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

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.
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.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME). PIM designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit(s). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Credit Designation
PIM designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit(s). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest
PIM assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of continuing medical education (CME) activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following planners and managers, Linda Graham, RN, BSN, BA, Jan Hixon, RN, BSN, MA, Trace Hutchison, PharmD, Julia Kirkwood, RN, BSN, and Jan Schultz, RN, MSN, CCMEP, hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months. Hazuki Aikawa: No real or apparent conflicts of interest

Method of Participation
There are no fees for participating and receiving CME credit for this activity. During the period November 2009, through November 30, 2010, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the posttest by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by project ID 6749. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Your statement of credit will be mailed to you within three weeks.

Media
Monograph

Disclosure of Unlabeled Use
This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. PIM, Millennium Medical Publishing, Inc., and Allos Therapeutics, Inc. do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Millennium Medical Publishing, Inc., and Allos Therapeutics, Inc. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Disclosures
Jonathan Said, MD—Consultant: Allos Therapeutics Inc.
Lauren Pinter-Brown, MD—Consultant: Allos Therapeutics Inc., Eisai; Non-CME services: Merck
Table of Contents

Peripheral T-cell Lymphoma: Diagnosis and Pathology
    Jonathan Said, MD  4

Peripheral T-cell Lymphoma: Clinical Features and Treatment Options
    Lauren Pinter-Brown, MD  8

Slide Library  12

CME Post-test  15

Evaluation Form  16

Disclaimer
Funding for this clinical roundtable monograph has been provided through an educational grant from Allos Therapeutics Inc. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc, the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2009 Millennium Medical Publishing, Inc. 611 Broadway, Suite 310, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.
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. 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. 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. Yet, there is still no definitive evidence that these subtypes correspond to distinctive clinicopathologic entities. 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, 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...
dose was increased from the usual 750 mg/m² to 1 g/m². 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 infection as well as a peri-rectal inflammation 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 (Lenner) lymphoma, which has characteristic small ‘squiggly’ lymphocytes with evenly dispersed granulomatous clusters of epithelioid histiocytes (Figure 2). It is important to not confuse these clusters with infectious granulomas. A second variant is follicular T-cell lymphoma, in which intranodal aggregates of irregular T-cells with clear cytoplasm can be seen. 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. 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 (TH) or cytotoxic T-cells (TC). CD4 is a marker for TH cells and CD8 is a marker for TC 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. We also need to determine if the malignant cells are alpha/beta (ab) or gamma/delta (δδ) T-cells. About 97% of PTCL-NOS cells have ab T-cell receptors and stain positive for T-cell receptor (TCR) F1 when they are exposed to an anti-TCR F1 antibody. This finding is helpful in distinguishing PTCL from δδ T-cell lymphomas and natural killer (NK) cell lymphomas, both of which would be negative for ab 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 (TCR) F1, but which are negative for both CD4 and CD8. Again, we know that this is an abnormal T-cell phenotype.

**Figure 2.** Peripheral T-cell lymphoma with granulomatous appearance.
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. Although PTCL-NOS may involve a subset of CD30-positive large cells, the expression is not uniform. Rare cases of PTCL-NOS are CD15-positive and CD30-positive; 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.

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

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 paratrabeicular 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.19 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

**References**

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 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. 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%. 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. 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.

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%, 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
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. 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, 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, and when one looks at the literature, it becomes clear from a variety of studies that this disease often responds to asparaginase.

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. 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.

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. A total of 109 patients received pralatrexate 30 mg/m² 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, 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/m² 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/m² 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, as well as denileukin difitox, 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.
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 cytogenetic abnormality is a deletion at chromosome 6q, although others have been described.25

The cellular phenotype in this particular patient was CD3-positive, CD56-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.

References

Slide Library

Extranodal NK/T Cell Lymphoma Nasal Type
- Commonly presents as destructive nasal or midline lesion in adults (median age 50)
- Most common in Asians and in Central and South America
- Extramedullary sites include skin, soft tissue, testis, upper respiratory tract, GIT
- Aggressive clinical course but radiation may be effective (usually with chemotherapy) with better prognosis for patients with localized disease.

