CASE REPORT
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ANAPLASTIC LYMPHOMA MIMICKING BREAST CARCINOMA

Linfoma anaplásico mimetizando carcinoma mamário

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ABSTRACT

This case describes an uncommon presentation of ALK-negative anaplastic large T-cell lymphoma with breast infiltration, mimicking triple-negative carcinoma. The incidence of ALK-negative anaplastic large T-cell lymphoma usually occurs in adults in their fifth and sixth decade of life and can affect lymph nodes and extranodal sites, including skin, soft tissue, and gastrointestinal tract. The non-Hodgkin's lymphoma of the breast is uncommon, accounting for 0.04 to 0.05% of all malignant breast tumors. Diagnosis of ALK-negative anaplastic large T-cell lymphoma is challenging both to physicians and pathologists. Based on the complete medical history, clinical and imaging exams and histopathological evaluation of the lesion site biopsy, it is possible to establish an adequate diagnosis. The case describes a woman aged 37 years with palpable nodules in the left breast as well as erythematous lesions on the right leg. The analysis of the breast nodules biopsy shows that they mimic triple-negative carcinoma. However, only with immunohistochemical examination was it possible to verify the expression of the CD30 antigen, and only after a complete systemic evaluation, the diagnosis of ALK-negative anaplastic large T-cell lymphoma was performed. Misdiagnosis can lead to inadequate therapy and result in disease progression or unnecessary damages to the patient.

KEYWORDS: Lymphoma, non-Hodgkin; lymphoma, large-cell, anaplastic ; breast neoplasms; T-cell lymphoma.

RESUMO

Este caso descreve uma incomum apresentação de linfoma anaplásico de grandes células T ALK negativo com infiltrado mamário, mimetizando carcinoma triplo negativo. A incidência do linfoma anaplásico de grandes células T ALK negativo, ocorre comumente em adultos na quinta e sexta década de vida e pode acometer linfonodos e locais extranodais, incluindo pele, tecido mole e trato gastrointestinal. O linfoma não-Hodgkin da mama é incomum, compondo 0,04 a 0,05% de todos os tumores de mama malignos. O diagnóstico de linfoma anaplásico de grandes células T ALK negativo é desafiador tanto para clínicos como para patologistas. O estabelecimento de um diagnóstico adequado é possível com base em histórico médico completo, exames clínicos e de imagem e avaliação histopatológica da biópsia do local da lesão. O caso relata uma mulher de 37 anos com nódulos palpáveis na mama esquerda em conjunto com lesões eritematosas na perna direita. Ao se analisar a biópsia dos nódulos da mama, esses mimetizavam carcinoma triplo negativo, no entanto, somente com exame imunohistoquímico foi possível verificar a expressão do antígeno CD30, e, apenas após uma avaliação sistêmica completa, foi realizado o diagnóstico de linfoma anaplásico de grandes células T ALK negativo. O diagnóstico equivocado pode acarretar terapia inadequada e resultar em progressão da doença ou em danos desnecessários ao paciente.

PALAVRAS-CHAVE: Linfoma não Hodgkin; linfoma anaplásico de células grandes; neoplasia da mama; linfoma de células T.

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INTRODUCTION

The ALK-negative anaplastic large T-cell lymphoma (ALCL) represents a non-Hodgkin lymphoma with expression of the CD30 antigen. Stein and his collaborators were the first ones to recognize a subtype of tumors with large cells exhibiting anomalous morphological features with prominent sinusoidal invasion and expressing the CD30 antigen (formerly known as Ki-1).[1]

Due to the lack of strict morphological criteria, some tumors were diagnosed as Ki-1 lymphomas only for constituting antigen CD30-positive large cells, regardless of the presentation of their cell phenotype (B, T or null).[1] Subsequently, the term Ki-1 lymphoma was substituted for anaplastic large cell lymphoma.

Although there has not been a clear consensus among pathologists concerning the definition of anaplastic, and even though some of these tumors consisted of small and medium cells, the term anaplastic large cell lymphoma was incorporated into most classifications. Afterward, it was found that a significant proportion of ALCL is associated with translocation t (2; 5) (p23; q35).[1] The cloning of this translocation and the production of antibodies, detecting the gene product — anaplastic lymphoma kinase (ALK) — meant great advance. Hence, ALCLs were divided into two main categories: those positive to ALK protein and those that lack these markers.[1]

In the third edition of the World Health Organization (WHO) classification of hematopoietic neoplasia, ALK-positive (ALK+) and -negative (ALK-) ALCL were considered a unique entity and defined as lymphomas consisting of lymphoid cells, which usually are large, have abundant and pleomorphic cytoplasm and whose nuclei, very often, are horseshoe-shaped.[1] The cells present CD30 antigen and, in most of the cases, proteins are associated with cytotoxic granules and epithelial membrane antigen (EMA).[1] Even though ALCL expressing ALK are relatively homogeneous, it became evident that cases with similar morphology and phenotypes, but without ALK expression, are much more heterogeneous. ALK- ALCL also differ from peripheral T-cell lymphomas.

