CASE REPORT
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Bilateral axillary lymphadenopathy: differential diagnosis and management

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ABSTRACT

Lymphonodopathy is an increase in volume and/or changes in the characteristics of lymph nodes, and it can be caused by benign or malignant diseases. Appropriate physical examination should define their clinical characteristics, and, if needed, complementary imaging or anatomopathological tests should be performed for diagnostic definition. In the present article, we report the case of a female patient, with sarcoidosis, who presented axillary lymph node disease, and the exams that followed until the diagnostic conclusion.

KEYWORDS: sarcoidosis; lymphadenopathy; lymph nodes; breast diseases; tuberculosis, lymph node.

INTRODUCTION

Axillary lymphadenopathy is characterized by an increase in volume or changes in lymph node morphology.[1] It can be detected with palpation on physical examination or alteration in imaging tests. Normal lymph nodes on a mammogram (MMG) are usually oval or reniform and have a radiolucent center, representing hilar fat. On ultrasound (US) imaging, the cortex is usually hypoechoic or even imperceptible, and the medulla is hyperechoic. Once compromised, either by benign or malignant diseases, the lymph node changes its shape and structure, showing different patterns in imaging tests.[2,3]

The most common causes of axillary lymphadenopathies are: carcinomas; lymphomas; benign reactive hyperplasia; non-granulomatous infections, such as those caused by the human immunodeficiency virus, syphilis, and hepatitis; granulomatous diseases, infectious or not, such as: sarcoidosis, toxoplasmosis, tuberculosis, atypical mycobacterioses, cat-scratch disease; and autoimmune or rheumatological diseases, such as lupus, rheumatoid arthritis, scleroderma, among others.[3-5]

The objective of the present study was to report a case of a patient attended at the Mastology outpatient clinic of Santa Casa in Belo Horizonte City, Minas Gerais State, who presented with bilateral axillary lymphadenopathy and had a final diagnosis of a rare disease, sarcoidosis. In the discussion, we present the main causes of axillary lymphadenopathy, the bases for its investigation, as well as histological aspects and clinical information on the most frequent differential diagnoses.

CASE REPORT

This is a case report of a patient attended at the Medical Specialties Center of Santa Casa de Belo Horizonte (SCBH). A bibliographic review was carried out on the PubMed database using the descriptors "axilla", "lymphadenopathy", "granulomatous lymphadenitis", "breast sarcoidosis", "sarcoidosis" and "occult breast cancer". The articles were sorted by the abstract and those with information on the epidemiology of axillary lymphadenopathy, description of its causative diseases, diagnostic methods, treatment, and differential diagnosis were selected for full reading. Articles that were not written in English were excluded. Reference books on breast diseases were also used.

The case in question is a female patient, 51 years old, who was being followed at the Mastology Service of SCBH after excision of a complex fibroadenoma in her left breast in 2016. In May 2019, she was referred by the Pneumology Service of Hospital Júlia Kubitschek (HJK), Minas Gerais State, for the evaluation of axillary lymphadenopathy, which had developed about six months earlier. There were no changes in the physical examination of her breasts. Upon examination of the underarms, enlarged but mobile and fibroelastic lymph nodes were palpable.

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Follow-up at the Pneumology Service began in 2017 due to a mediastinal mass, which was biopsied with mediastinoscopy, and histology confirmed the diagnosis of sarcoidosis. The patient denied other comorbidities and, when inquired about family history, she reported a sister diagnosed with breast cancer at 40 yearsold.

Given that the patient had started the investigation at HJK, she came to the Mastology Service of SCBH with a breast US performed on April 25, 2019 (Figure 1), in which enlarged lymph nodes were seen in both underarms, with cortical thickening and displacement of the fatty hilum to the periphery (thus, the nodes were considered atypical). The largest one measured 42.7 × 20.8 × 21.8 millimeters (mm) on the left axilla and 41.9 × 13.8 × 25.2 mm on the right axilla. No solid or cystic nodules were identified in the breasts, and the test was classified as category 4 by the lexicon of the Breast Imaging Reporting and Data System (BI-RADS).[6] A MMG was performed on May 30, 2019 (Figure 2), in which the breasts were classified as heterogeneously dense; no breast lesions were identified, but the presence of bilateral axillary nodules with increased size and density were found — category 0, according to the BI-RADS classification.[6]

