

Lymphadenopathy In Hodgkin's Disease Of The Nodular-sclerosing Subtype: Case Presentation

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Abstract

Practitioners frequently examine patients that present with non-specific signs and symptoms such as swelling at lymph node sites, fatigue, night sweats fevers, weight loss, and itching. Even though these symptoms are non-specific, a detailed history and physical examination is necessary to develop differential diagnosis. Differential diagnoses to be considered with these symptoms include Hodgkin's disease, non-Hodgkin's lymphoma, and malignancy. The purpose of this article is to report a patient diagnosed with Hodgkin's disease whose only presenting symptoms were lymphadenopathy, rash, and fatigue. Practitioners need to be familiar with the diagnosis and treatment modalities of Hodgkin's disease as well as the side effects and long term effects of the treatment since patients may elect for diagnoses in a medical center setting but prefer to be treated in their own communities.

CHIEF COMPLAINT

"I have had swollen glands with 'knots' in my neck for one year. Each doctor's visit I was given another antibiotic. I developed bronchitis and pneumonia and the x-ray showed a mass."

HISTORY OF PRESENT ILLNESS

Forty-four year old white female presents to a medical center hospital with a history of enlarged cervical and supraclavicular lymph nodes on the right side of her neck for approximately one year. Enlarged nodes were first noted in January 1998. Several courses of antibiotics were given for what was thought to be an upper respiratory infection, bronchitis, or sinus infection. She then underwent a hysterectomy in March of 1998 due to fibroids. Recovery from the hysterectomy was complicated by progressive fatigue. The fatigue and swollen lymph nodes continued to be a problem and several more courses of antibiotics were given. Her neck continued to be swollen and sore on the right side. The left side of her neck also became enlarged and tender. She reports intermittent hoarseness for the past 3 months. In December 1998 a chest x-ray revealed a mediastinal mass. She then underwent CT scan of the chest. A biopsy of the right supraclavicular lymph node in February 1999 revealed a diagnosis of lymphoma. Patient is here to obtain a plan for treatment that can be implemented in her hometown.

CURRENT HEALTH HABITS

Does not smoke or use recreational drugs. Drinks an occasional glass of wine with dinner approximately once a month.

MEDICATIONS

- Zoloft 50 mg once a day for depression.
- Cozaar 50 mg once a day for hypertension.
- Estrogen 1.25 mg for hormone replacement therapy.
- Valium 5 mg prn anxiety. This was prescribed after her diagnosis of lymphoma.

PAST MEDICAL HISTORY

She has been healthy and well until January 1998. Has a 5-year history of hypertension, which is well controlled on Cozaar. Has had some depression and anger since her divorce several years ago.

ALLERGIES.

States that Demerol and Morphine caused her arm to swell and she felt like a truck was sitting on her chest. Instructed by medical personnel to never take those medications again.

FAMILY HISTORY.

Her maternal grandfather died from cancer. Doesn't know what type of cancer. Paternal aunt died from stomach cancer around age 60. Another paternal aunt died from breast cancer around the age of 40.

PERSONAL/SOCIAL HISTORY

44 year-old white female that teaches school and loves her job. She has been divorced for several years. She has three teen-age children that live with her.

PHYSICAL EXAM

General. Well-developed, well-nourished, well dressed woman who appears anxious. Hair is nicely groomed and she is wearing make-up. Vital signs: T-36.2 C., P-62, R-16, BP-122/84, Wt.-78.4 kg., Ht.-162 cm.

Mental Status. Good spirits although clearly anxious and mentions several times throughout the exam that she wants us to cure her.

Skin, Hair, and Nails. Erythematous rash present on the back of thighs with multiple scabbed areas. Rash is more extensive on the left posterior thigh and extends across the entire width of the thigh to the outer medial area beneath the buttocks. Right thigh rash is smaller and extends to the right outer posterior portion of the thigh beneath the buttocks. Hair is dyed black and well groomed. No other rashes noted on her body.