In the fourth edition of the WHO classification, ALK+ ALCL was determined as a distinct entity, while ALK- ALCL, as provisory.[1] However, in 2016, the WHO updated the classification of lymphoid neoplasms, and, therefore, ALK- ALCL was determined as a defined rather than provisory entity, since it presents specific cytogenetic subsets that seem to have prognostic implications.[2] In this same update, the breast implant-associated anaplastic large T-cell lymphoma was classified as a new provisional entity distinguished from ALK- ALCL and determined as a noninvasive disease associated with better prognosis.[2]

The incidence of ALK- ALCL usually occurs in adults in their sixth decade of life and presents worse prognosis than ALK+ ALCL, that affects more often children and young adults.[3] Men are more commonly affected than women at a ratio of 1.5:1.[3] Patients usually present adenopathy and, often, B symptoms (fever, night sweats, and weight loss). ALK- ALCL may affect lymph nodes and extranodal sites, including skin, soft tissues, and gastrointestinal tract.[3]

The neoplasia is featured by large pleomorphic cells, some with prominent nucleoli and multinucleation, that have a variable number of characteristic cells, horseshoe- or kidney-shaped nuclei, and inconsistently express EMA.[4,5]

Due to morphological variations, the ALK- ALCL may lead to greater diagnostic difficulties — since it mimics other types of lymphoma and can also have a cohesive growth pattern, mimicking nonhematologic malignant neoplasias, like sarcomas, carcinomas, tumors of germ cells and melanoma.[6,7] Thus, clinic history and staging data are essential to determine the initial site of presentation, the extent of extracutaneous involvement, and the order of events in the disease course.[8]

Non-Hodgkin's lymphoma of the breast is uncommon, accounting for 0.04 to 0.5% of all malignant breast tumors.[9] Most primary breast lymphomas are B-cell phenotype or have not been immunophenotyped; only rare cases have been reported as large T-cell lymphoma infiltrating breast tissue.[9]

Therefore, this article aims to report a case of ALK- ALCL — infiltrating breast tissue, mimicking primary breast neoplasia — considering how rare this location is and the difficulties in the diagnostic process. This case report highlights the importance of anatomopathological examination of surgical specimens associated with the patient's clinical data to help in the immunohistochemical and morphological differential diagnosis, leading to specific treatment and avoiding unnecessary procedures.

CASE REPORT

Female patient, 37 years of age, cleaning assistant, obesity level 1, was admitted to the Medical Clinic of *Hospital Regional de Presidente Prudente* in May 2017, presenting for about a month two palpable nodules associated with nipple retraction in the union of the lower quadrants of the left breast and erythematous-violaceous lesions with well-defined contours, varied sizes, hyperchromic and without secretion on the inner side of the right leg. On physical examination, the patient was in a good overall condition, afebrile, anicteric and acyanotic, denied fever or weight loss in recent months, but reported having previously had inguinal ipsilateral lymph node enlargement with spontaneous resolution.

During hospitalization, a complete blood count was performed, as well as imaging examinations and core biopsy (removal of a breast tissue sample with a thick needle). Laboratory tests presented leukogram with no changes, complete blood count with erythrocyte sedimentation rate altered to 33 mm/h (reference range up to 20 mm/h) and increased lactic dehydrogenase, 1,073 U/L (reference range 200 to 480 U/L).

Thorax computed tomography showed enlarged lymph nodes in the axillary chain bilaterally and multiple nodular images were seen in the left breast.

In the anatomopathological examination of the core biopsy, the microscopy, the breast tissue presented areas with infiltration by large cells neoplasia with intense anaplasia and atypical mitotic figures, with cell cohesion, delimited by fibrillar connective tissue proliferation (Figure 1). The neoplastic cells have pleomorphic and hyperchromatic nuclei and prominent nucleoli, with atypical mitotic figures, morphologically favoring the diagnosis of high-grade breast carcinoma (Figures 2 and 3). The initial immunohistochemical profile was negative for estrogen, progesterone, and androgens receptors, as well asfor E-cadherin and lack of overexpression of the HER2 oncogene, mimicking breast carcinoma with a triple-negative molecular classification. However, diagnostic investigation was continued due to the acquisition of clinical and laboratory information about the patient.

