Dr. Alexandria K. Maurer (Medicine): A 73-year-old woman with a history of chronic lymphocytic leukemia (CLL) was admitted to this hospital because of right inguinal lymphadenopathy, fever, and drenching night sweats.

The patient had been in her usual state of health and had been undergoing active medical surveillance for CLL until 2 weeks before this presentation, when swelling of the right groin developed. During the next 2 weeks, the swollen area increased in size. Drenching night sweats and daily fevers developed; temperatures taken at home were as high as 38.3°C. The patient called her hematologist’s office and was asked to present to the emergency department of this hospital for evaluation.

The patient had received a diagnosis of CLL 27 years earlier. At that time, lymphocytosis developed and an evaluation revealed pelvic lymphadenopathy. The patient underwent resection of the left ovary and a nearby retroperitoneal mass. On pathological evaluation, the ovarian tissue was normal, but findings in the nodal tissue were consistent with CLL. During the next 12 years, the patient had slowly progressive lymphocytosis and stable splenomegaly, and she underwent active surveillance with periodic complete blood counts and physical examinations.

Fifteen years before this presentation, fatigue and anemia developed and a 3-month course of chlorambucil was administered, with improvement in lymphocytosis and anemia. During the next 3 years, the patient received three additional courses of chlorambucil for symptomatic anemia, each of which was followed by a period of remission. Nine years before this presentation, anemia, thrombocytopenia, and splenomegaly developed and fludarabine and rituximab were administered, with improvement in blood counts and splenomegaly. Three years before this presentation, during post-treatment surveillance, fatigue, worsening anemia, and splenomegaly developed and idelalisib and rituximab were administered, with improvement in symptoms. After 1 year, all treatment was stopped because of a diffuse rash that was attributed to idelalisib. Two months before this presentation, the patient had a white-cell count of 19,000 per cubic millimeter (reference range, 4500 to 11,000).
In addition, several years before this presentation, hypogammaglobulinemia developed in association with rituximab treatment and was complicated by recurrent sinopulmonary infections, and intravenous immune globulin (IVIG) treatment was initiated. In the past, the patient had undergone resection of squamous-cell carcinoma from the right leg and of multiple basal-cell carcinomas. Other history included recurrent herpes simplex virus (HSV) type 1 infection of the genitals (for which she received acyclovir as needed), diverticulosis, a burst fracture of the first lumbar vertebra after a fall, and shingles due to herpes zoster infection of the right L2 dermatome. Four years before this presentation, she was treated empirically for *Borrelia burgdorferi* infection.

The patient had no known drug allergies. Her medications included subcutaneous IVIG every other week, a multivitamin, calcium carbonate, vitamin C, lysine, and acyclovir as needed. She had smoked tobacco for 10 years but had quit 40 years before this presentation. She drank alcohol occasionally and did not use illicit drugs. Her husband had died 1 year before this presentation, and she was not sexually active. She was a retired librarian, lived in Massachusetts, and had not traveled outside the United States. She had no pets or exposures to cats. She enjoyed gardening and took daily walks outside. Her family history included heart disease in her mother and skin cancer in her father.

In the emergency department, the patient reported ongoing daily fevers and night sweats, as well as an unspecified amount of weight loss over the past month. She reported no headaches, sore throat, cough, abdominal pain, nausea, vomiting, diarrhea, dysuria, vaginal discharge, or rash. On physical examination, the temperature was 37.4°C, the pulse 84 beats per minute, the blood pressure 140/63 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 92% while she was breathing ambient air. The weight was 61 kg, the height 158 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 24.7. The patient did not appear ill. The abdomen was nondistended, with normal bowel sounds and no tenderness on palpation. The spleen was palpable. Multiple right inguinal lymph nodes were enlarged, measuring 2 to 5 cm in maximal diameter; the nodes were hard, nonmobile, and mildly tender, and there were no overlying skin changes. Multiple left inguinal lymph nodes measured 1 to 2 cm in maximal diameter. There was no lymphadenopathy in the occipital, posterior auricular, anterior cervical, posterior cervical, axillary, epitrochlear, or supraclavicular region. There were no rashes or skin lesions. The remainder of the physical examination was normal.