The patient was referred with a report of negative serologies for infectious diseases and, considering her personal history of sarcoidosis, the most likely etiological hypothesis for axillary lymphadenopathy was this benign disease. Magnetic resonance

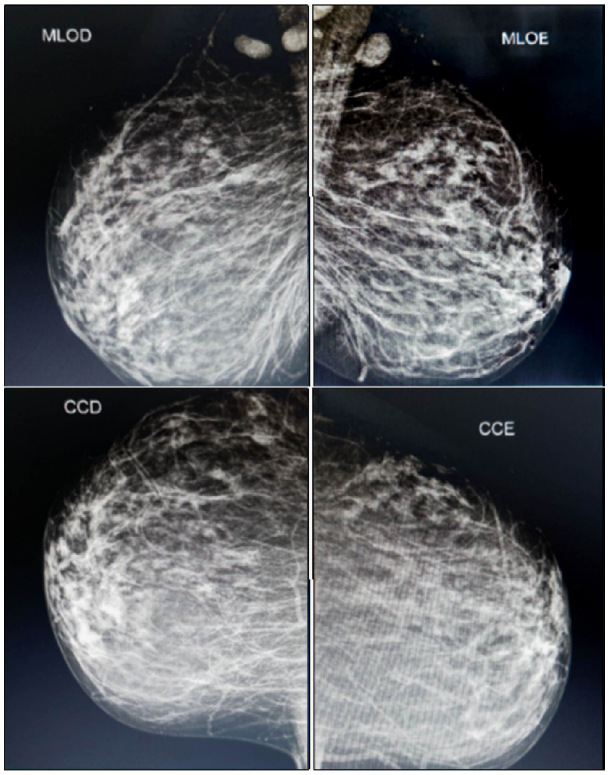


Figure 2. Mammogram from May 30th, 2019. Left and right oblique mediolateral view. Heterogeneously dense breasts. Bilateral axillary nodules with increased size and density. Category 0 (BI-RADS).

