

Breast Infiltration of Acute Lymphoblastic Leukemia: Case Report and Review of the Literature

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ABSTRACT

Infiltration of the breast by acute leukemia is extremely rare. It is known that the relapse of acute lymphoblastic leukemia outside blood and hematopoietic tissue usually occurs in the central nervous system and testicles. Relapses have been reported in other sites following transplantation and, when this occurs, the prognosis is poor. However, a relationship has been observed between young pregnant women and acute lymphoblastic leukemia relapse in the breast as a characteristic site. Extramedullary relapses are more common in acute myelogenous leukemia, and this is why we are presenting this case report. **Case report:** A female patient of 22 years of age with B phenotype acute lymphoblastic leukemia diagnosed in September 2009, received an induction chemotherapy regimen based on prednisone, vincristine and daunorubicin from 2009 to 2012. A complete hematologic response was acquired. In March 2013 a bone marrow relapse was documented. At that time she was 16 weeks pregnant. She received an alternative regimen of Larson (Cancer and Leukemia Group B); (Induction with: cyclophosphamide, daunorubicin, vincristine, prednisone, and asparaginase. Early intensification: methotrexate, cyclophosphamide, mercaptopurine, cytarabine, vincristine, asparaginase. Central nervous system prophylaxis: with methotrexate. Late intensification: doxorubicin, vincristine, dexamethasone, cyclophosphamide, biguanide, cytarabine. Maintenance: vincristine, prednisone, methotrexate, mercaptopurine). At 26 weeks of pregnancy she received treatment with two cycles of cytarabine 75 mg/m²/day for four days and central nervous system prophylaxis with cytarabine 40 mg and dexamethasone 8 mg as re-induction

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regimen. The pregnancy was interrupted at 36 weeks, resulting in a male child weighing 2,985 g, APGAR score 8/9, without apparent complications. The patient later attended the consultancy with neurological disorders and a nodule in the upper external quadrant of the left breast that was painful on palpation and so a diagnosis protocol was initiated. **Conclusions:** An association is observed between pregnancy, breastfeeding, and the acute lymphoblastic leukemia infiltration into the mammary gland. The association and the genetic molecular profile should be described. (J CANCEROL. 2015;2:117-22)

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INTRODUCTION

Breast tumors have been described since 1878¹. However, metastasis to the breast by extra-mammary malignancies is unusual and initially described in 1903². Retraction of the nipple may be absent, but affection of the axillary lymph nodes is common. When discovered, lesions to the breast are usually solitary masses in 85% of cases and located in the upper external quadrant in 66% of cases. The metastases are usually multiple and bilateral, but are characteristically large solitary tumors^{1,2}.

Affection of the breast by hematological malignancies is quite uncommon. It can be found in non-Hodgkin's lymphoma, acute myeloid leukemia, and rarely as multiple myeloma (and when this occurs it is related to a plasmacytoma). However, infiltration of the breast by acute lymphoblastic leukemia (ALL) is very rare. It was first reported by Williams in 1912. It is more commonly observed in women with ALL and relapse posterior to a bone marrow transplant³.

CASE REPORT

Female patient of 22 years of age, diagnosed with B phenotype ALL in September 2009, classified as standard risk, received treatment with prednisone, vincristine, daunorubicin, and central nervous system (CNS) prophylaxis with methotrexate, cytarabine and hydrocortisone, resulting in complete remission

and completing maintenance. In March 2013 the patient was 16 weeks pregnant (WoP) and began to show signs of an anemic syndrome and so she was put on a treatment regimen alternative to Larson. Ten weeks later (with 26 WoP) she was referred to a third level hospital for evaluation. On arrival, a bone marrow aspiration revealed a count of < 5% lymphoid blasts and so she initiated chemotherapy with cytarabine as well as CNS prophylaxis. On 27 July 2013 her pregnancy terminated with the birth of a child at 36.6 weeks of gestation, weighing 2,985 g, APGAR score 8/9.

After birth the patient had a bilateral tubal occlusion. On 12 August 2013 a bone marrow aspiration revealed infiltration of lymphoid blasts, CD34: 58%, HLA-DR: 64%, Dtt: 65%, CD10: 75%, CD19: 69, CD20: 63, CD22: 74%. A second relapse is documented and management is initiated with R-Hyper CVAD 1A (cyclophosphamide, vincristine, doxorubicin, dexamethasone).