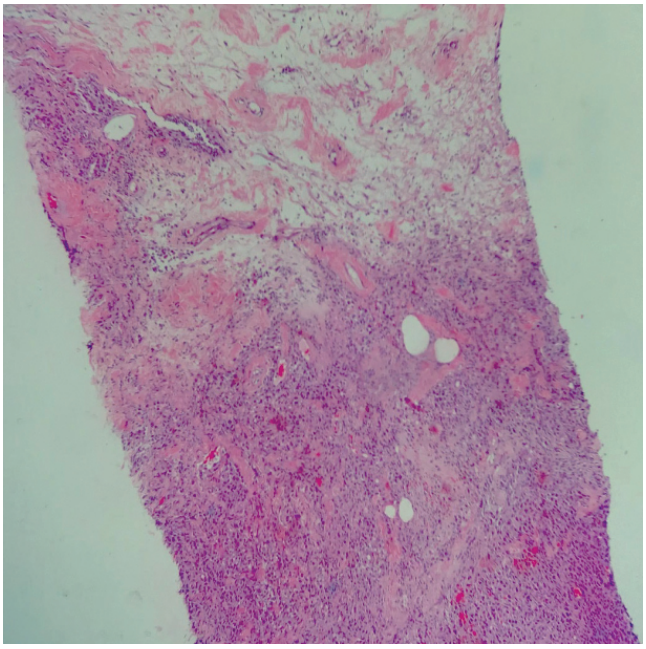

Figure 1. Hematoxylin-Eosin Staining, increase 10x, core biopsy, malignant neoplasia infiltrating breast parenchyma.

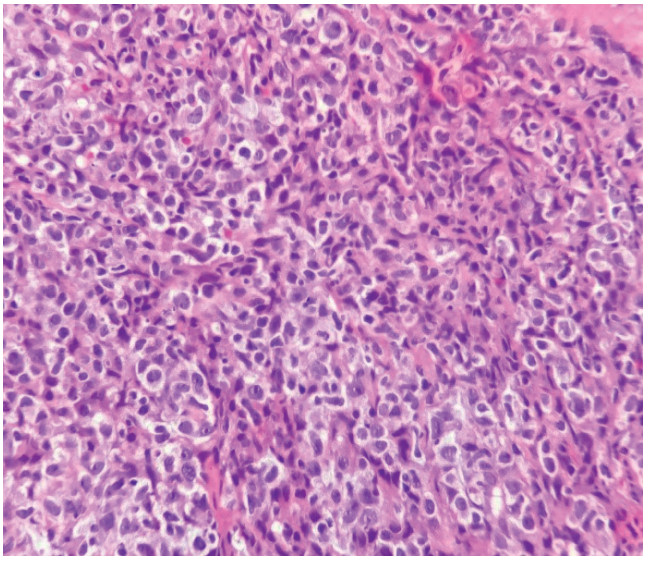

Figure 2. Hematoxylin-Eosin Staining, increase 20x, core biopsy, anaplastic large T-cell lymphoma with presence of pleomorphic cells, sometimes multinucleated, with prominent nucleoli and atypical mitotic figures, making up a solid block of cohesive standards, mimicking carcinoma.

Thus, the immunocytochemical panel was expanded to CD20, CD5, CD45, CD30, and ALK markers, taking into account it is an ALK-negative anaplastic large T-cell lymphoma, due to lack of ALK protein (Figure 4), with expression of antigens CD30 (Figure 5), CD5, CD45 and high rate of cellular proliferation (KI-67). Chart 1 shows the results of the markers used in the immunohistochemical evaluation.

The therapy instituted consisted of 8 cycles of chemotherapy every 28 days, using the therapeutic scheme called CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone). One month after the first cycle, there was good chemotherapy response with significant regression of the breast tumor and the skin lesions.