Blood levels of electrolytes, glucose, uric acid, lactic acid, and haptoglobin were normal, as were results of renal-function tests and the prothrombin time. Urinalysis revealed clear yellow urine, with a specific gravity of 1.024 (reference range, 1.001 to 1.035) and a pH of 5.0 (reference range, 5.0 to 9.0) and with no blood, ketones, glucose, protein, nitrites, or urobiligen. Blood cultures had no growth. Other laboratory test results are shown in Table 1. Imaging studies were obtained, and the patient was admitted to the hospital.

**Dr. Shahein H. Tajmir:** Chest radiography revealed no consolidation or evidence of pulmonary edema. Computed tomography (CT) of the chest, abdomen, and pelvis, performed after the administration of intravenous contrast material, revealed multiple enlarged mediastinal and hilar lymph nodes with dystrophic calcification, as well as a nodule measuring 1 cm in diameter in the peripheral lung, abutting the pleura. There was evidence of diverticulosis, an unchanged compression fracture of the first lumbar vertebra, and stable enlargement of the spleen (measuring 24 cm in length; reference range, ≤12 cm), with internal heterogeneous attenuation and scattered areas of splenic parenchymal calcification. There were multiple enlarged right inguinal lymph nodes with internal heterogeneity; the largest (dominant) lymph node measured 5 cm in diameter and had surrounding fat stranding. Right external iliac and pelvic sidewall lymph nodes measured up to 4 cm in diameter, and left pelvic sidewall lymph nodes were also enlarged.

Assessment of the area from the neck to the proximal thigh with the use of 18F-Fluorodeoxyglucose (FDG)–positron-emission tomography and CT (PET-CT) revealed intense FDG uptake in the right inguinal lymph nodes, approximately three times the uptake in the liver (Fig. 1). The dominant node had central photopenia suggestive of necrosis. Right external iliac and pelvic sidewall
lymph nodes had moderate FDG uptake, greater than the uptake in the liver. In the chest, a high right paratracheal lymph node had moderate FDG uptake, slightly greater than the uptake in the liver, and a subpleural nodule in the left upper lobe had mild FDG uptake. The level of FDG uptake in the spleen was lower than the level in the liver, with no focal uptake abnormality.

**Dr. Maurer:** On the second hospital day, fine-needle aspiration and core biopsy of the dominant right inguinal lymph node were performed.

**Dr. Lucas R. Massoth:** Examination of the core biopsy specimen revealed a dense monomorphic infiltrate of small mature lymphocytes with scant cytoplasm (Fig. 2A). Some areas of the tumor were necrotic, but there was no evidence of large-cell transformation (Fig. 2B). Flow cytometry and immunohistochemical staining revealed monoclonal B cells that had an immunophenotype characteristic of CLL (Fig. 2C and 2D).

**Dr. Maurer:** Additional diagnostic tests were performed.

### Differential Diagnosis

**Dr. Jacob D. Soumerai:** I cared for this patient and am aware of the diagnosis in this case. This 73-year-old woman, who had a 27-year history of CLL, presented with fever, drenching night sweats, and weight loss. The most striking feature of her presentation was rapidly progressive right inguinal lymphadenopathy. I will construct my differential diagnosis around these features.
CLL and Related Lymphoid Cancers

Progression of CLL

Could this patient have progression of CLL that developed during a period in which she was not receiving therapy? Over the past 27 years, her CLL has been characterized by recurring episodes of slowly progressive leukemic, nodal, and splenic involvement. Her current symptoms suggest a marked deviation from her established pattern of disease and are unlikely to be explained by progression of CLL alone. In addition, the prominent systemic symptoms, rapid progression, and asymmetric lymphadenopathy would all be highly unusual in CLL.

