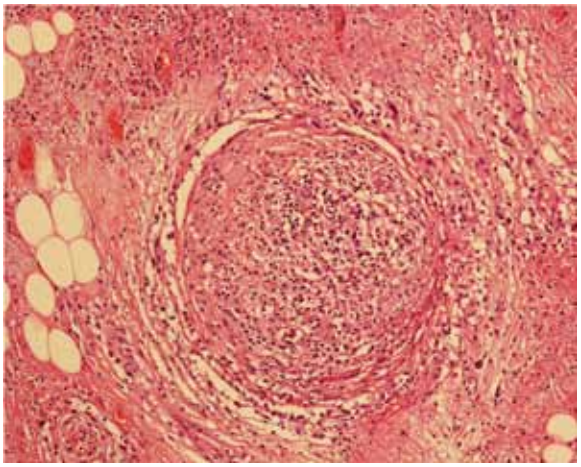

Figure 4. NK/T-cell lymphoma nasal type with angioinvasion and angiodestruction.

chemotherapeutic agent or agents to use. Clinicians must move away from the one-size-fits-all approach to PTCL, which is still too common. For example, in this case study, bexarotene was prescribed by the patient's private physician, although it is specifically used for the indolent peripheral T-cell lymphoma, mycosis fungoides and has not been studied in extranodal NK/T-cell lymphoma.[8] On the other hand, the choice of asparaginase in this case really would not be intuitive. It is a drug that is used for acute leukemia,[9] and it plays almost no role in the treatment of non-Hodgkin lymphoma. Yet, extranodal NK/T-cell lymphoma, nasal type, is almost always associated with EBV,[10] and when one looks at the literature, it becomes clear from a variety of studies that this disease often responds to asparaginase.[11, 12]

Other aggressive subtypes of PTCL also illustrate how important it is for the clinician to carefully consider the presentation and causality of the disease before embarking upon a treatment plan. One good example is adult T-cell leukemia/lymphoma, which is known to be caused by the retrovirus HTLV-1. It has specific treatments, including zidovudine and interferon, that have been found to be particularly effective in this disease subtype.[13] Another good example is angioimmunoblastic T-cell lymphoma. This disease has a very specific clinical presentation characterized by paraneoplastic or autoimmune phenomenon that accompany the lymphoma, such as autoimmune hemolysis, rashes, arthralgias, and effusions; this disease also has specific treatments such as single-agent prednisone for debilitated patients, cyclosporine, lenalidomide, and interferon.[14]

Beyond these established treatments, there are a number of novel agents that may be useful in specific types of PTCL that are currently in the developmental pipeline or have been recently approved by the U.S. Food and Drug Administration (FDA). Enrollment in clinical trials for these and other emerging agents should be encouraged for all patients with PTCL.

The most recently approved agent is pralatrexate, a folate analog metabolic inhibitor indicated for the treatment of patients with relapsed or refractory PTCL. This indication is based on overall response rate (ORR) data from the PROPEL trial, which was an open-label, multicenter, international trial that enrolled patients with PTCL who had relapsed or had progressive disease following prior therapy.[15] A total of 109 patients received pralatrexate 30 mg/m^2 intravenously once weekly for 6 weeks followed by a 1-week break. Patients who had a response or stable disease (SD) continued to receive additional cycles until they experienced disease progression or unacceptable toxicity. The ORR was 27% (95% confidence interval [CI], 19–36%) and the median response duration was 9.4 months (range, 1–503 days). Thirteen patients had response durations of at least 14 weeks; 6 of these 13 patients achieved a CR, 1 patient had a CR unconfirmed, and the remaining 6 patients had PRs.

In this trial, serious adverse events, which included mucositis, thrombocytopenia, nausea, fatigue, anemia, constipation, pyrexia, edema, cough, epistaxis, vomiting, neutropenia, and diarrhea, were reported in 44% of patients. Adverse events caused dose reductions in 31% of patients, dose omission in 69%, and treatment withdrawal in 23%. Overall, 85% of scheduled doses were administered; 8 deaths were reported within 30 days of the last pralatrexate dose, 7 were attributed to progressive disease, and 1 was due to cardiopulmonary arrest possibly related to pralatrexate.