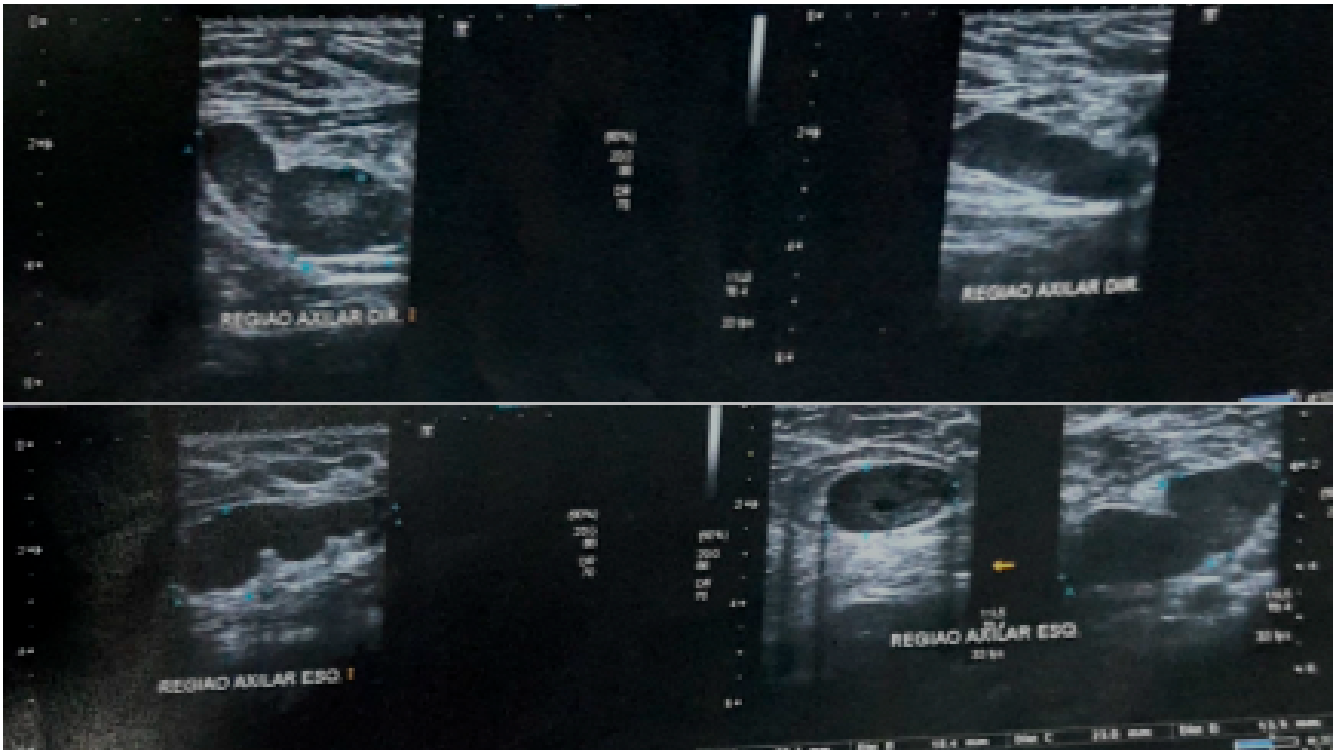


Figure 1. Right (upper) and left (lower) axillary ultrasound performed on April 25, 2019. Lymph nodes increased in size are seen bilaterally, with thickening of the cortex and displacement of the fatty hilum to the periphery. Category 4 (BI-RADS).

imaging (MRI) of the breasts could have been requested to assess the presence of occult breast carcinoma, especially in the context of a patient with increased risk (positive family history), but due to the difficulty of accessing this exam in the Brazilian Unified Health System (*Sistema Único de Saúde* – SUS), it was not requested. The decision was made to obtain a histological sample of the nodes with a bilateral core biopsy (fragment biopsy with a thick needle) guided by ultrasound imaging. In September 2019, the patient returned with a histological result compatible with granulomatous lymphadenitis on her left and right axillas. In the clinical context, this result corroborated the diagnosis of sarcoidosis affecting peripheral lymph nodes and allowed the medical team to safely rule out an overlapping malignancy.

The patient was then referred back to the Pneumology Service, and currently does not undergo any treatment since she is oligosymptomatic.

Table 1. Causes of axillary lymphadenopathy.

Benign reactive hyperplasias
Carcinomas
Lymphomas
Infectious granulomatous diseases
Toxoplasmosis
Tuberculosis
Cat-scratch disease
Non-infectious granulomatous disease
Sarcoidosis
Non-granulomatous infectious diseases
Human immunodeficiency virus (HIV)
Syphilis
Autoimmune
Rheumatological
Lupus
Rheumatoid arthritis
Scleroderma
Others

DISCUSSION

Causes of axillary lymphadenopathy

When facing axillary lymphadenopathy, several causes must be considered as differential diagnoses. In a retrospective study by the University of Southern California, evaluating 925 patients who underwent lymph node biopsies from 1973 to 1977, 60% of the lymph nodes had benign lesions, 28% had carcinomas, and 12% had lymphomas. For peripheral nodal biopsies (cervical, axillary, inguinal) 56% were related to benign lesions; 29% to carcinomas; and 15% to lymphomas. Considering only the axillary lymph nodes, 60% had benign hyperplastic, granulomatous, or adenitis. Twenty-three percent had lymphoma as a cause, and carcinomas were responsible for 18% of the cases. Statistically, age is the most important factor in estimating the likelihood of whether lymphadenopathy is due to a benign or malignant process – the older the age, the greater the risk of malignancy.[1]

In a retrospective study at the Medical School of Ribeirão Preto City, São Paulo State (Brazil), 54% of axillary tumors were of malignant origin, including lymphoma, breast carcinoma, or contralateral breast carcinoma metastasis, as well as other sites such as thyroid, ovaries, and stomach. The remaining 45% were secondary to benign inflammatory, reactive causes, or even ectopic breast tissue and lipoma.[7]

