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Night sweats: review of evaluation with an illustrative case

John J. Wolf, DO, FACOFP

From St. John West Shore Hospital, Westlake, OH.

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Summary Night sweats can be a symptom of several life-threatening conditions such as lymphoma, HIV infection, or bacterial endocarditis. They may also be an indication of several endocrine problems, sleep apnea, or GERD. This article reviews a differential diagnosis and the appropriate diagnostic tests to assist the primary care physician in making a timely and accurate diagnosis. A case of sarcoidosis is reviewed. Diagnosis of sarcoidosis and treatment are discussed to exemplify an interesting condition discovered when a patient complained of night sweats.

Introduction

When a patient complains of night sweats, primary care physicians need to have a high index of suspicion for a number of medical conditions. Night sweats can be a symptom of serious life-threatening but also potentially treatable conditions. The physician should be able to generate an appropriate differential diagnosis and list of tests that are available to minimize time to diagnosis. This can become one of the most rewarding diagnostic entities in primary care medicine and a very effective teaching symptom for medical students and residents.

Case overview

A 38-year-old overweight Caucasian male presented to his primary care provider complaining of a two-week history of being intermittently achy, feeling hot and cold, having severe headaches, drenching night sweats, intermittent daytime fevers up to 101 °F, and ankle swelling. He denied weight loss, cough, diarrhea, chest pain, shortness of breath, or rash. In addition, he denied recent travel, contact with tuberculosis, or any known exposure to other illnesses. His wife and two children were not ill. The patient had never been had symptoms like this, took no medications regularly, and had no known infectious exposures at work. He played soccer weekly in an adult soccer league, and his symptoms did not detract significantly from his athletic endeavors.

The initial exam revealed an overweight, somewhat ill-appearing young man who was alert, oriented, and cooperative. His right eye revealed moderate medial conjunctivitis. The pharynx was cobble-stoned and had clear postnasal drainage. There was no cervical, axial, or inguinal lymphadenopathy. Auscultation of his heart revealed a regular rhythm and rate without murmur or rubs. The lungs were clear, with good volume on inspiration and expiration. The ankle examination was not impressive.

Initially, the patient was treated for a possible sinusitis with a third-generation cephalosporin antibiotic and a decongestant. One week later, the symptoms were not resolving. His knees had started to ache, and he complained of a vague shortness of breath. A chest x-ray revealed bilateral hilar adenopathy and an ill-defined infiltration on the left side. A complete blood count was normal except for mild eosinophilia. One of his transaminase tests was slightly elevated (alanine aminotransferase 74; normal range 30–65 U/L), but other liver function tests were normal. Blood cultures were negative. Six days later a thoracic computed

Corresponding author: John J. Wolf, St. John West Shore Hospital, 29000 Center Ridge Road, Westlake, OH 44145.
E-mail address: Jjwolf3@yahoo.com.

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tomography scan revealed multiple, predominantly peripheral pleural-based lung opacities and multiple mediastinal and hilar lymph nodes bilaterally. The case was discussed with a pulmonologist, who promptly evaluated the patient. The pulmonologist honed in on the suspected diagnosis, performed the additional confirmatory testing, and made the diagnosis (See Case discussion).

Evaluation of night sweats

The symptom of night sweats should never be taken lightly. It is usually accompanied by other symptoms or it occurs in persons with chronic medical conditions. Night sweats can be caused by malignancies, infections, endocrine problems, certain medications, and other interesting conditions.[1] A thorough history is essential and should focus on recent travel, new medications, weight changes, pulmonary, gastrointestinal, and arthritic complaints. A complete physical examination is paramount. Special attention to the heart, lungs, and lymphatic system is recommended. Several radiographic and laboratory tests are required initially to begin narrowing the differential diagnosis.

Selected differential diagnosis

Lymphomas and leukemias are known to be associated with night sweats. The presence of firm lymphadenopathy in the absence of infection should require a complete blood count, lymph node biopsy, and bone marrow biopsy.[2] Night sweats are seen more often in Hodgkin's disease than in Non-Hodgkin's disease.

Tuberculosis and acquired immunodeficiency syndrome (AIDS) often produce symptoms of night sweats, fever, and weight loss. A travel and sexual history, as well as infectious contact history, are critical. AIDS-related infections may also produce night sweats.[1] A person with AIDS is at higher risk of contracting tuberculosis. Each should be tested for when one is diagnosed.