Earlier in the pipeline is lenalidomide, a thalidomide analog with antineoplastic, immunomodulatory, and antiangiogenic properties, which is in phase II studies for use in T-cell lymphomas. In a study by Dueck and colleagues,[16] patients with relapsed and refractory T-cell lymphomas other than mycosis fungoides were prescribed oral lenalidomide (25 mg daily) on days 1–21 of each 28-day cycle, with standardized dose reductions for toxicity. Treatment continued until disease progression, death, or unacceptable toxicity. The primary endpoint was ORR, and secondary endpoints were CR and PR rates, PFS, OS, and safety. An interim analysis was presented at the 2009 annual meeting of the American Society of Clinical Oncology with 23 patients who were evaluable for response. Responses were seen in patients with anaplastic, angioimmunoblastic, and PTCL-NOS histologies. The ORR was 30%; all were PRs, and 2 patients had SD for at least 3 cycles. The median PFS was 96 days (range, 8–696 days) and the median OS was 241 days (range, 8–696+ days). The toxicity profile of the drug was similar to that seen in previous trials of oral lenalidomide for multiple myeloma. Larger studies

with this agent in PTCL are in development and should be interesting to follow.

Another drug in phase II trials for PTCL and cutaneous T-cell lymphoma (CTCL) is romidepsin, a histone deacetylase inhibitor. Piekarz and colleagues presented interim phase II data at the 2008 annual meeting of the American Society of Hematology.[17] This open-label study enrolled 43 patients with relapsed or refractory PTCL or primary cutaneous anaplastic large cell lymphoma. Patients received romidepsin 14 mg/m^2 as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle. The ORR was 39%, and the overall median duration of response was 8.3 months (range, 1.6 months to 4.8+ years). The investigators reported that the drug was well-tolerated. The most frequent drug-related adverse events were generally mild and included nausea (86%; none were grade 3), fatigue (79%; none were grade 3), decreased platelets (70%; 7% was grade 3), and decreased absolute granulocyte count (63%; 5% was grade 3). There was 1 death in the trial; the patient had significant cardiovascular disease and had achieved a CR. The death was considered possibly related to treatment. A single-agent registration trial of romidepsin in patients with progressive or relapsed PTCL following prior systemic therapy is currently enrolling patients in the United States and Europe.

Belinostat is a second histone deacetylase inhibitor that is showing promise for PTCL. Phase II trial results were announced in March of 2009 at an international lymphoma meeting by Foss and colleagues.[18] In the study, 12 patients with PTCL and 16 patients with CTLC were treated with belinostat 1,000 mg/m^2 administered as a 30-minute intravenous infusion on days 1–5 of a 3-week cycle, for a median of 2 cycles. Of 11 evaluable patients in the PTCL arm, there were 2 CRs (18%) and 5 patients with SD. In the CTLC arm, there was 1 CR and 3 PRs. Overall, the authors found the study drug to be well-tolerated, and most adverse events were grade 1 or 2. Grade 3 adverse events attributed to belinostat occurred in 7 patients and included peripheral edema, apraxia, adynamic ileus, and infections. Only 1 related grade 4 adverse event (thrombocytopenia) was noted. Based on these data, belinostat was granted Orphan Drug designation by the FDA for the treatment of relapsed or refractory PTCL, and a phase III trial is underway. An oral formulation of this agent is also under investigation in phase I trials.

Other investigational agents that are even earlier in the pipeline for PTCL include bortezomib, a proteasome inhibitor that is approved in the United States for treating relapsed multiple myeloma and mantle cell lymphoma,[19] as well as denileukin diftitox,[20] a genetically engineered fusion toxin protein consisting of the amino acid sequences for the enzymatically-active portion of diphtheria toxin fused to the sequence of human interleukin-2 (IL-2). The resulting molecule is cytotoxic for cells bearing the target IL-2 receptor expressed on malignant cells. This agent has been approved for the treatment of patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor.

Biologic therapies are being explored in PTCL as well. For example, alemtuzumab, a CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia, has been tested in combination with CHOP chemotherapy as first-line treatment for PTCL. In an Italian study of 24 patients, a CR was achieved by 17 (71%) patients and a PR by 1 patient.[21] The most frequent side effects were grade 4 neutropenia and cytomegalovirus reactivation. Major infections were Jakob-Creutzfeldt virus reactivation, pulmonary invasive aspergillosis, *Staphylococcus* sepsis, and pneumonia. Further studies are planned for this regimen.

Case 2: Question and Answer Forum

How can the clinician differentiate between early-stage extranodal NK/T-cell lymphoma, nasal type, and persistent sinusitis?

L.P-B. Extranodal NK/T-cell lymphoma, nasal type is a very important disease for the clinician and the pathologist to be aware of because it can be a very difficult diagnosis to make. The patient often presents with a lot of inflammation and ulceration, which can be mistaken for sinusitis with sometimes tragic consequences. Therefore, in cases of patients with long-standing congestion and a pathology report indicating a diagnosis of persistent sinusitis, I would advise all clinicians to have the biopsy samples seen by a medical pathologist who is aware of how to distinguish sinusitis from extranodal NK/T-cell lymphoma, nasal type. When the disease is caught early, it can be successfully treated in many cases, but once it has disseminated, the prognosis becomes poor.