Progress and treatment

She received chemotherapy with R-Hyper CVAD 1A on 24 August 2013 with recovery aspiration without infiltration. On 26 September 2013 a phase 1B of R Hyper CVAD was indicated, but the patient did not attend. On 17 November 2013 she attended the emergency room for headache of one week of evolution, clinical palpebral ptosis of the right eye, anisocoria with palpebral opening of the right eye pupil of 4 mm with very little response to light,

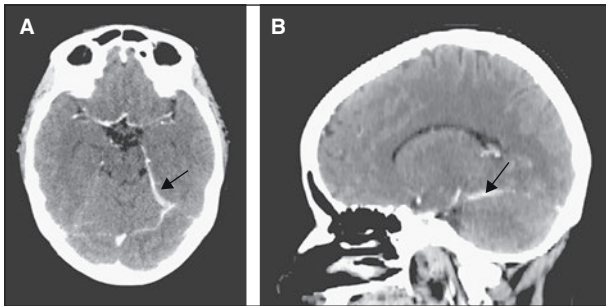


Figure 1. A and B show abnormal reinforcement of the tentorium cerebelli, predominantly the left side, due to probable infiltration of the central nervous system, and confirmed by computerized axial tomography.

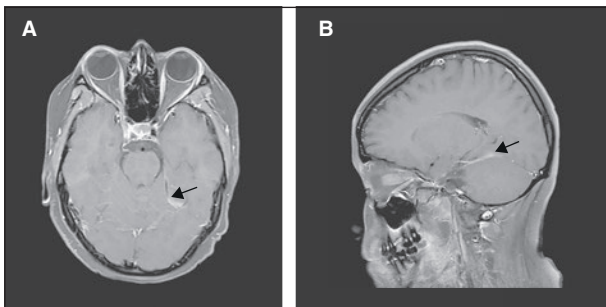


Figure 2. These magnetic resonance images, A and B, show the meningeal highlight of the lesion by increasing the signal strength in accordance with the contrast at a level of the tentorium cerebelli, this suggesting infiltration of this level as a first possibility.

limitation of abduction and infraduction, discrete weakness of the right side of the face without Bell's phenomenon; she managed good mobilization of the frontalis, nasalis and orbicularis muscles of the eyelids but not the lips (reacted to increased pressure), strength 5/5, REM+, cerebellum normal. At this time it was 85 days since the last chemotherapy session. A simple and contrasted cranial computed tomography (CT) scan, diagnostic lumbar puncture, and new bone marrow aspiration/biopsy/immunophenotype were requested. The CT scan revealed abnormal reinforcement of the tentorium cerebelli, predominantly the left side, due to probable infiltration at this level, this reinforcement being confirmed by magnetic resonance imaging (MRI) (Fig. 1 and 2) The lumbar puncture was negative for cytology and cytochemistry, the cerebrospinal fluid culture was also negative; nevertheless, in

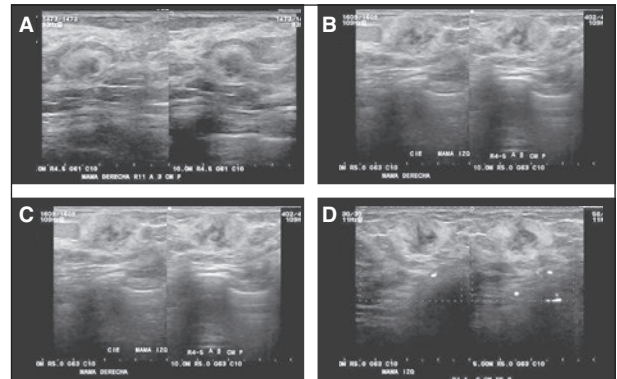


Figure 3. The breast ultrasound shows that in R11 right at 4 cm from the nipple there is a solid heterogeneous echogenic lesion with poorly defined margins of 14.0 × 27.0 × 13.5 mm. No other focal lesions are identified in the right breast.

view of the CT and MRI findings it was decided to initiate intrathecal chemotherapy with cytarabine 40 mg, dexamethasone 8 mg, and methotrexate 12.5 mg twice a week.