Suspicion for histoplasmosis and coccidioidomycosis can be gleaned from a travel history.[2] Infected individuals present with productive cough, fever, and night sweats. The Ohio River Valley population has an increased risk of histoplasmosis. Coccidioidomycosis is endemic in the Southwestern United States. Recent vacationers and frequent business travelers are prone to acquiring it.

Bacterial endocarditis may cause night sweats because of transient bacteremia. Other symptoms would include fever, chills, fatigue and malaise, as well as a new heart murmur. The risk factors for endocarditis include prosthetic heart valve, intravenous drug abuse, recent pacemaker, longer-term intravenous use (i.e., peripherally inserted central catheter lines), and recent illness requiring intensive care treatment. Blood cultures, an erythrocyte sedimentation rate (ESR) and echocardiogram are essential for diagnosis.[3]

Diabetics may develop night sweats because of nocturnal hypoglycemic episodes. Asking patients to check 3:00 AM glucose measurements or when they develop symptoms may aid in diagnosis. Pheochromocytoma causes labile hypertension, palpitations, or paroxysms of headache and flushing. Hyperthyroidism can also cause similar symptoms. Carcinoid tumors will cause flushing, watery diarrhea, hypotension, or edema. Night sweats may be an important symptom in all of these conditions.[1]

Other interesting conditions the primary care physician must consider include obstructive sleep apnea, gastroesophageal reflux disease, and infectious mononucleosis.[1] A history of snoring and daytime fatigue, or of heartburn, will lead the physician to the correct diagnosis—if the patient is asked! Severe fatigue, sore throat, and posterior lymphadenopathy are hallmarks of the well-known "kissing disease."

Medications may also be implicated in the etiology of night sweats. Antipyretics' effects wear off in several hours. Night sweats can be prominent during the perimenopausal and menopausal period. An elevated FSH helps to confirm suspicion. Abuse of alcohol and heroin may produce night sweats. Autonomic overactivity, possibly because of a somatic dysfunction of the cervical or thoracic spine, is another cause of night sweats. In addition, environmental conditions can be important; having the room thermostat set too high or using too many blankets and bed covers may be the most benign reasons for night sweats.[1] However simple this may seem, providing this information to the physician gives insight into a patient's possible impaired functional and mental abilities, especially in the elderly.

Case discussion

This patient was diagnosed with an entity not mentioned above. The clues to his diagnosis lie in his history, physical examination, and diagnostic testing results. For this diagnosis to be accurate, all three entities must be in agreement. The patient'scondition was a granulomatous disease that has no known cause. It is not contagious and most often affects people between 20 and 40 years of age, with a slight female predominance. In the United States, it is more common in African Americans. In Europe, there is a Caucasian predominance. This patient was diagnosed with acute sarcoidosis.

Sarcoidosis is an inflammatory process manifested by an accumulation of T helper-inducer lymphocytes (CD4 cells) and mononuclear phagocytes in affected organs. The CD4 cells release lymphokines that attract and activate mononuclear phagocytes locally. Granuloma formation is the result. In some cases, the process continues, causing fibrosis. The organ's architecture is disturbed, but rarely its function.[4]

Sarcoidosis is a systemic condition, but most patients have only respiratory symptoms because the lung is almost always involved. Acute and subacute sarcoidosis develops over several weeks and manifests constitutional symptoms such as fever, night sweats, fatigue, malaise, anorexia, or

weight loss. Symptoms may include cough, dyspnea, chest discomfort, and/or polyarthritis.[5] The insidious form of sarcoidosis is much more common in the United States, with 40 to 70% of cases in this category. These individuals are more likely to develop chronic sarcoidosis, with permanent damage to the lungs and other organs.[4]

Because sarcoidosis is a systemic condition, many organs can be affected. Most commonly, though, the lungs, lymph nodes, skin, and eyes are involved. Lung involvement typically causes dyspnea, especially with exertion, and dry cough. Hemoptysis and sputum production are rare. Cervical, epitrochlear, axillary, and/or inguinal lymphadenopathy occurs in 75 to 90% of all patients. Palpation causes no pain and, unlike tuberculosis, the nodes do not ulcerate.[4]

The skin is involved in about 25% of cases. The most common lesions are erythema nodosum, plaques, maculopapular eruptions, and subcutaneous nodules. Although skin manifestations may be disfiguring, treatment is not required. Clubbing of the fingers may also be seen, usually in cases of extensive pulmonary fibrosis.[4]