What features should the pathologist be aware of when considering a diagnosis of extranodal NK/T-cell lymphoma, nasal type?

JS This disease is pathologically very interesting because the vast majority are NK-cell lymphomas, although you certainly do see cases with T-cell phenotype. Morphologically, there is a spectrum of cell sizes, ranging from small to very large; the larger the cells are, the more abnormal they look. However, the prominent inflammatory component can mask the neoplastic process. One clue that can be used to unmask the malignancy is to stain for Epstein-Barr-encoded RNA (EBER), because extranodal NK/T-cell lymphoma nasal type is almost always associated with the Epstein-Barr virus, and will stain strongly for EBER. In addition, these cells are often angiocentric and angio-invasive, meaning that the malignant cells tend to infiltrate around blood vessels

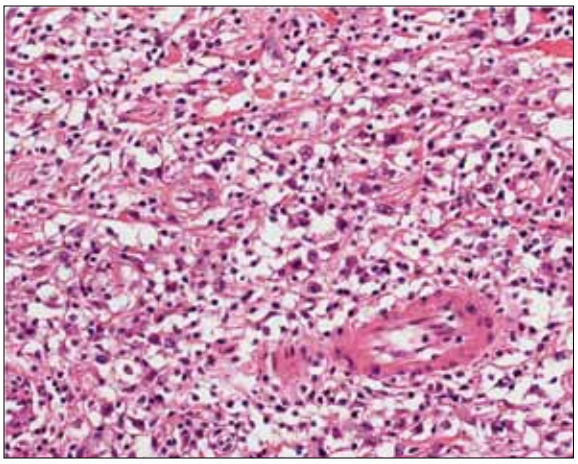

Figure 5. Cellular pleomorphism in NK/T-cell lymphoma nasal type.

and often destroy them. For this reason, there can be much necrosis, which may be located away from the tumor.

In this case, the nasal sinus biopsy for this patient displayed quite a bit of necrosis, a mixed inflammatory infiltrate, and large neoplastic cells with irregular nuclei. Biopsies were also taken from the skin of the patient's nose and right leg, both of which showed typical ulceration and necrosis. There was cellular infiltrate in the ulcer, which had the same phenotype that was found in the nasal sinus biopsy (Figure 5).

Looking in general at extranodal NK/T-cells phenotypically,[22] staining for CD3 epsilon in paraffin sections is always positive because it is present in both T and NK cells. Surface CD3 is usually absent, favoring an NK cell origin for most cases. When of the NK type, the malignant cells are positive for CD56, which is a NK-cell maker, but are usually negative for CD57. Expression of other T-cell antigens is variable. CD2 and CD8 are almost always expressed, but not CD4. The cells usually show a marked cytotoxic phenotype, expressing granzyme B, perforin, and T-cell intracellular antigen-1 (TIA-1).TCR gene rearrangement studies are usually negative, although it is important to keep in mind that a minority of cases can be derived from γδ T-cells.[23]

Genotypically, the malignant cells often have p53 abnormalities and multi-drug resistance gene expression.[24] In terms of cytogenetics, the most common cytogenic abnormality is a deletion at chromosome 6q, although others have been described.[25]

The cellular phenotype in this particular patient was CD3-positive, C56-positive, and EBV-positive, and negative for CD4, CD8, CD5, CD15, and CD20. This profile indicated that the cells were not B-cells or T-cells, but rather NK-cells. The Ki-67 staining showed a very high proliferation rate of about 90%. Together, these pathological features were typical of extranodal NK/T-cell lymphoma.

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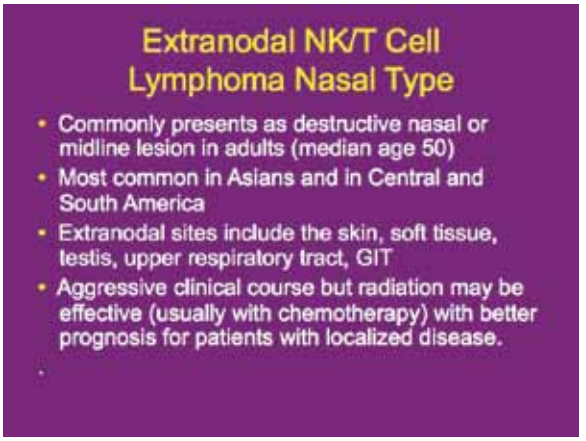