The most common causes of axillary lymphadenopathies are described in Table 1. They are: carcinomas; lymphomas; benign reactive hyperplasias; non-infectious granulomatous diseases, such as sarcoidosis; granulomatous infectious diseases, such as toxoplasmosis, tuberculosis, and cat-scratch disease; non-granulomatous infectious diseases such as the human immunodeficiency virus (HIV) and syphilis; and autoimmune or rheumatological conditions, such as lupus, rheumatoid arthritis, scleroderma; among others.[4,3] Treatment will vary according to the cause, and may involve surgery, antibiotic therapy, chemotherapy, or even clinical observation.[8]

Investigation

When a patient presents with lymphadenopathy a good anamnesis should be done in order to identify associated symptoms, signs of systemic or localized disease, and epidemiological information that may suggest its etiology. Age is also an important factor, as the chance of malignancy increases in patients over 40 years of age.[9]

On physical examination, the consistency of lymph nodes and whether they are matted to each other or to deep planes should be assessed. Palpating other lymph node chains to define if the involvement is localized or generalized (affecting two or more non-contiguous lymph node chains) is also important. Recent travels, contact with animals, as well as the presence of symptoms of autoimmune diseases should be evaluated.[1,10]

Complete blood count, serologies, chest X-rays, and other specific tests must be requested according to each suspected diagnosis. In axillary lymphadenopathy specifically, MMG and US of breasts and axillae must be used to study the breasts, in addition to assessing the lymph nodes.[8]

With MMG, lymph nodes can be seen in the mediolateral oblique incidence (MLO) and, when normal, they are typically small, oval, kidney-shaped or lobulated, with a radiolucent center representing the hilar fat. Although there is no consensus on the size, in general, those up to 2 cm are considered normal. Round, high-density lymph nodes, with no hilar fat, irregular, ill-defined or spiculated margins, and the presence of calcifications are considered abnormal.[2,11,12] Some lymph nodes can be "pushed" out of the image field

during compression in the MLO view, allowing only partial viewing. The axillary tangential view allows the assessment of underarm abnormalities which are not well characterized in standard views.[2,13]

Axillary US is the best imaging method to assess lymph nodes, with a sensitivity of 56 to 72%, and specificity of 70 to 90% for malignancy. At US, normal lymph nodes are elliptical, with a thin or even imperceptible hypoechogenic cortex and an echogenic hilum. This method also allows the assessment of vascularization, which usually has a hilar pattern. When affected by diseases, these characteristics can be lost, and the lymph nodes tend to become more rounded, with thickening of the cortex greater than 3.0 mm, decreased fatty hilum or even absence of it. A peripheral and transcapsular flow seen on Doppler favors the suspicion of malignancy.[2,3,13,14]

Pathology

In cases in which the clinical history associated with complementary exams is not able to define the etiology, the altered lymph nodes must be sampled for safe diagnosis with fine needle aspiration (FNA) or core biopsy. A meta-analysis by Houssami et al. reported a sensitivity of 72.2 and 83.3%, respectively, for FNA and core biopsy, to detect malignancy. This difference was not statistically significant in agreement with the findings of a prospective study that compared the effectiveness of both methods, guided by ultrasound.[15]

Technically, FNA is easier to perform and has a lower cost, but it is essential to obtain a representative quantity of non-bloody aspirate , in order to allow for an adequate interpretation of cytology, which must be performed by an experienced cytopathologist. FNA is adequate to diagnose reactive hyperplasia, granulomatous lymphadenopathies, and the presence of carcinoma metastases.[16] One of the most important limitations of FNA is the high false negative rate for Hodgkin's lymphoma (HL). Besides that, it does not allow for a differentiation of the subtypes of non-Hodgkin lymphomas (NHL).[17]

Cytology with histiocyte aggregates, which may or may not contain multinucleated giant cells, favors the diagnosis of granuloma. The presence of a necrotic background suggests caseous granuloma and, possibly, tuberculosis or other mycobacterioses. Cytological findings should be associated with clinical history and other diagnostic tests, for example, culture for mycobacteria on suspicion of tuberculosis, IgG and IgM serology on suspicion of toxoplasmosis, and chest X-rays to search for signs compatible with sarcoidosis or tuberculosis.[17]