Head and Neck. Neck is swollen bilaterally and tender especially at the site of the biopsy. Supraclavicular biopsy site is healing well and the incision edges are pink with minimal swelling. Bilateral supraclavicular lymphadenopathy present on exam, the largest measuring 2.0 cm in diameter. Head is normocephalic. Tympanic membranes are pink and pearly bilaterally. Red reflex present bilaterally. PERL.

Throat and Mouth. No lesions. Oral mucosa is pink with adequate saliva. Teeth are in good repair.

Respiratory. Breath sounds are clear and equal bilaterally.

Cardiac. Apical and radial pulses are equal bilaterally. S1 and S2 with regular rhythm auscultated. Dorsalis pedis pulses and posterior tibial pulses are strong bilaterally. Good capillary refill present at less than two seconds. No murmurs noted.

Abdomen. Abdomen soft and flat with hypoactive bowel

sounds. Unable to palpate spleen or liver. No masses felt upon palpation.

Musculoskeletal. Moves all extremities without difficulty. Small fat pad present posterior to right medial malleolus. Strong bilateral hand grips.

Neurological. Bilateral facial symmetry present. No drooping of the eyelids or mouth. Tongue protrudes at midline. Symmetrical smile present. Alert and oriented x 3. Cranial nerves II-XII are intact.

DIAGNOSTIC

- CT scans of chest, abdomen, pelvis routine lab-work
- Bone marrow biopsies Gallium scan
- Chest radiograph – PA & lateral view
Echocardiogram

DIFFERENTIAL DIAGNOSIS

- Hodgkins disease
- Non-Hodgkins Lymphoma
- Malignancy of the mediastinum
- Differential Diagnosis

Three common differential diagnoses associated with supraclavicular adenopathy are Hodgkin's disease, non-Hodgkins lymphoma, and malignancy of the mediastinum. The differential diagnoses associated with lymphadenopathy are determined by the location of the enlarged node. Cervical adenopathy may be present in 56% of healthy adults without any appearance of infection.¹ However one should be aware that cervical adenopathy is a common finding in Hodgkin's disease.² Normal individuals may have small palpable nodes in the neck, axilla, and groin.² Nodes that are palpable in areas other than the neck, axilla, or groin or that are larger than 1 cm in size may be an a potential abnormal finding.² Generalized lymphadenopathy can be associated with infectious processes, hypersensitive reactions, metabolic disorders, and neoplasia such as Hodgkin's disease in the advanced stage and non-Hodgkin's lymphoma. Localized lymphadenopathy in any region can be associated with Hodgkin's disease and non-Hodgkin's lymphoma. Supraclavicular lymph node enlargement on the right side is associated with pulmonary malignancy, mediastinal

malignancy, and esophageal malignancy. Left sided supraclavicular adenopathy is associated with intra-abdominal malignancy, renal malignancy, and testicular or ovarian malignancy.² It is important to obtain a detailed history and physical examination. Questions regarding recent illnesses, infections, or exposures to chemical carcinogens are necessary and should be thoroughly explored.³

Hodgkin's disease is associated with certain age groups. The age groups most susceptible to Hodgkin's disease in the United States are young adults between the ages of 15 to 35 years and adults over age 50. Hodgkin's disease is also more prevalent in men.⁴ Newly noted lymph nodes that are firm, freely moveable, and non-tender are a common symptom of Hodgkin's disease and may be the first clinical findings. Superficial lymph node enlargement is present in 70% of patients with Hodgkin's disease.⁴ Adenopathy in the neck or supraclavicular area is present in approximately 50% of patients with Hodgkin's disease.⁴ Twenty-five to thirty percent of patients may have other symptoms such as fever, night sweats, fatigue and unexplained weight loss of greater than ten percent over six months.⁴