There was a relapse as shown by bone marrow aspiration infiltrated by ALL 10% blasts, flow cytometry with CD34 55.6%, CD10 63.9%. The patient presented nodular lesions of the left breast of two days evolution. Ultrasonography reported two predominantly echogenic heterogeneous lesions located at the junction of the glandular and pre-glandular fatty tissue with one lesion located in R3/4, 5 cm from the nipple (Fig. 3 and 4). Mammography reported bilateral, heterogeneous echogenic lesions (Fig. 5 and 6).

An aspiration biopsy of the breast was performed. The histopathological study reported leukemia/lymphoblastic lymphoma immunophenotype B: CD10+, CD79a+, PAX5+, TdT+, CD3-, CD99-. An extension of the same procedure was performed with Wright' stain and lymphoblasts were observed (Fig. 7-9)

The diagnosis was leukemia/lymphoblastic lymphoma B with systemic relapse, infiltration of the CNS and breast. Phase IB of Hyper CVAD chemotherapy with a delay of 88 days for economic reasons. She was discharged on completion of the chemotherapy, with complete reversion of the

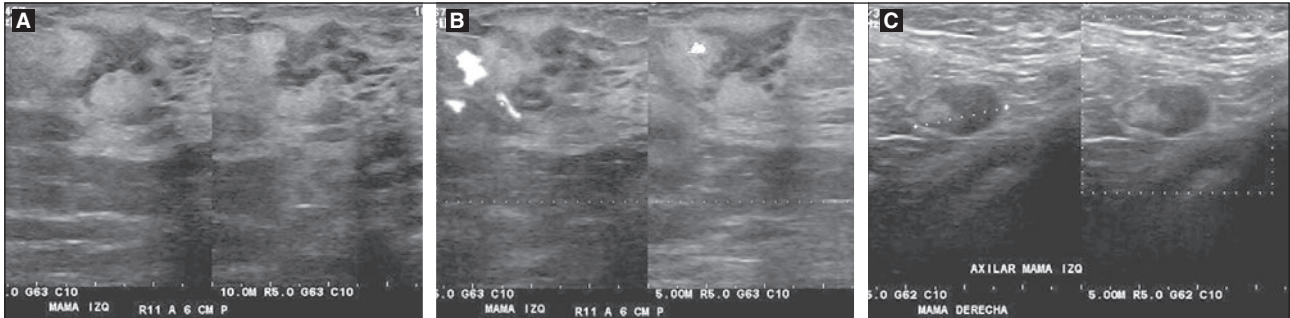


Figure 4. The image of the left breast shows a nodule with an echogenic center, suggestive of a ganglion of 15 mm in R2-3 at 12 cm from the nipple. In R4-5 at 8 cm from the nipple there is an ovoid lesion with predominantly heterogeneous echogenicity, echogenic interior, and with poorly defined maximum margins of approximately $22.9 \times 12.8 \times 22.0$ mm. Another lesion of similar characteristics and larger size is observed in R11 at 6 cm from the nipple, with peripheral vascularity. The retroareolar regions show no disorders. There are bilateral axillary ganglions showing cortical eccentric and concentric thickening.

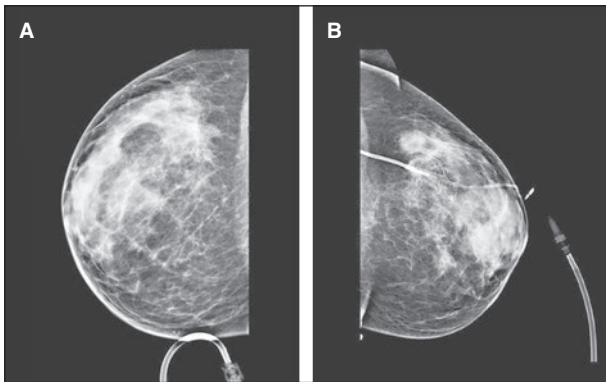


Figure 5. Digital mammography: predominantly heterogeneous dense fibroglandular breast parenchyma is distributed in the four quadrants, mainly the upper, external quadrants. An ovoid isodense nodule with poorly defined margins without associated findings can be seen in the posterior third interline of the left external quadrants.