DISCUSSION

The non-Hodgkin's lymphoma of the breast is uncommon, accounting for 0.04 to 0.05% of all malignant breast tumors.[9] It comprises 2.2% of extranodal non-Hodgkin's lymphomas and 0.38% of all non-Hodgkin's lymphomas.[10,11] Most primary breast lymphomas are B-cell phenotype or have not been immunophenotyped; only a few cases have been reported as large T-cell lymphoma infiltrating breast tissue.[9]

The vast majority of cases show clonal rearrangement of T-cell gene receptors, whether or not they express T-cell antigens.[1]

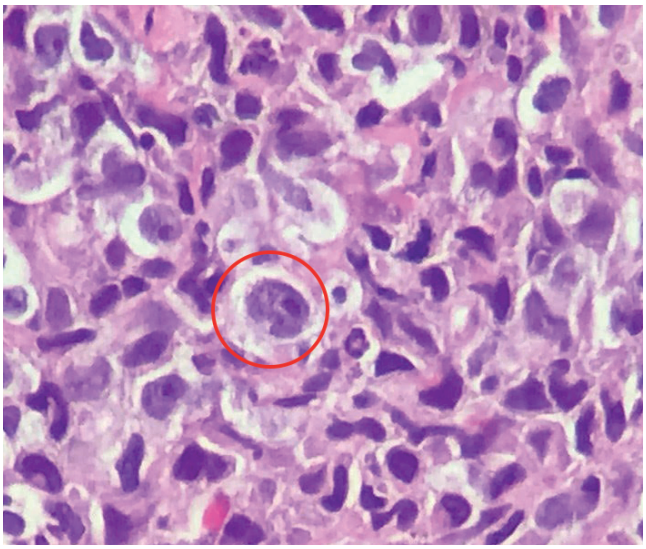

Figure 3. Hematoxylin-Eosin Staining, increase 100x, breast core biopsy, "horseshoe-shaped cell" with bleaching of the Golgi apparatus, characteristic of anaplastic large T-cell lymphoma.

Primary cytogenetic abnormalities do not recur frequently. Studies indicate a tendency of ALK- ALCL to differ (concerning chromosome gain or loss) from peripheral T-cell lymphoma and ALK+ ALCL.[1]

Recently, specific chromosomal rearrangements to ALK- ALCL, Dual Specificity Phosphatase 22 (DUSP22) and Tumor Protein P63 (TP63), unique and mutually exclusive, have been identified, which is important to further prognosis stratification.[12] Studies have shown that the chromosomal rearrangement of the DUSP22 has a five-year overall survival rate of 90%.[12] On the other hand, TP63 rearrangements show worse prognosis with a five-year overall survival of 15% and poor response to the initial treatment.[12] At the moment, the pathogenesis of these rearrangements is unknown and remains under investigation.[8]

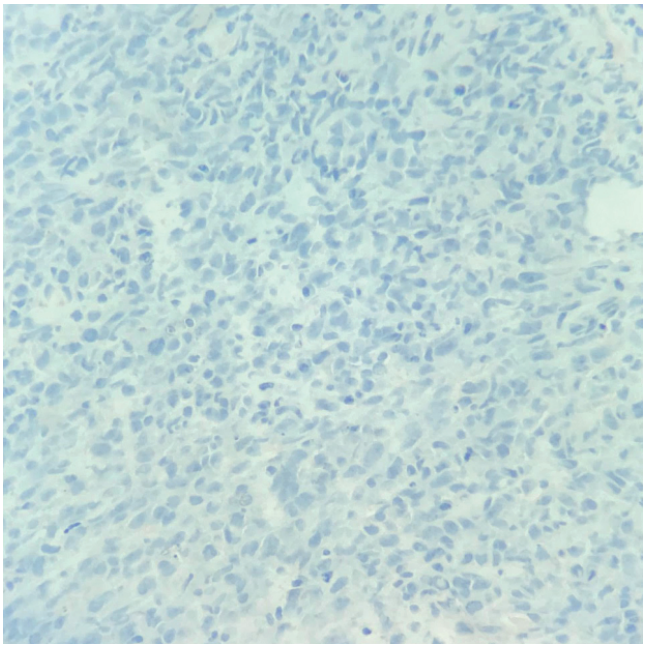

Figure 4. Immunohistochemical marker to ALK/p80, lack of immunoexpression in tumor cells.