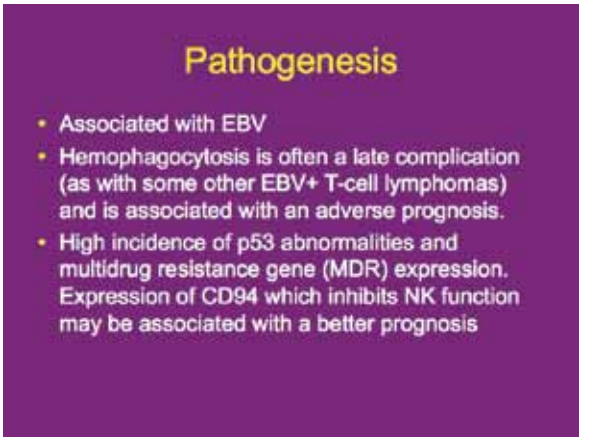

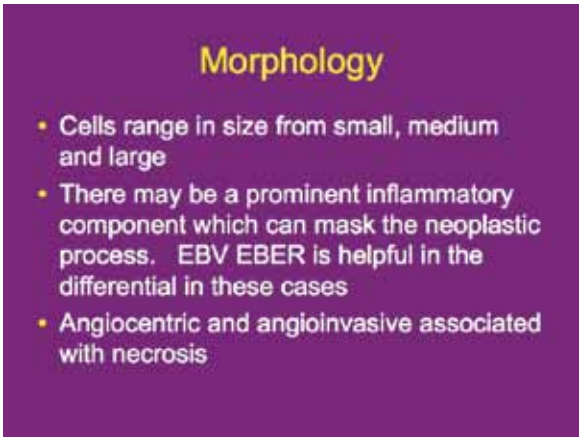

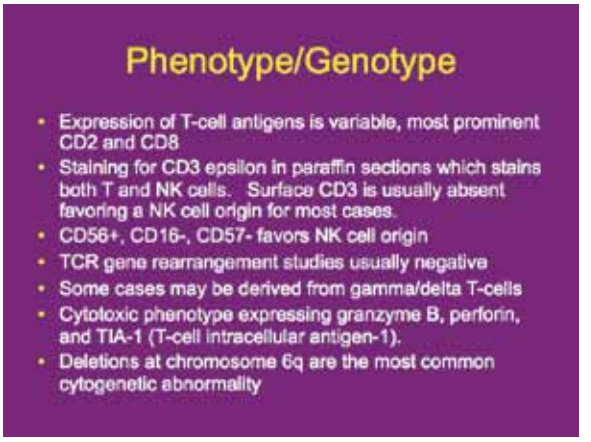

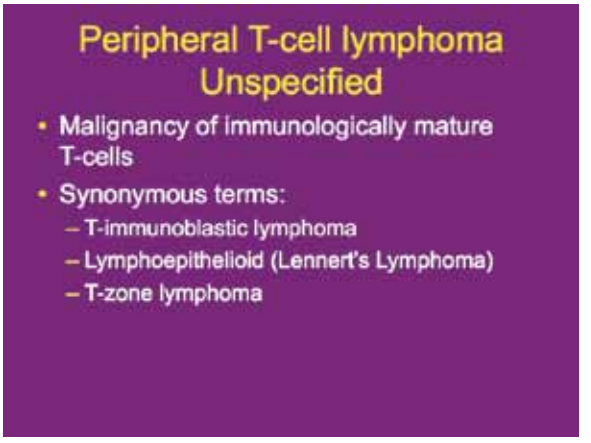

PTCL General Features

- Most common subtype of PTCL (30%)
- Broad spectrum of morphologic appearances and also used to classify T-cell lymphomas that do not fit into any of the other WHO categories.
- Involves lymph nodes, bone marrow, spleen, liver. May present at extranodal sites (skin, GIT) where diagnosis requires exclusion of other entities.
- May have paraneoplastic features including eosinophilia and hemophagocytic syndrome

PTCL- Morphology

- Nodal effacement by a diffuse growth of neoplastic T-cells often accompanied by reactive histiocytes and high endothelial venules
- Range in cell sizes but cells tend to have clear cytoplasm and irregular nuclei
- Multinucleated tumor giant cells and Hodgkin-like cells may be seen.
- Inflammatory component of histiocytes, eosinophils, plasma cells, and large B-cells