A brief description of Hodgkin's disease, staging, treatment and effects of treatment as it relates to this patient are discussed. The clinical characteristics of Hodgkin's disease, classification, staging, and treatment have been described elsewhere.^{5,6,7}

There are four types of Hodgkin's disease: (1) lymphocyte predominant, (2) nodular sclerosis, (3) mixed cellularity, and (4) lymphocyte depleted. The nodular sclerosis subtype is the most common histological type of Hodgkin's disease in the United States.⁷ This subtype is more common in young female patients and young patients with substantial mediastinal disease and is characterized by bands of dense collagen dividing nodules of neoplastic and reactive cells.⁷ It typically involves cervical, supraclavicular, and mediastinal lymph nodes.

Non-Hodgkin's lymphoma and a mediastinal malignancy may present with the same type of supraclavicular adenopathy and symptoms as Hodgkin's disease. Non-Hodgkin's lymphoma may be seen in the thyroid, breast, gastrointestinal tract, brain, ovaries, testes, and skin. Hodgkin's disease is rarely seen in these areas.⁸ Lymph nodes associated with a malignancy are usually stone hard, fixed, or matted.²

The only way to differentiate these diseases from each other is by microscopic examination. Even though lymph nodes can be seen on computerized axial tomography scan and some tumors can be visualized on chest radiographs, a differential diagnosis cannot be made using these tests. The diagnosis of Hodgkin's disease must be made from a biopsy of a lymph node or other tissues. The biopsy must contain adequate tissue for a microscopic diagnosis.

The presence of the Reed-Sternberg cell is an important factor in differentiating Hodgkin's disease from other lymphomas.⁷ However, it should be noted that Reed-Sternberg-like cells have also been reported in infectious mononucleosis, non-Hodgkin's lymphomas, and in carcinomas and sarcomas.⁷ Viral reactions from smallpox vaccination and herpes zoster can imitate the features of Reed-Sternberg cells.¹⁰ The Reed-Sternberg cell and a background of normal lymphocytes, plasma cells, and eosinophils should be present in order to make a diagnosis of Hodgkin's disease.^{7,9} The biopsy of this patient showed atypical lymphoid cells that have some features of Reed-Sternberg cells and their mononuclear variants. A diagnosis of Hodgkin's disease, nodular sclerosis Stage I was made based on the histologic and immunohistochemical findings.

Once a diagnosis is obtained, the extent of the disease must be determined. This process is called staging. The tests that were completed on this patient to determine staging were computerized axial tomography scan of the chest, abdomen, pelvis, and bone marrow biopsy. Laboratory evaluation, gallium scan, and echocardiogram were also done. The computerized axial tomography (CAT) scan of the chest showed massive mediastinal adenopathy extending cephalad into the neck inferiorly to the aortic route posteriorly around the right paratracheal region and right pulmonary artery. A one-centimeter right internal mammary lymph node was identified. No pleural effusion was evident. Multiple whole body nuclear bone images showed marked increased Gallium uptake involving the base of the neck, bilateral supraclavicular regions, and superior mediastinum consistent with active lymphoma. A small to moderate sized pericardial effusion was noted on both the CAT scan and the echocardiogram. Cardiac function must always be evaluated prior to the administration of Doxorubicin which can be cardiotoxic. Even though a pericardial effusion was noted there wasn't any evidence of tamponade and the ejection fraction was normal at 55-60 percent. The bone marrow did not show any evidence of disease. The chest PA and lateral showed anterior and superior mediastinal adenopathy

consistent with lymphoma.

The Ann Arbor staging system developed in 1971 is one method utilized to determine the stage of the disease. 2, 4 A second staging system developed in 1989 known as the Cotswold Staging Classification is a method that has been modified from the Ann Arbor classification system and may also be used. 5,7 Hodgkin's disease and non-Hodgkin's lymphoma is organized into four stages in the Ann Arbor method of staging. Disease that is localized to a single lymph node or group is called Stage I. Disease that has more than one lymph node group involved, but is confined to one side of the diaphragm is classified as Stage II. Stage III originates in the lymph nodes or the spleen and occurs on both sides of the diaphragm. Stage IV is diagnosed when the liver or bone marrow is involved.