Eye involvement also occurs in about 25% of cases and can cause blindness. Approximately 75% of patients have anterior uveitis that may develop rapidly and resolve spontaneously over 6 to 12 months. The conjunctiva and lacrimal glands may be involved, causing a keratoconjunctivitis sicca syndrome.[4]

Joint involvement occurs in 25 to 50% of cases. Muscle and bone involvement is rare. Arthralgias and arthritis occur mostly in large joints and can be migratory. The symptoms are transient but can become chronic and cause deformities.[4]

Diagnostic testing for night sweats

A streamlined lab and x-ray evaluation of patients with night sweats can lead to a fairly rapid diagnosis. Initially, a comprehensive metabolic panel, complete blood count, thyroid-stimulating hormone, purified protein derivative (tuberculosis test), human immunodeficiency virus (HIV; if history dictates), ESR, and chest x-ray should be ordered. According to the referenced literature, if these tests are negative, it is prudent to try an anti-gastroesophageal reflux medication. If symptoms persist, blood cultures should be obtained including HACEK (*Haemophilus* sp., *Actinobacillus, Cardiobacterium, Eikenella, Kingella*) organisms, and an echocardiogram would be indicated.[2-5]

Depending on the physician's suspicion of the above differential diagnoses, other tests will then be ordered. For pheochromocytoma, a 24-hour urine collection for catecholamines or metanephrines is necessary. Carcinoid tumors secrete high levels of urinary 5-hydroxyindoleacetic acid. Obstructive sleep apnea can be assessed with a sleep study. An elevated follicle-stimulating hormone may identify early menopausal night sweats.[2,4,5]

Laboratory abnormalities indicating sarcoidosis include lymphocytopenia, increased ESR, elevated angiotensin-converting enzyme, and adenopathy on chest x-ray. Confirmatory testing includes bronchoscopy. Cultures of bronchoalveolar lavage fluid are performed for fungal and bacterial organisms. A whole-body gallium-67 study may be indicated when considering the diagnosis of lymphoma, or to demonstrate the extent of disease in other organs.[2]

Sarcoidosis cannot be diagnosed with certainty unless a combination of clinical, radiographic, and histologic, and laboratory findings are obtained. Serologic testing for HIV should always be done in patients with sarcoidosis because of the prevalence of HIV in the general population and the overlap of symptoms of both diseases. Overall prognosis for individuals with sarcoidosis is good. However, approximately 50% have some permanent organ dysfunction. For most of these 50%, the organ dysfunction is mild, stable, and rarely progresses.[4]

This patient'spertinent symptoms included night sweats, headache, fatigue, and arthralgias that began approximately two weeks before presenting to the office. Pertinent laboratory findings included a C-reactive protein of 2.2 (reference $<$1.0 mg/dL). Angiotensin-1 converting enzyme of 97 (reference 12–68 U/L), normal complete blood count, negative peripheral antinuclear cytoplasmic antibodies, negative fungal culture and acid-fast bacillus concentration of bronchial washings, negative PPD, and negative HIV test. Radiologically, the patient had multiple mediastinal and hilar lymph nodes bilaterally.

Sarcoidosis treatment

Because the disease clears spontaneously in 50% of patients, the difficulty lies in determining which patients to treat. Glucocorticoids are the treatment of choice. Only anecdotal or uncontrolled reports support the use of several other medications. Unless the respiratory symptoms are significant, it is prudent to observe active pulmonary sarcoidosis for 2–3 months. Similarly, significant systemic symptoms of fevers, fatigue, and/or weight loss may be reasons to begin treatment with glucocorticoids.[6]

Prednisone is dosed at 1 mg/kg for 4–6 weeks, then gradually tapered over 2–3 months. Alternate-day and high-dose intravenous prednisone has been used by some clinicians but is not more effective than daily oral therapy. There is no evidence that inhaled glucocorticoids are effective. This patient was treated with daily oral prednisone and tapered as described above. His symptoms completely resolved within two weeks of treatment initiation.[6]

Conclusions

The symptom of night sweats is an important clue to several significant diseases and conditions. Clinicians should be comfortable evaluating patients with this symptom. This paper reviews a differential diagnosis and diagnostic testing

that should help clarify the evaluation of night sweats. A case of sarcoidosis presenting during the course of a typical office visit is also reviewed. Sarcoidosis is a disease that is caused by an exaggerated cellular immune response. It most commonly affects 20- to 40-year-old adults. Treatment of significantly symptomatic sarcoidosis is accomplished with oral prednisone therapy and the prognosis is good.

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