PTCL – Histologic Variants

- Lymphoepithelioid (Lennert) lymphoma
  - Small 'squiggly' lymphocytes with evenly dispersed granulomatous clusters of epithelioid histiocytes
- T-zone lymphoma
  - Perifollicular grown sparing follicles
- Follicular T-cell Lymphoma
  - Intrafollicular aggregates of irregular T-cells with clear cytoplasm may mimic follicular B-cell lymphoma

PTCL – Phenotype/Genotype

- Variably express multiple T-cell markers including CD3
- Frequently lose pan-T-cell markers most commonly CD7 and then CD2
- Most are CD4+, have alpha beta T-cell receptors, and stain for T-cell receptor Beta F1. This finding is helpful in distinguishing PTCL from gamma delta T-cell lymphomas and NK cell lymphomas
- Fewer cases have gamma/delta T-cell receptors and a subset stain for CD8.
- CD4/CD8 double positive and double negative cases may occur
- Cases with cytotoxic activity (TIA1+, granzyme+, or perforin+) may be more aggressive
- Most have T-cell receptor gene rearrangements
- May be CD30+ in a subset of large cells, unlike CD30+ ALCL which are more uniformly positive.
- Rare cases are CD15+CD30+ and must be distinguished from Hodgkin Lymphoma
- There may be aberrant expression of B-cell markers including CD20
- EBV+ cases may have worse prognosis particularly in the elderly
- Unlike AITL negative for CD10, BCL6, PD1, and CXCL13
- High proliferation rates and Ki67 scores associated with an adverse prognosis
- Complex karyotypes with no specific chromosomal abnormalities

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Notes

Clinical and Pathological Diagnosis of Peripheral T-cell Lymphoma and Emerging Treatment Options: A Case-based Discussion

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following entities is NOT categorized as PTCL-NOS in the most recent WHO classification?

   a. Lennert lymphoma
   b. T-zone lymphoma
   c. angioimmunoblastic T-cell lymphoma
   d. T-immunoblastic lymphoma

2. Which of the following phenotypic profiles would be consistent with a diagnosis of PTCL-NOS?

   a. cells that are positive for CD3, CD2, CD5, and CD7
   b. cells that are CD3-negative
   c. cells that are positive for CD10, BCL6, PD-1, and CXCL13
   d. cells that are CD3-positive but CD2-, CD5-, and CD7-negative

3. In the majority of cases of PTCL-NOS, the malignant cells are:

   a. CD4-positive
   b. CD8-positive
   c. CD30-positive
   d. CD15-positive

4. Which of the following is NOT associated with a worse prognosis for patients with PTCL-NOS?

   a. Malignant cells with cytotoxic activity
   b. CD-8 positivity
   c. Epstein-Barr virus positivity
   d. High Ki-67 scores

5. According to the National Comprehensive Cancer Network guidelines for Non-Hodgkin Lymphomas, what is the preferred first-line treatment for PTCL-NOS?

   a. clinical trial
   b. CHOP chemotherapy
   c. HDS chemotherapy followed by autologous transplantation (ASCT)
   d. CHOP chemotherapy plus alemtuzumab

6. In the PROPEL trial of pralatrexate for relapsed or refractory PTCL, the ORR was:

   a. 13%
   b. 19%
   c. 27%
   d. 36%

7. Which of the following investigational agents is a proteasome inhibitor?

   a. lenalidomide
   b. bortezomib
   c. denileukin diftitox
   d. belinostat

8. Belinostat and romidepsin are both:

   a. monoclonal antibodies against CD30
   b. novel fusion proteins
   c. monoclonal antibodies against CD52
   d. histone deacetylase inhibitors

9. Which of the following features of a biopsy sample would prompt a pathologist to consider the diagnosis of extranodal NK/T-cell lymphoma in a patient with persistent sinusitis?

   a. a marked inflammatory component
   b. a large amount of small T-lymphocytes
   c. positive stain for EBER
   d. none of the above

10. True or False? All extranodal NK/T-cell lymphomas display a deletion at chromosome 6q.

    a. True
    b. False

Evaluation Form: Clinical and Pathological Diagnosis of Peripheral T-cell Lymphoma and Emerging Treatment Options: A Case-based Discussion

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Describe new study findings from recent presentations abstracts/poster summaries in the natural history of peripheral T-cell lymphoma.	1 2 3 4 5
2. Explain how pathological diagnosis impacts clinical treatment of peripheral T-Cell lymphoma.	1 2 3 4 5
3. Describe how to integrate the latest knowledge on methods for diagnosing and treating patients with peripheral T-Cell lymphoma.	1 2 3 4 5
4. Identify future research directions for all therapies in peripheral T-Cell lymphoma.	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

What barriers do you see to making a change in your practice? _____

Which of the following best describes the impact of this activity on your performance?
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

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