Patients are also evaluated for presence of specific symptoms of fever in excess of 38.5 C, night sweats requiring a change of clothes, or a 10% weight loss over 6 months. These symptoms are identified as "B" symptoms and suggest bulky disease and a worse prognosis.^{10,12} The B follows the stage number. If these symptoms are absent then the patient is classified as an "A". This patient was staged as IA meaning that she has disease in one group of nodes and she does not have any symptoms of fever, night sweats or weight loss.

Her lactate dehydrogenase (LDH) was elevated which may signify a bulky or rapidly growing tumor. Her alkaline phosphatase was mildly elevated at 132 with 126 the upper limit of normal. Her white blood cell count was 4.1. Other lab work was within normal limits.

TREATMENT

The extent and stage of the disease determine treatment. Radiation is the primary treatment modality for Hodgkin's disease. The radiation is used to kill the cells and chemotherapy is used to shrink the tumor. Patients with early Hodgkin's disease (IA and IIA) may be treated with radiotherapy. Patients with disseminated Hodgkin's (III and IV) disease are usually treated with combination chemotherapy and radiation therapy. Patients with a large mediastinal mass are usually treated with both chemotherapy and radiation therapy regardless of the stage.¹¹ The recommended treatment plan for this patient was six cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) to be followed by four weeks of radiation therapy to the mantle and upper 2/3 of the abdomen. The patient will receive ABVD on day one and day fifteen for six cycles.

According to Freedman and Nadler, 85 percent of patients with Hodgkin's disease can be cured with appropriate treatment. Freedman and Nadler discuss a chemotherapy regimen that utilizes a combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) that produces complete remission in 85 to 90 percent of patients. This treatment is associated with significant toxicity including increased risk of infection, sterility, and an increased risk of developing acute leukemia four to six years following treatment. 2, 6 One research study compared the use of MOPP to ABVD individually, using combination therapy, and alternating therapy in an effort to determine which chemotherapy is the best. 12 This trial reported that combination MOPP/ABVD or ABVD alone was more successful than MOPP alone in obtaining complete remission and failure-free survival on patients with a poor prognosis. In low risk patients ABVD and MOPP were equally effective. ABVD had the advantages of an antitumor effect, less acute and chronic myelotoxicity than MOPP but reported severe pulmonary toxicity of 6 percent.¹² ABVD has also been reported to spare fertility although this was not of concern with this patient.¹²

This patient is a divorced female who is responsible for the care of three children. She needs to work to support her family and to continue medical insurance coverage. She requested to receive ABVD/radiation treatment in her hometown by a local oncologist so that she could care for her children and continue to work. The physician will send orders to her oncologist for ABVD chemotherapy and radiation treatment. Re-evaluation of her treatment plan will be done after completing two cycles of chemotherapy. She will have a porta-cath placed for chemotherapy however this treatment can be given peripherally.

SHORT TERM TOXICITY

Short-term toxic side effects of MOPP and ABVD chemotherapy include neutropenia, thrombocytopenia, anemia, infection, peripheral neuropathy, alopecia, nausea and vomiting, and pulmonary toxicity.¹²

