THE PATIENT
52-year-old woman

EXAM FINDINGS
At a well woman visit, the patient's vital signs and physical exam were normal, with the exception of 3 enlarged left inguinal lymph nodes and approximately 5 enlarged right inguinal lymph nodes.

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THE CASE
A 52-year-old woman presented to our family clinic for a well woman exam. The only complaints she had were fatigue, which she attributed to a work day that began at 4 am, and hot flashes. She denied fever, weight loss, abdominal pain, medication use, or recent foreign travel. She had a history of hyperlipidemia and surgical removal of a cutaneous melanoma at age 12.

Her vital signs and physical exam were normal with the exception of 3 enlarged left inguinal lymph nodes and approximately 5 enlarged right inguinal lymph nodes. The nodes were freely moveable and non-tender. No additional lymphadenopathy or splenomegaly was found.

THE DIAGNOSIS
The patient's work-up included a Pap smear, complete blood count (CBC), comprehensive metabolic panel (CMP), and pelvic and inguinal ultrasound. All tests were normal, except the ultrasound, which revealed 3 solid left inguinal lymph nodes measuring 1.2 to 1.6 cm and 6 solid right inguinal lymph nodes measuring 1.1 to 1.8 cm. An abdominal and pelvic computed tomography (CT) scan with contrast identified nonspecific mesenteric, inguinal, retrocrural, and retroperitoneal adenopathy. An open biopsy of the largest inguinal lymph node revealed follicular lymphoma, a form of non-Hodgkin's lymphoma. (Hodgkin's and non-Hodgkin's lymphoma (NHL) are uncommon causes of inguinal lymphadenopathy.[1])

We consulted Oncology and they recommended a positron emission tomography (PET)/CT scan, which showed widespread lymphadenopathy. A bone marrow biopsy confirmed follicular lymphoma grade II, Ann Arbor stage III.

DISCUSSION
Generalized lymphadenopathy involves lymph node enlargement in more than one region of the body. Lymph nodes >1 cm in adults are considered abnormal and the differential diagnosis is broad (**TABLE**[2-5]). A patient's age is a significant factor in the evaluation of peripheral lymphadenopathy.[2-5] Results from one study of 628 patients who underwent nodal biopsy for peripheral lymphadenopathy revealed approximately 80% of nodes in patients under age 30 were noncancerous and likely had an infectious cause.[3] However, among patients over age 50, only 40% were noncancerous.[3]

Node enlargement can be palpated in the head, neck, axilla, inguinal, and popliteal areas. Inguinal lymph nodes up to 2 cm in size may be palpable in healthy patients who spend time barefoot outdoors, have chronic leg trauma or infections, or have sexually transmitted infections.[6] However, any lymph node >1 cm in adults should be considered abnormal.[2-5]

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TABLE

Adult peripheral lymphadenopathy: The differential is broad[2-5]

Malignancies	Infections	Autoimmune disorders	Miscellaneous
• Kaposi's sarcoma • Leukemias • Lymphoma • Metastases • Skin cancer	• Brucellosis • Coccidioidomycosis • Cytomegalovirus • Human immunodeficiency virus • Infectious mononucleosis • Lyme disease • Lymphogranuloma venereum • Mycobacterial infection • Syphilis • Toxoplasmosis • Tuberculosis • Tularemia • Typhoid fever • Viral hepatitis	• Dermatomyositis • Rheumatoid arthritis • Sjögren's syndrome • Systemic lupus erythematosus	• Amyloidosis • Miscellaneous (autotoxins, antivenoms, streptokinase, vaccines) • Sarcoidosis • Serum sickness medications (such as allopurinol, atenolol, barbiturates, captopril, carbamazepine, cephalosporins, fluoxetine, gold injections, griseofulvin, hydralazine, penicillin, phenytoin, primidone, pyrimethamine, quinidine, sulfonamides, sulindac)

Method of diagnosis depends on malignancy risk

A definitive diagnosis in patients with lymph nodes >1 cm can be made by open lymph node biopsy (the gold standard) or fine needle aspiration (FNA); however, these procedures are rarely needed if malignancy risk is low.

Data on the prevalence of malignant peripheral lymphadenopathy is limited.[4] Fijten et al reported that among 2556 patients who presented to a family medicine clinic with unexplained lymphadenopathy, the prevalence of malignancy was as low as 1.1%.[7] However, the prevalence of malignant lymph nodes among patients referred to a surgical center for biopsy by primary care physicians was approximately 40% to 60%.[3] This highlights the importance of a thorough history, physical exam, and referral when appropriate to increase the yield of diagnostic biopsies.

Low risk for malignancy is suggested when lymphadenopathy is present for less than 2 weeks or persists for more than one year with no increase in size.[2] Benign causes such as sexually transmitted infections, Epstein-Barr virus, or medications should be treated appropriately. With no cause identified, 4 weeks of observation is recommended before biopsy.[2,4,5,8] CT, PET, and biopsy should be considered early for large, concerning masses. No evidence supports empiric antibiotic use for unknown causes.[2,5]

High risk for malignancy is suggested in patients who are ≥50 years, present with constitutional symptoms, have lymphadenopathy >1 cm in >2 regions of the body, history of cancer, or have nodes that are rapidly enlarging, firm, fixed, or painless.[2,3,5,7,9] Supraclavicular lymphadenopathy has the highest risk for malignancy, especially in patients ≥40 years.[7] Enlarged iliac, popliteal, epitrochlear, and umbilical lymph nodes are never normal.[2,4,5,7,10] Biopsy should be considered early in these patients.[2-4,7] FNA or core needle biopsy is acceptable for an initial diagnosis, but negative results may require open biopsy.[1,5,8] Prior to biopsy, imaging with ultrasound is recommended.[1,2,8,11]

Our patient was offered rituximab alone or rituximab in addition to cyclophosphamide, hydroxydoxorubicin, vincristine,

and prednisone (R-CHOP). The patient chose rituximab alone, which resulted in a 30% reduction in the size of her intra-abdominal disease. At this point, the patient and her oncologist chose to stop treatment and monitor her clinically.

Three months later, the patient returned to our family clinic complaining of postnasal drip, throat pain, and neck fullness that she'd had for one month that weren't responsive to over-the-counter remedies and antibiotics. A supervised osteopathic medical student's exam revealed right tonsillar enlargement (grade 3+) with minimal erythema and no exudates. A neck CT confirmed right tonsillar enlargement. The patient was referred to Otolaryngology, and the surgeon performed a tonsillectomy that demonstrated disease progression to follicular lymphoma grade IIIa. Given the new findings, Oncology recommended R-CHOP and the patient agreed.

The patient completed R-CHOP and her cancer was in remission one year later.

THE TAKEAWAY

Peripheral lymphadenopathy presents a diagnostic challenge that requires a thorough history and physical exam. General wellness exams should incorporate a comprehensive physical that includes the palpation of lymph nodes. Exam challenges include distinguishing benign lymphadenopathy (reactive lymphadenitis) from malignant lymphadenopathy.

In patients with low risk for malignancy, a period of 4 weeks of observation is reasonable. Biopsy should be considered early for risk factors including patient's age ≥50, constitutional symptoms, lymphadenopathy >1 cm in >2 regions of the body, history of cancer, or rapidly enlarging nodes. JFP

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