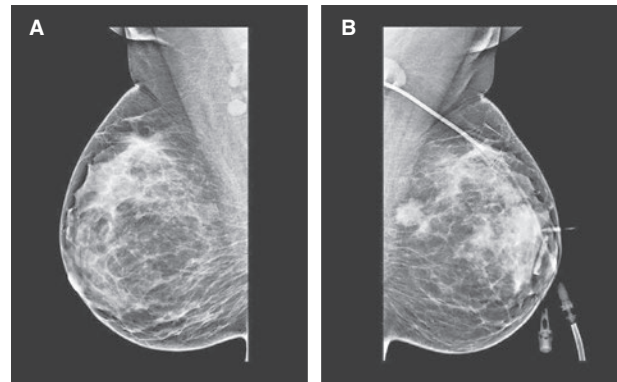


Figure 6. Digital mammography: presence of isolated left calcification of benign characteristics. There are dense bilateral axillary ganglions with loss of the radiolucent center. Breast Imaging Reporting and Data System (BIRADS) 4.

neurological symptoms. On day 9 another breast ultrasonography was performed and no longer revealed the nodular lesions observed previously. Disease free period of two months as the patient was lost and did not continue chemotherapy due to lack of resources, 14 January 2014, a new relapse is documented.

Discussion

The extramedullary manifestations of the acute leukemia include chloromas, leukemia cutis, meningeal leukemia, and infiltration of the gums. The translocation

(8; 21) and CD56 are the primary risk factors, usually expressed in acute myeloid leukemia.

However, in ALL the extramedullary infiltration sites are usually the CNS, testicles, liver, and spleen. Infiltration of the breast by ALL is very rare^{4,5}.

Clinically, affection of the breast is usually bilateral and massive, and the cells may be confused with neuroblastomas or rhabdomyosarcoma. Breast lesions in adults should always be subjected to differential diagnosis: granulocytic sarcoma, endocrine carcinoma, bullous carcinoma, and small cell lymphoma⁶.

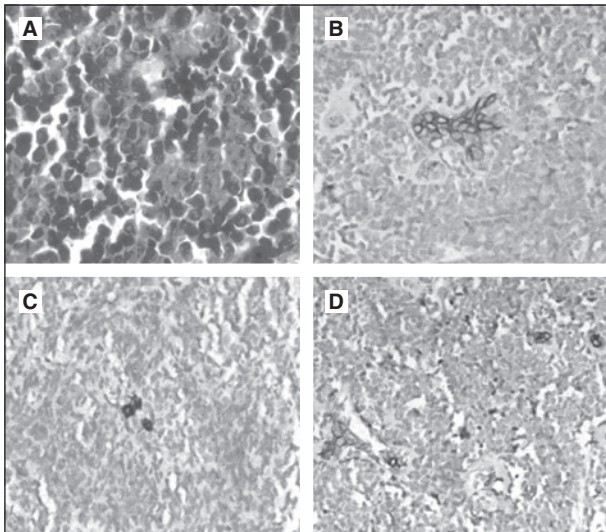


Figure 7. Showing a hematoxylin and eosin (A) slice. Immunohistochemical studies identified very few normal breast conducts, the rest correspond to the malignancy. Mammaglobin (B), CK7 (C) and GCDFP-15 (D). There is a hematoxylin and eosin (A) slice. In addition, immunohistochemical studies for mammaglobin (B), CK7 (C) and GCDFP-15 (D) were performed and proved positive in normal breast parenchyma, trapped by the malignancy, which is negative for these markers.