During treatment with chemotherapy her lab work will need to be monitored closely by a physician or nurse practitioner. Neutrophils fall to dangerous levels around 13 days after the last dose of chemotherapy.¹² After day 14 the neutrophils start to recover and slowly come up. Many patients are given neupogen to increase the production of neutrophils. Patients are instructed to always be within one hour of an emergency room during the days that their blood counts are dangerously

low. They are also instructed to come to the hospital immediately for a temperature of 101.3F. Patients on chemotherapy are also prone to low platelets, low potassium and magnesium levels that may need to be monitored several times a week depending on the patient's response to the treatment. This lab work can be monitored by a nurse practitioner and toxic effects treated as needed. This patient is young, attractive and concerned about her appearance. One of her primary concerns is hair loss from chemotherapy. She was reassured that her hair will grow back. New hair growth begins approximately four weeks following the last dose of chemotherapy.¹⁵ Hair may take up to a year to return to its former condition.¹⁵ Chemotherapy and radiotherapy are associated with herpes zoster, impaired antibody response to vaccination, gonadal dysfunction, psychosocial problems such as discrimination in employment and in obtaining insurance. ⁷ Many patients are unable to continue working due to the side effects of the disease and the side effects of the treatment. This patient is a schoolteacher. She will be finished with both courses of chemotherapy by the time school is out for the summer. She will have time to recover from her chemotherapy and radiation treatments prior to going back to school in the fall.

Side effects of mantle radiation include xerostomia which can accelerate dental caries, altered taste perception, laryngeal mucositis, fatigue, anorexia, nausea, emesis, weight loss, and mild erythema of skin that progresses to hyperpigmentation and dry desquamation. ⁵

LONG TERM EFFECTS

The literature shows overall chance for long term survival has a wide range from 47% to 90% dependent on multiple factors including age, subtype of disease, stage of disease, and type of treatment. ^{5,6,7,14} If the patient does not show progress after two courses of chemotherapy, the treatment plan will be changed. If she is not cured or if she has a relapse there are other treatments such as high-dose chemotherapy and autologous or allogeneic hematopoietic stem-cell rescue. The patient could potentially require treatment over a period of several years. The long-term implications of this disease are determined by the method of treatment. Treating this disease can create several other health problems. Cardiotoxicity is a serious long-term effect caused by the use of cardiotoxic chemotherapeutic agents and radiation therapy. The incidence of cardiotoxicity is higher with the use of anthracyclines such as Doxorubicin (Adriamycin) and can develop within 1 – 20 years after treatment.¹⁶ Myocardial cell damage due to the cumulative

dose of Doxorubicin can cause long term irreversible effects on the contractility of the heart. The risk of congestive heart failure is low until a cumulative dose of 550 mg/m² of Adriamycin is obtained. However, congestive heart failure has been observed in people who have only received 40-mg/m² total dose.¹⁶ Radiation treatment to the heart or areas adjacent to the heart can also increase the risk of cardiotoxicity, accelerate coronary artery disease and increase the risk of fatal myocardial infarctions. ^{4,5,17} Other radiation induced heart disease syndromes include acute pericarditis with or without tamponade, pericardial effusion with or without tamponade, pericardial constriction, valve defects and conduction abnormalities. ¹⁸

Other long-term effects are pulmonary fibrosis from bleomycin and radiation, hypothyroidism, myelopathy, dental caries, pericarditis, Ihermitte's phenomenon, and brachial plexopathy from radiation. ⁵ Peripheral neuropathy is a common neurotoxic effect of vinblastine.¹⁹ Secondary malignancies such as acute myeloid leukemia and diffuse high-grade lymphoma from radiation may develop after treatment for Hodgkin's disease. ^{7,20,21} Solid tumor occurrence is higher in the survivors of Hodgkin's disease than in the general population. ²¹ She could be cured from the Hodgkin's disease only to develop a more serious malignancy from the treatment. Yearly comprehensive physical examinations are recommended after cancer treatment completion in order to detect secondary malignancies promptly.

CONCLUSION

Practitioners frequently encounter patients with non-specific symptoms of lymphadenopathy and fatigue. This case presentation reinforces the importance of a thorough history and physical examination along with scheduled follow-up visits of patients who have lymphadenopathy. Consideration of a lymph node biopsy and oncology consultation following a trial of antibiotics may be necessary in patients who do not respond to the antibiotics.

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