CLL with Acquisition of High-Risk Cytogenetic Lesions

In a cohort of patients with CLL from whom samples were collected before initial therapy and during periods of disease relapse, genetic sequencing revealed clonal evolution and frequent acquisition of high-risk genetic lesions in patients with relapsed or refractory CLL.\textsuperscript{1,2} Previously, this patient had a favorable prognosis on the basis of the degree of mutation in the vari-

Figure 1. Imaging Studies.

Positron-emission tomographic (PET) images (Panels A, C, and E) and fused PET-CT images (Panels B, D, and F) were obtained after the administration of \textsuperscript{18}F-fluorodeoxyglucose (FDG). There is markedly intense FDG uptake in the right inguinal lymph nodes (Panels A and B), including the dominant, necrotic node (Panel B, arrow). There is moderate FDG uptake in other nodes (Panels C and D), including an external iliac node (Panel D, arrow), a common iliac node, and a pelvic sidewall node (Panel D, arrowhead). The level of FDG uptake in the spleen is lower than the level in the liver, with no focal uptake abnormality (Panels E and F).
able region of the immunoglobulin heavy-chain gene (IGHV) and the absence of cytogenetic abnormalities associated with poor outcomes, such as a deletion in chromosome 17p or 11q or a mutation in TP53, ATM, SF3B1, or NOTCH1.3-13 Acquisition of a high-risk mutation could result in an aggressive disease course. However, if this patient had a high-risk genetic lesion, even the most biologically aggressive type, I would expect her to have symmetric lymphadenopathy, rather than predominantly right inguinal lymphadenopathy, because CLL is a systemic disease.

**CLL with Richter’s Transformation**

This patient’s rapidly growing and asymmetric lymphadenopathy, unexplained fever, drenching night sweats, and weight loss raise the possibility of Richter’s transformation, a syndrome in which diffuse large B-cell lymphoma (DLBCL), or in rare cases classic Hodgkin’s lymphoma, arises in a patient with CLL.14-19 Most cases of DLBCL are directly clonally related to the underlying CLL and share the same immunoglobulin heavy-chain gene (IGH) rearrangement, but some cases are clonally unrelated to the underlying CLL and have a distinct IGH rearrangement. Richter’s transformation occurs in 2 to 9% of patients with CLL and is most likely to develop 2 to 4 years after the diagnosis of CLL, although it may occur at any time during a patient’s disease course. The development of a markedly elevated lactate dehydrogenase level in a patient with CLL who does not have associated hemolysis arouses concern about Richter’s transformation; this patient’s minimally elevated lactate dehydrogenase level is nonspecific and does not help us diagnostically.

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**Figure 2. Core Biopsy Specimen of the Dominant Right Inguinal Lymph Node.**

A hematoxylin and eosin stain shows a monomorphous infiltrate of small lymphoid cells, a finding consistent with chronic lymphocytic leukemia (CLL) (Panel A). Foci of necrosis are visible (Panel B). An immunohistochemical stain for PAX5, a B-cell marker, is strongly positive in cell nuclei (Panel C). An immunohistochemical stain for CD5, a T-cell marker that is aberrantly expressed in CLL, is positive in cell membranes (Panel D).
IMAGING STUDIES AND BIOPSY
Do any clues from this patient's imaging studies help to guide the differential diagnosis? Lesions associated with CLL often have a level of FDG avidity that is at or slightly above the level in the liver, with some heterogeneity, whereas lesions associated with Richter's transformation typically have a high level of FDG avidity.20,21 This patient's right inguinal lymph nodes had high FDG avidity, which would be unusual in CLL but is consistent with Richter's transformation. If Richter's transformation is suspected in a patient with CLL, an FDG-PET scan is the preferred imaging study to visualize the most appropriate lymph node to target during an excisional or core biopsy, which is then performed to determine whether Richter's transformation is present.

