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A Young Woman with Recurrent Lymphadenopathy and Fatigue

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ABSTRACT

A young woman with a two-year history of recurrent cervical lymphadenopathy, fatigue, and systemic symptoms underwent an extensive evaluation for infectious, malignant, and auto-immune causes, all of which were unrevealing. Despite persistent symptoms, initial diagnostic frameworks failed to yield a unifying explanation, prompting repeated reassessment and expansion of the differential diagnosis. This case highlights the limitations of exhaustive testing in the absence of diagnostic clarity and underscores the importance of iterative clinical reasoning, diagnostic flexibility, and reconsideration of common conditions presenting in atypical ways.

CASE PRESENTATION

A 28-year-old woman with a history of hypertension, type 2 diabetes mellitus, hyperlipidemia, obesity, well-controlled asthma (on as-needed albuterol), fibromyalgia, depression, and GERD was referred for evaluation of recurrent lymphadenopathy and chronic fatigue.

Two years before presentation, she developed 3 weeks of fever, sore throat, neck lymphadenopathy (LAD), and debilitating fatigue. A heterophile antibody test (Monospot) performed in clinic was positive and a CT scan obtained at that time reportedly demonstrated cervical lymphadenopathy and hepatosplenomegaly. A diagnosis of infectious mononucleosis was made and the patient received counseling on supportive care.

However, her symptoms persisted. During the subsequent two years, she began having recurrent episodes every 1–2 months, each lasting 3–4 days, characterized by swelling “near the ears” and under the jaw that she described as swollen lymph nodes. The nodes were sometimes tender, but never persisted beyond one week. Episodes were also associated with occasional nonproductive cough, oral ulcers, and scratchy throat. She sometimes recorded a low-grade temperature when she checked at home, but had no drenching night sweats or weight loss. She denied voice change, dysphagia, dyspnea, tongue swelling, or other airway symptoms.

Between episodes, she had chronic fatigue and intermittent myalgias and arthralgias attributed to fibromyalgia. She also reported intermittent episodes of dropping objects because of weakness in her hands; these episodes continued outside the swelling flares. She noted persistent dry mouth, but no dry eyes. She had aphthous oral ulcers several times per year but had none at the time of evaluation.

As her diet was low in vegetables and fruits, initially her primary care provider suggested nutritional

deficiency despite normal labs and a multivitamin was started. Then, two courses of prednisone and one course of acyclovir were prescribed by her primary care clinician. None of these interventions improved her episodic symptoms. A possible hypersensitivity to toothpaste was considered, but her symptoms did not improve with switching the toothpaste. An otolaryngologist performed nasal endoscopy and attributed symptoms to reflux; however, she denied current heartburn, sour taste, nausea, or regurgitation and reported that her typical GERD symptoms were overall well controlled on her medications.

Her medications included a selective serotonin reuptake inhibitor, a proton-pump inhibitor, an oral contraceptive pill, and a multivitamin. Amitriptyline had been started approximately two years earlier for insomnia. She denied tobacco use, reported binge alcohol use (up to 10 drinks per night on weekends), and occasional marijuana use. She worked as a telemarketer. She lived with two dogs and was not sexually active. Family history was notable for sarcoidosis in her father and diabetes mellitus in multiple first-degree relatives.

Due to a family history of rheumatologic disease, a workup was sent and the patient was referred to the rheumatology clinic for consideration of possible autoimmune causes of her symptoms with initial suspicions for Sjogren's, sarcoidosis, or a periodic fever syndrome.

On examination between episodes, she appeared well. The mouth and oropharynx were normal. There was mild diffuse tenderness to palpation of the neck and back musculature. The left knee had a small effusion, but was without warmth or erythema. No rashes, hepatosplenomegaly, or lymphadenopathy were present between episodes. On examination during episodes, she had mobile, tender cervical LAD, approximately 1 cm in diameter, and erythema of the uvula was noted. Chest auscultation remained normal, and the remainder of her exam was unchanged.

Prior infectious evaluation was negative, including testing for HIV, CMV, toxoplasmosis, Bartonella, tuberculosis (QuantiFERON), hepatitis A/B/C, and syphilis (FTA-Abs). EBV PCR was negative; EBV serologies showed VCA IgM positivity, VCA IgG positivity, and EBNA positivity. Autoimmune testing showed an ANA titer varying between 1:80 and 1:320; ENA panel was negative, complements were normal, and urinalysis with urine protein quantification was normal. Selected laboratory data is available in Table 1.

Table 1. Selected Laboratory Data

Test	Result
ANA	1:160
ENA panel	Negative
C3/C4	Normal
RF/CCP	Negative
ANCA	Negative
ESR	33 mm/hr
CRP	1.1 mg/L
ACE	106 (elevated)
CK	Normal
LDH	Normal
CMP	Normal
Quantitative Immunoglobulins	IgA, IgG, and IgM normal
SPEP/SIFE/SFLC/UPEP	Normal
Urinalysis/Urine protein-creatinine ratio	Normal
X-ray hands	Normal
X-ray knees	Mild medial osteoarthritis bilaterally

General surgery was consulted and performed point-of-care ultrasonography, which showed small, benign-appearing lymph nodes, and biopsy was not recommended. A PET/CT obtained two years after the initial mononucleosis-like illness showed no abnormal hypermetabolic lymphadenopathy and resolution of her previously noted hepatosplenomegaly. A benign appearing left ovarian cyst was noted.