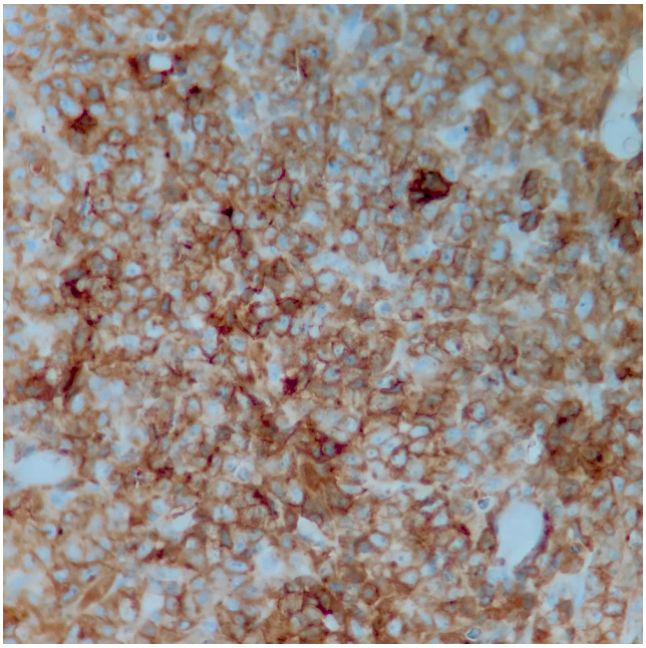

Figure 5. Immunohistochemical marker to CD30, showing diffuse positivity and homogeneous expression of this marker in tumor cells.

This article reported a case of a 37-year-old woman with ALK- ALCL. According to literature, this type of lymphoma affects more men than women, at a ratio of 1.5-:1.[3] Regarding age range, it mainly affects adults from 40 to 65 years of age.[1]

Clinical manifestations of this type of cancer are heterogeneous. Many patients have systemic B symptoms (fever, night sweats, and weight loss), present high score on the International Prognostic Index, and aggressive clinical course.[13,14] However, a subset of patients has a less aggressive course because of the type of chromosomal rearrangement presented.[12]

Patients may have peripheral or abdominal lymphadenopathy, or extranodal tumor.[1] The most frequent ALK- ALCL extranodal involvement is seen in the cutaneous, hepatic, and gastrointestinal tract areas. In the study by Savage et al.,[3] from 55 patients with ALK- ALCL diagnosis, only one presented extranodal involvement in the breast. In the case reported here, there were palpable nodules in the left breast, leading to local skin retraction. The description of this type of presentation in this neoplasia is uncommon. However, the patient also presented multiple erythematous-violaceous lesions of well-defined contours, different sizes, hyperchromic and without secretion, located on the inner side of the right leg. These lesions, presented by the reported patient, match the literary description of the lymphoma under discussion. In this case, that helped in the performance of the immunohistochemical examinations of the percutaneous breast biopsy.

Chart 1. Immunohistochemical evaluation.

CerbB-2 Oncoprotein (Her-2 Sp3)	Negative (score 0)
EstrogenReceptor (SP1)	Negative
ProgesteroneReceptor (SP2)	Negative
E-cadherin (36)	Negative
Androgen Receptor (SP107)	Negative
ALK/p80	Negative
CD20 (L26)	Negative
Ki-67 (MAb SP6)	High rate of cellular proliferation
CD5 (LEU-1)	Positive
CD30 (Ber-H2)	Positive
CD45 (T29/33)	Positive
GATA3 (L50-823)	Positive

Otherwise, the diagnosis could easily be misleading, since, histologically, the breast specimen analyzed alone is similar to the triple-negative carcinoma. As well as in the immunohistochemical assessment, the absence of expression of estrogen (ER) and progesterone receptors (PR), and HER2 usually characterizes a triple-negative breast cancer, responsible for 10 to 15% of invasive breast cancers, more often affecting patients under 50 years of age, presenting an aggressive type of tumor and decrease survival when compared to other subtypes.[15] Only other chemical markers like CD30 were assessed, depending on the case association — since the biopsies of both the left breast core and the right leg skin lesions were sent separately and without clinical correlation to the pathology department.

An review article reported that most patients with ALK- ALCL received CHOP treatment or similar, like the patient reported in this case. Specific therapies for this subtype have not yet been introduced, but the CD30-targeted therapies have proven to be effective.[8]

The International T-Cell Lymphoma Project revealed that patients with AKL- ALCL have an overall five-year survival of 49%.[16] Other chemotherapy combinations did not produce better outcomes when compared to CHOP. The ALK- ALCL neoplasia usually present lower response rates to the initial treatment, with a chance of 45% to 65% of recurrence with the first-line treatment.[3] In a prospective study, the initial treatment with CHOP produced a complete response in 39% of patients with ALK- ALCL.[17]

CONCLUSION

The diagnosis of ALK- ALCL is challenging for both physicians and pathologists, given the histopathological spectrum of findings. This case reported an unusual presentation of this pathology with appearance in breast tumor. Although rare, the breast may be a incidence area of this neoplasia. The adequate diagnosis, in this case, was possible because of the association of clinical data with immunological complementary exams, from the breast nodule sample as well as the biopsy of the skin lesion. Accurate diagnosis avoids inadequate therapies and unnecessary procedures to an ALK- ALCL.

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