In this patient, a core biopsy specimen was obtained, with the use of an 18-gauge core needle, from the dominant right inguinal lymph node, and examination of the specimen revealed only evidence of CLL. Because the patient's clinical and imaging findings are not consistent with CLL alone, it is possible that a sampling error resulted in failure to identify the disease process that was driving her presentation. Even a core biopsy specimen of the highest quality represents only a small fraction of the lymph node. Because DLBCL can be focal, it can be easily missed without extensive tissue sampling. On the basis of the results of the core biopsy alone, we cannot rule out Richter's transformation, but I will consider other causes of localized lymphadenopathy.

INGUINAL LYMPHADENOPATHY
On the right side, the leg, genital, buttock, pelvis, and abdominal wall below the umbilicus drain to the right inguinal lymph nodes. An infection or cancer that originates in one of these anatomical sites could explain the patient's right inguinal lymphadenopathy. She has a history of varicella-zoster virus reactivation, recurrent HSV infection, and squamous-cell carcinoma of the skin, conditions that are all probably related to her underlying CLL and possibly related to her previous treatments for CLL. Impaired cell-mediated immune function in CLL leads to an increased risk of infection and of secondary cancer. The impaired immune function may be due to abnormal interactions between activated T cells and nonmalignant B cells, quantitative and functional defects in natural killer cells, and dysfunctional dendritic cells that initiate a weakened T-cell response.22-24

Cancer
Patients with CLL have an increased risk of invasive and metastatic squamous-cell carcinoma.25,26 In this case, the absence of a suspicious skin lesion on examination argues against this condition as the cause of the inguinal lymphadenopathy. However, spontaneous regression of cutaneous melanoma can occur despite metastases to regional lymph nodes or distant sites.27 Therefore, metastasis of melanoma to the right inguinal region from an unknown primary cutaneous site remains a possibility.

Infection
This patient has hypogammaglobulinemia related to underlying CLL and to exposure to therapy with the anti-CD20 monoclonal antibody rituximab.28 Hypogammaglobulinemia may confer a predisposition to soft-tissue infection, which can lead to inguinal lymphadenopathy. However, the patient's risk of such infection has been mitigated by the ongoing administration of IVIG.

The nucleoside analogue fludarabine, which was used to treat CLL in this patient, is especially toxic to T cells and produces a sustained and profound decrease in the CD4+ T-cell count. Her exposure to fludarabine conferred a predisposition to many infections, particularly infections with the herpesviruses, invasive fungal pathogens, and mycobacteria. Although there is an extensive list of infections associated with the use of rituximab, fludarabine, chlorambucil, and idelalisib, most of these infections occur during or shortly after treatment and are unlikely causes of localized lymphadenopathy.

An active skin or soft-tissue infection would result in red, warm, edematous, or tender skin, a finding that is absent in this patient. An active primary sexually transmitted infection such as syphilis, genital herpes, lymphogranuloma venereum, or chancroid would result in genital lesions, a finding that is also absent. In addition, syphilitic lymphadenitis would not usually cause B symptoms (i.e., weight loss, night sweats, and fever). Because the patient has spent a lot of time outdoors, glandular tularemia is a possibility.
Her right inguinal lymphadenopathy could be infectious lymphadenitis. Although this condition is often caused by Staphylococcus aureus or streptococci species, her history of CLL and treatment exposures increase her risk of mycobacterial, invasive fungal, or HSV lymphadenitis.

When I performed a clinical evaluation of the patient, I thought that her presentation was inconsistent with CLL alone. I was most concerned about Richter’s transformation, most likely with DLBCL. Other possibilities were infectious lymphadenitis and infiltration of lymph nodes by melanoma from an unknown primary cutaneous site. I recommended excisional biopsy of the dominant right inguinal lymph node.

Dr. Jacob D. Soumerai’s Diagnosis

Richter’s transformation of chronic lymphocytic leukemia.