DISCUSSION

The key to this case is constructing an accurate problem representation to allow for an appropriate differential diagnosis to be constructed. Her initial symptoms —an acute febrile illness with pharyngitis, cervical lymphadenopathy, and hepatosplenomegaly was consistent with infectious mononucleosis from Epstein-Barr Virus which was confirmed on testing. It is important to consider that her current chronic and intermittent symptoms may not be related to this initial coincident infection.

Given her symptoms have persisted for two years, investigation is focused on chronic conditions, which by nature are different than acute conditions. There are two key concepts of understanding chronic conditions that help us analyze this case: first, all chronic conditions may commonly present with intermittent symptoms; and second, all symptoms of chronic conditions frequently have contributions from multiple sources. Cervical lymphadenopathy, for example, has a large differential diagnosis including infectious, neoplastic, lymphoproliferative, and autoimmune causes. Most commonly, viral and reactive etiologies are the cause of cervical lymphadenopathy, but these are usually acute in nature. EBV does not typically cause cervical lymphadenopathy to extend beyond 4-6 weeks. Chronic cervical lymphadenopathy raises concern for a lymphoproliferative, autoimmune, or chronic infectious disorder. Table 2 provides several examples of these conditions.

It becomes important at this stage for a physician to determine whether further investigation should be obtained to screen for occult visceral pathology. Many chronic disorders can develop insidiously and cause pathology unnoticed by the patient. Several examples of this are diabetes mellitus, chronic kidney disease, and colon cancer, which is why screening tests are used to catch these conditions. The likelihood of missing a chronic pathology is higher for patients who do not have access to healthcare or have chosen not to seek regular healthcare. Our patient's access to regular healthcare and consistent seeking of medical advice makes missing an insidious pathology less likely, but does not eliminate this possibility.

Table 2. Differential for Chronic Cervical Lymphadenopathy

Chronic Infection	HIV, Mycobacteria, Toxoplasmosis, Syphilis, Histoplasmosis
Immune Mediated	Lupus/Sjogren's, Sarcoidosis, IgG4-RD, Autoinflammatory, Histiocytosis
Lymphoproliferative	Lymphoma, Kikuchi-Fujimoto, Head/Neck Malignancy, Metastatic Cancer, Leukemia

A PET/CT was obtained but did not reveal any concerning findings. This and the additional examination of the lymph nodes by an experienced clinician reassures that the current complaints of the patient are more likely to be reactive. For this patient, the standard workup has been performed and was unrevealing.

Chronic reactive cervical lymphadenopathy is usually due to a local disease and may be an indirect complication of inflammation nearby. When a disease's first presentation is an indirect complication, it is considered an atypical presentation and will frequently not trigger a clinician's illness script. These situations can be challenging to investigate.

In this case, we see the center of gravity is in the head/neck area. If we zoom in closer, it seems to be in the oral mucosa or pharynx. Given that this is the center of gravity, we can consider recurrent lymphadenopathy to be a secondary consequence of a primary problem affecting the oral mucosa or pharynx. We then see that the patient has a number of contributing factors to cause reactive cervical lymphadenopathy including binge alcohol use, diabetes, and dry mouth with possible exacerbation from amitriptyline.

At this point we employ another concept of chronic conditions which is that even if all symptoms are explained, they do not preclude the possibility of another chronic condition contributing to the same symptoms. A standard example of this concept is that cardiovascular disease can be caused by longstanding hypertension, but this does not preclude additional contributions from other diseases, like diabetes mellitus. However, diagnosing an overlapping condition can be extremely challenging in certain cases.

An important contributing factor that has not been considered that causes both dry mouth and chronic fatigue is now more recognizable. Sleep-disordered breathing is known to cause chronic or recurrent uvulitis, dry mouth, and oral mucosal disease. There are associations as well with laryngopharyngeal reflux. Reactive cervical lymphadenopathy may occur in response to localized oral mucosal inflammation. Although she did not report snoring or apneic events at night, it is important to consider that these may be missed as she was living by herself. Obstructive sleep apnea is being increasingly recognized in younger patients. It can be missed when physicians are misled to search for inflammatory causes or tasked to decipher the relevance of positive rheumatologic serologies. Chronic conditions are some of the most challenging to diagnose, and recognizing the conceptual differences between acute and chronic disease will help the clinician determine the next best steps in investigation.

Diagnostic Principles for Chronic Conditions

1) All chronic conditions may commonly present with intermittent symptoms. Manifestations may not all be present at the initial presentation. Longitudinal revision of diagnosis over the course of a patient's illness is standard.

2) All symptoms of chronic conditions frequently have multifactorial contributions. Immediate certainty of the cause of a patient's symptom cannot be provided.

3) Chronic conditions frequently cause occult pathologies, unnoticed by the patient. An indirect complication can occasionally be the presenting complaint, and this can be misleading.

4) A symptom or sign can be caused by multiple overlapping conditions. Chronic conditions overlap more frequently than acute conditions. These overlapping associations can occur in patterns that are recognizable, but typically will not have a clear, logical explanation.

5) Many chronic conditions have nonspecific illness scripts or are relatively asymptomatic, requiring a different type of clinical problem solving for investigation when compared with acute conditions.

6) The results of any test at one point in time is less important than internal consistency over time when diagnosing chronic conditions. The patient's story can be more reliable than diagnostic test results.

7) Treatment response is less specific in chronic conditions than acute conditions. The patient's most prominent symptoms may be due to previous damage rather than an active process.

FINAL DIAGNOSIS

Obstructive Sleep Apnea

The patient underwent a sleep study which confirmed the diagnosis and has experienced significant clinical improvement with CPAP.

KEY TEACHING POINTS

- Chronic conditions often present intermittently
- Symptoms are frequently multifactorial
- Diagnostic clarity evolves over time

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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REFERENCES

None