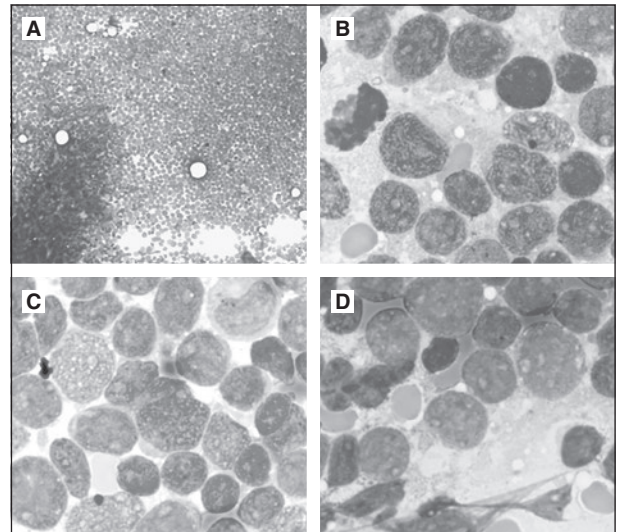


Figure 8. Fine needle aspiration biopsy of the breast lesion with Wright's stain in A showing the infiltration pattern. B, C and D are a magnified view showing the atypical lymphoid blasts.

Relapses in ovaries, kidney, eyes, muscle, and bones have been reported. In the majority of the cases of relapse in the breast, the cases presented were in advanced stages. However, in general terms, this group of patients has a worse prognosis, not because of the relapse site, but because of the relapse itself. Young adolescent women have a

greater risk of affectation of the breast and so they should undergo regular revisions during follow-up as they may present a lesion before relapse to the bone marrow⁷⁻⁹. It has been observed that patients who have undergone radiotherapy for breast cancer may be affected by acute leukemia in the breast tissue.

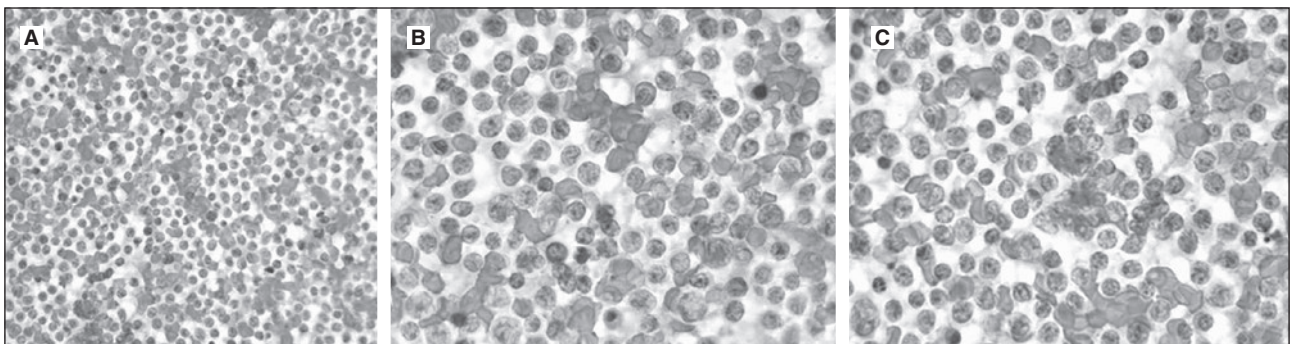


Figure 9. Once again, the Papanicolaou stain reveals the infiltration pattern in A and a magnified view, B and C, reveals abundant small to medium size neoplastic lymphocytes, chromatin in thick lumps limited to the periphery, some with evident nucleolus and others with sunken nucleolus. No breast epithelium is identified among this material.

Breast affectation by leukemia or lymphoma represents 0.25% of all breast tumors. Patients with non-Hodgkin's lymphoma in the breast have better prognosis compared to adults with ALL in the breast. Treatment includes systemic chemotherapy, radiotherapy and surgery had no role in the treatment³.

The effectiveness of chemotherapy is complete response as this is a systemic disease and should be treated as such. Radiotherapy is not very indicated as this disease is, by definition, systemic.

A high incidence of infiltration of CNS has been observed in acute myeloid leukemia (AML), and the skin by ALL. Extramedullary disease is usually resistant to treatment.

In 1952 Gelin described infiltration of the breast in a pregnant woman, observing a relationship between the hormones and the malignancy. A gynecological pattern and infiltration of the CNS have also been observed. Having a recent pregnancy is considered a factor for poor prognosis of response to treatment

for leukemia, especially ALL⁶. (It is thought that the hormonal stimulus influences infiltration at this level, the case of infiltration of ALL outside the CNS or testicles being considered rather uncommon).

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