Core biopsy provides a greater amount of material, allowing histological study. It should be preferred if the nodule is well visualized and easily accessible.[15,16] In case of suspected lymphoma, core-biopsy can be performed, but ideally, complete excision of the lymph node allows for adequate assessment, diagnosis, and classification of the disease.[18]

Histologically, *Mycobacterium TB* produces specific chronic granulomatous inflammation with giant Langerhans cells, caseous necrosis and calcifications. Satellite microabscesses surrounding the central necrosis area can be seen in cat-scratch disease. Non-necrotizing epithelioid granulomas with multinucleated giant cells are a characteristic feature of sarcoidosis.[17]

Reed-Sternberg cells present in a background of polymorphonuclear inflammatory cells are characteristically observed in HL.[17] In NHL, morphology and the lymph node architecture are important to define the disease's subtype, thus justifying its complete excision. Immunohistochemistry also plays a fundamental role in the subclassification of the various forms of NHL, which occurs according to their derivation from B or T lymphocytes, or natural killer cells.[19]

Sarcoidosis

Sarcoidosis is a rare systemic granulomatous disease of obscure etiology. Most often, it affects lungs and intrathoracic lymph nodes, but it can affect any body organ, including peripheral lymph nodes. In 80% of cases, it affects adults between 20 and 50 years of age, and in up to 10% of cases there is a positive family history of the disease.[14]

The diagnosis of sarcoidosis should be suspected in middle-aged adults, with unexplained cough, dyspnea, and systemic symptoms. Nonspecific symptoms, such as fever, myalgia, and arthralgia may be associated. Extrapulmonary manifestations are most often found in the spleen (splenomegaly), in the eyes (uveitis, vascular changes in the retina, nodules in the conjunctiva, enlargement of the lacrimal gland), in the skin (papules, nodules, plaques, erythema nodosum), and in the peripheral lymph nodes (most often cervical and supraclavicular). Approximately 50% of patients are asymptomatic. The acute appearance of erythema nodosum, associated with bilateral hilar lymphadenopathy, fever, polyarthritis, and uveitis, is called Löfgren syndrome, and is typical of sarcoidosis.[20-22]

The diagnosis of sarcoidosis comprises three criteria:

- compatible clinical and radiological presentation;
- pathological evidence of non-necrotizing granulomas;
- exclusion of other diseases with similar presentation.[14]

Chest radiography is the basic exam to stage the disease, and computed tomography should be reserved for suspected cases of complications, such as pulmonary fibrosis, bronchiectasis, infection, or malignancy.[20-22]

Spontaneous remission can occur in up to two thirds of cases, and is more common in the first years of the disease. Another 10 to 30% of patients evolve to a chronic and progressive course, which can be characterized by cough, exertional dyspnea, arthralgia, night sweats, weight loss, and fatigue.[20,21]

Corticosteroid therapy should be indicated for more advanced, progressive disease, or those cases with an important extrapulmonary manifestation, for a minimum course of 12 months. Recurrence after interrupting treatment is not uncommon and occurs more frequently from two to six months after discontinuation of the drug, being rare after three years of corticosteroid suspension. Other agents such as methotrexate and azathioprine can be used.[14,21]

In some cases of severe and progressive disease, lung transplantation may be indicated.[21] In our review, no indication for surgical excision of the affected lymph nodes was found.

Tuberculous lymphadenitis

Tuberculous lymphadenitis is one of the forms of extrapulmonary manifestation of tuberculosis, with a peak between 30 and 40 years of age, affecting more women than men, in a 1.4:1 ratio.