Pathological Discussion

Dr. Massoth: The diagnostic test was an excisional biopsy of right inguinal lymph nodes and surrounding fibroadipose tissue. Histologic examination of nodal tissue revealed evidence of diffuse involvement by the known CLL. There was an increased number of paraimmunoblasts in many areas, and plasmacytic cells that contained immunoglobulin inclusions were also prominent (Fig. 3A). On immunohistochemical staining, the plasmacytic cells were kappa-restricted, a finding that indicates plasma-cell differentiation of the CLL clone. Features of Richter’s transformation (sheets of large cells) were not seen.

The dominant right inguinal lymph node was remarkable for widespread regions of necrosis that had extensive involvement of the node capsule and extension into perinodal soft tissues. The appearance of the necrosis ranged from “burned out,” with an absence of associated inflammatory cells, to intensely suppurative, with an abundance of neutrophils and karyorrhectic debris (Fig. 3B and 3C). Palisading histiocytes and aggregates of kappa-restricted plasmacytic cells surrounded the areas of suppuration.

Regions in the suppurative necrosis had pleomorphic-appearing cells with features of viral cytopathic effect suggestive of HSV, including multinucleation, molding of adjacent nuclei, and margination of chromatin to the nuclear periphery (Fig. 3D and 3E). Nuclei with a ground-glass appearance and eosinophilic intranuclear inclusions of viral particles were abundant. Immunohistochemical staining for HSV types 1 and 2 was strongly positive in cells with viral cytopathy (Fig. 3F), a finding that established the diagnosis of HSV lymphadenitis. Additional special and immunohistochemical stains for the detection of bacteria, mycobacteria, fungi, and other viruses were negative.

HSV is a rare cause of isolated lymphadenitis and is classically associated with underlying CLL. The virus results in a necrotizing lymphadenitis that often localizes to the paracortical and capsular regions and extends into extranodal soft tissues. Histiocytic proliferation typically surrounds these well-defined necrotic regions, but overt granuloma formation is not a characteristic feature. Sites of active viral replication generate a strong neutrophilic response, which is often absent in older lesions.

Reported cases of HSV lymphadenitis in patients with CLL have shown an increase in the number of paraimmunoblasts and prolymphocyte forms in the background lymphoma, which was seen in this case. Paraimmunoblasts and prolymphocytes are normally numerous in pseudofollicular proliferation centers of CLL; a diffuse increase in the number of these cells can be seen with superimposed HSV lymphadenitis but might also arouse concern about Richter’s transformation. As such, an increase in the number of large cells in patients with CLL should be interpreted with caution in the presence of HSV infection.

Discussion of Management

Dr. Martin S. Hirsch: HSV is ubiquitous and has two major types; type 1 and type 2. In the past, HSV type 1 was thought to primarily cause infections of the face (e.g., lip or eye) and HSV type 2 was considered to primarily cause genital infections. Over the past several decades, this distinction has broken down, and now many infections of the oral labia are known to be caused by HSV type 2 and many genital infections are related to HSV type 1. Primary HSV infections are associated with neuronal transport of the virus to re-
Figure 3. Excisional Biopsy Specimen of the Dominant Right Inguinal Lymph Node.

A hematoxylin and eosin stain shows features of CLL (Panel A), including interspersed plasmacytic cells that contain large intracytoplasmic immunoglobulin inclusions (arrowhead) and an increased number of paraimmunoblasts, which are enlarged B-cell forms with prominent nucleoli (arrow). Well-defined regions of necrosis vary from acellular (Panel B) to acutely suppurative (Panel C). The acutely suppurative areas (Panel C) contain abundant neutrophils and cellular debris (arrowhead) and are surrounded by histiocytic inflammation (arrow). Regions in the suppurative necrosis contain large cells with features of viral cytopathic effect (Panels D and E), including multinucleation, nuclear molding (Panel E, arrow), and margination of chromatin (Panel E, arrowhead). An immunohistochemical stain for herpes simplex virus types 1 and 2 is strongly positive in the infected cells (Panel F).
gional ganglia and lifetime persistence of the virus in ganglion cells, with intermittent viral reactivation and recurrent lesions. Immunocompromise associated with the neonatal period, advanced age, immunodeficiency, or immunosuppression can lead to viral reactivation and replication, as well as increased clinical severity.