Pathogenesis
- Associated with EBV
- Hemophagocytosis is often a late complication (as with some other EBV+ T-cell lymphomas) and is associated with an adverse prognosis.
- High incidence of p53 abnormalities and multidrug resistance gene (MDR) expression. Expression of CD94 which inhibits NK function may be associated with a better prognosis.

Morphology
- Cells range in size from small, medium and large
- There may be a prominent inflammatory component which can mask the neoplastic process. EBV EBER is helpful in the differential in these cases
- Angiocentric and angioinvasive associated with necrosis

Phenotype/Genotype
- Expression of T-cell antigens is variable, most prominent CD2 and CD3
- Staining for CD3 epsilon in paraffin sections which stains both T and NK cells. Surface CD3 is usually absent favoring a NK cell origin for most cases.
- CD5+ , CD15+, CD57+ favors NK cell origin
- TCR gene rearrangement studies usually negative
- Some cases may be derived from gamma/delta T-cells
- Cytotoxic phenotype expressing granzyme B, perforin, and TIA-1 (T-cell intracellular antigen-1)
- Deletions at chromosome 6q are the most common cytogenetic abnormality

Clinical features T/NK nasal type
- Present with mass lesion, nasal obstruction, or epistaxis
- May have facial destruction
- Can spread to nasopharynx, sinuses, orbit, oral cavity
- May disseminate to skin, GIT, testis, cervical nodes
- Phenotype CD2+. CD55+, cytoplasmic CD3e, cytotoxic granules, EBV+

Peripheral T-cell lymphoma Unspecified
- Malignancy of immunologically mature T-cells
- Synonymous terms:
  - T-immunoblastic lymphoma
  - Lymphoepithelioid (Lennert’s Lymphoma)
  - T-zone lymphoma
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 fall 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 granulomatosus clusters of epithelioid histiocytes
- T-zone lymphoma
  - Parafollicular growth sparing follicles
- Follicular T-cell Lymphoma
  - Intrabulbar aggregates of irregular T-cells with clear cytoplasm may mimic follicular B-cell lymphoma

PTCL – Phenotype/Genotype

- Variable expression of T-cell markers including CD3
- Frequent loss of 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 (T-beta). 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 an unusual stain for CD8.
- CD4/CD8 double positive and double negative cases may occur.
- Cases with cytotoxic activity (TIA1+, granzyme+, 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.
- New cases are CD715+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 ANTL, negative for CD10, BCL6, PD1, and CXCL13.
- High proliferation rates and 16q127 score associated with an adverse prognosis.
- Complex karyotypes with no specific chromosomal abnormalities.

For a free electronic download of these slides, please direct your browser to the following web address:
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

Project ID: 6749
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.  
2. Explain how pathological diagnosis impacts clinical treatment of peripheral T-Cell lymphoma.  
3. Describe how to integrate the latest knowledge on methods for diagnosing and treating patients with peripheral T-Cell lymphoma.  
4. Identify future research directions for all therapies in peripheral T-Cell lymphoma.

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

The content presented:
Enhanced my current knowledge base  1  2  3  4  5  
Addressed my most pressing questions  1  2  3  4  5  
Promoted improvements or quality in health care  1  2  3  4  5  
Was scientifically rigorous and evidence-based  1  2  3  4  5  
Avoided commercial bias or influence  1  2  3  4  5

Would you be willing to participate in a post-activity follow-up survey?  ☐ Yes  ☐ No

Please list any topics you would like to see addressed in future educational activities:

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on “Find Post-tests by Course” and search by project ID 6749. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

Request for Credit
Name ___________________________ Degree ________________________
Organization _____________________ Specialty ____________________
Address ____________________________
City, State, Zip ____________________
Telephone _________________________ Fax ________________ E-mail ____________
Signature __________________________ Date ________________

For Physicians Only:  I certify my actual time spent to complete this educational activity to be: ________
☑ I participated in the entire activity and claim 1.0 credits.  
☑ I participated in only part of the activity and claim _____ credits.