Patients have a history of lymph node enlargement in a single chain, usually cervical, with an evolution of one to two months. Systemic symptoms are more common when concomitant infection with the HIV is present.[23]

Some diagnostic tests can be useful to raise the suspicion of tuberculous lymphadenitis such as the tuberculin skin test (TST), and the interferon-gamma release (IGRA) tests. In Brazil, the available IGRA test is QuantiFERON®-TB, which quantifies, with an immuno-enzymatic assay (ELISA), the levels of interferon-gamma released by memory T cells after stimulation of the whole blood with specific antigens of *M. tuberculosis*.[23-25]

The TST's specificity is 97%. False positive reactions can occur in individuals infected with other mycobacteria or vaccinated with BCG *(Bacillus Calmette–Guérin)*, especially if vaccinated or revaccinated after the first year of life. TST's sensitivity is 77%, and false negative results can occur if poorly conserved tuberculin is used, if the patient has an altered immune response, in the presence of other acute viral, bacterial or fungal infections, among other causes.[23,24]

The disadvantages of TST are the need for direct application to the patient, it requires a second visit to read the result, it is examiner dependent, and, mainly, the number of false positives due to previous BCG.[24]

Since IGRA tests are unaffected by previous BCG administration or infection by non-tuberculous mycobacteria (with rare exceptions), they have high specificity and sensitivity, up to 98 and 86%, respectively. Other advantages of this test are that it is carried out on a blood sample, reducing adverse effects, the need for only one visit, and inexistence of biased reading.[23,24]

The definitive diagnosis occurs after a cytological sample by FNA or with histology with alcohol-acid resistant staining containing chronic granuloma with giant Langerhans cells, caseous necrosis and calcifications, associated with the culture or polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*. Chest radiography may be altered in 20 to 40% of cases.[23,26]

Treatment is the same used for pulmonary tuberculosis – rifampicin, isoniazid, ethambutol, and pyrazinamide for two months, followed by four months of rifampicin and isoniazid – although the response is slower. There may be persistent pain and an increase in the volume of lymph nodes while using the medications (which is called a paradoxical reaction), and surgical excision can be considered in case of severe discomfort.[27]

Occult breast carcinoma

Occult breast carcinoma is a rare form of breast cancer, responsible for roughly 1% of all cases, and constitutes a diagnostic and therapeutic challenge. It is defined when there is histological confirmation of involvement of axillary lymph nodes due to carcinoma of mammary origin in the absence of clinical and radiological evidence of disease in the breast.[5,28,29]

Lymphadenopathy is most commonly unilateral. MMG and US should be requested in the investigation and, in case of negative findings in the breast, MRI offers additional data, with a sensitivity between 36 and 86% to detect lesions. When there are no MRI findings, we are facing a truly occult carcinoma.[30,31]

According to the most recent National Comprehensive Cancer Network (NCCN) guidelines for surgical treatment, modified radical mastectomy or axillary lymph node dissection with breast irradiation can be performed. Indications for chemotherapy, hormone therapy, and target therapy should follow the indications for non-occult tumors. In cases of T0 N2-3 M0 disease, neoadjuvant therapy may be performed, followed by surgical treatment.[28]

With the analysis of our patient's case, we found that the imaging exams did not show any breast lesion. Histology provided a safe diagnosis, with the exclusion of metastasis or primary neoplasia in axillary lymph nodes, making it possible to refer the patient to the Pneumology service. She will continue to perform breast cancer screening as indicated for her age and personal risk.

CONCLUSION

In the presentation of axillary lymphadenopathy, several differential diagnoses must be considered, including benign and malignant diseases. Each of them has a specific treatment, which can be surgical, with medications or even consist of observation, just like in this case. The prevalence of benign causes is greater than that of malignant causes, and the diagnosis is based on clinical history and physical examination, associated with adequate exams and histological sampling, when necessary. In view of the increased incidence of cancer

over the years in our country, the percentage of lymph nodes with malignant involvement may increase.[31]

In the present case report, lymphadenopathy was caused by a rare benign condition of unknown etiology — sarcoidosis. The patient is oligosymptomatic, undergoing outpatient follow-up at the HJK Pneumology Service, and she also undergoes clinical examination and screening for breast cancer at the Mastology Service of Santa Casa de Belo Horizonte.

AUTHORS' CONTRIBUTIONS

P.C.: Conceptualization, investigation, methodology, formal analysis, validation, writing – original draft, writing – review & editing.

C.V.: Conceptualization, supervision, validation, writing – original draft, writing – review & editing.

D.B.: Validation, supervision, writing – review & editing.

D.P.: Project administration, supervision, writing – review & editing.

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