HSV reactivation in CLL is common. Although it usually results in localized skin ulcerations, it may be associated with more severe and widespread infection. However, clinically obvious HSV lymphadenitis in CLL is rare, with fewer than 40 cases reported. HSV lymphadenitis in CLL is most often detected unexpectedly when lymph node biopsy is performed to rule out Richter’s transformation, as in this case. The onset of HSV lymphadenitis in CLL occurs between 50 and 86 years of age, and the incidence does not differ between sexes.

The primary antiviral therapy for HSV infection is acyclovir or one of its derivatives, valacyclovir or famiclovir. Although controlled trials have shown that acyclovir and its derivatives are effective agents for the treatment of several HSV-associated conditions (e.g., encephalitis), data regarding the use of these agents for the treatment of HSV lymphadenitis are limited because of the rarity of this entity. Occasional cases of HSV lymphadenitis have resolved spontaneously, without antiviral therapy, and thus there is no standard treatment for this condition. Nevertheless, given the potential consequences of not treating this serious infection in an immunocompromised host, it would be reasonable to initiate a course of intravenous acyclovir followed by a prolonged course of oral valacyclovir. Because of the persistent immunocompromise seen in patients with CLL, lifelong antiviral suppression may be indicated, although partial viral suppression in an immunocompromised host may lead to acyclovir resistance. Should acyclovir resistance occur, it usually involves the emergence of mutations with thymidine kinase deficiency that generally remain susceptible to treatment with alternative agents such as foscarnet or cidofovir. In addition, agents that are currently being studied for the treatment of HSV infection (e.g., helicase–primase inhibitors) may be useful but have not yet been studied for the treatment of HSV lymphadenitis.

Dr. Soumerai: This patient underwent urgent evaluation to rule out severe systemic disease, including HSV encephalitis, hepatitis, and pneumonia. No manifestation of HSV infection other than lymphadenitis was identified. She received intravenous acyclovir, and within 24 hours after the initiation of antiviral therapy, her B symptoms resolved and she was discharged from the hospital with a 2-week course of oral valacyclovir.

Four months later, progressive pancytopenia and discomfort in the left upper quadrant developed. A bone marrow examination revealed extensive involvement by CLL. A CT scan of the chest, abdomen, and pelvis showed progressive generalized lymphadenopathy and hepatosplenomegaly, although the right pelvic sidewall lymph node had decreased in size.

Dr. Nickpreet Singh (Medicine): Was immunohistochemical staining for HSV types 1 and 2 performed on the earlier core biopsy?

Dr. Massoth: No, it was not. There was no obvious evidence of viral cytopathic effect, and the focus was on ruling out Richter’s transformation.

Dr. Michael Mansour (Medicine): Is vaccination against other viruses warranted in patients with CLL?

Dr. Soumerai: I recommend that patients with CLL receive the recombinant adjuvanted zoster vaccine.

Dr. Sarah E. Turbett (Medicine): Can varicella–zoster virus cause lymphadenitis?

Dr. Hirsch: I have not seen a case of varicella–zoster virus as a cause of isolated lymphadenitis in CLL. In theory, varicella–zoster virus could cause a similar syndrome, and lymphadenopathy can accompany dermatomal or disseminated zoster in patients with CLL, but the few cases of isolated lymphadenitis in CLL have predominantly been associated with HSV.

ANATOMICAL DIAGNOSES

Herpes simplex virus lymphadenitis.

Chronic lymphocytic leukemia.

This case was presented at the Medical Case Conference.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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