

CASE REPORT

Occult breast cancer: Case report and literature revision



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KEYWORDS

Occult breast cancer;
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Abstract Occult breast cancer is a rare presentation of breast cancer (<1%), as an isolated axillary lymphadenopathy. It represents a diagnostic challenge, gradually improved by technological innovations. The difficulty in deciding therapeutic conduct lays in the paucity of prospective studies and thereby of consensus. We present a brief review of the literature, concerning the case report of a 56-year-old woman diagnosed with this type of cancer at our center, after presenting with an axillary nodule. No relevant abnormality in the breast or other organs was found. Immunohistochemical and imaging diagnosis are assessed as well as treatment, which consisted of homolateral axillary lymph node resection, followed by chemotherapy, radiation therapy and hormone therapy.

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PALABRAS CLAVE

Cáncer oculto mama;
Adenopatía

Cáncer oculto de mama: Presentación de un caso clínico y revisión de la literatura

Resumen El cáncer oculto de mama es una forma inusual de cáncer de mama (menos del 1%) y se presenta como una linfadenopatía axilar aislada. El diagnóstico supone un desafío, que gracias a las innovaciones tecnológicas está mejorando gradualmente. La dificultad en decidir la conducta terapéutica se debe a la escasez de estudios prospectivos y, por lo tanto, de consenso. Presentamos una breve revisión de la literatura, con relación al informe del caso de una mujer de 56 años, diagnosticada con este tipo de cáncer en nuestro centro, después de presentar

Abbreviations: ALND, axillary lymph node dissection; CEA, carcinoembryonic antigen; CK7, cytokeratin 7; CK20, cytokeratin 20; CT, computed tomography; ER, estrogen receptor; GCDP15, gross cystic disease fluid protein 15; HepPar1, hepatocyte specific antigen; HER2, epidermal growth factor receptor 2; HT, hormone therapy; IHC, immunohistochemical results; MRI, magnetic resonance imaging; OBC, occult breast cancer; PrR, progesterone receptors; RCC, renal cell carcinoma antigen; TFF1, trefoil factor 1; WBRT, whole breast radiation therapy.

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un nódulo axilar. No se encontraron anomalías relevantes en la mama ni en otros órganos. Se evalúa el diagnóstico inmunohistoquímico y por imagen, así como el tratamiento que consistió en una resección homolateral de los ganglios linfáticos axilares, seguido de quimioterapia, radioterapia y terapia hormonal.

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Introduction

Occult breast cancer (OBC) is a subgroup of cancer of unknown primary site. It is characterized by an axillary metastasis, pathologically resembling from a breast cancer, with no abnormality on clinical nor diagnostic work-up.^{1,2} It accounts for less than 1% of all diagnosed breast cancers^{2–7} and its initial presentation as an isolated axillary lymphadenopathy is a clinical challenge.⁸ Treatment lacks consensus and tends to progressively become more conservative.

Clinical case

A 56-year-old women was admitted to our institution in January 2017 to clarify an asymptomatic right axillary lump. She was postmenopausal (2014), and besides having chronic hypertension, was otherwise healthy. Previous surgeries included 3 cesarean sections, tubal ligation and spine intervention; she presented no smoking habits or alcohol consumption; she denied previous intake of oral contraceptives or hormone replacement therapy, and had no relevant family history.

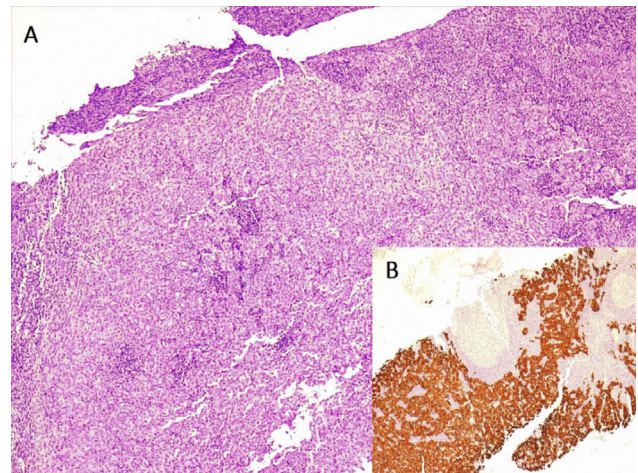


Figure 2 Biopsy specimen, collected by needle biopsy of the right axillary adenopathy with large polygonar cells in H&E staining (A). Inset (B) illustrates CK7 positive staining.

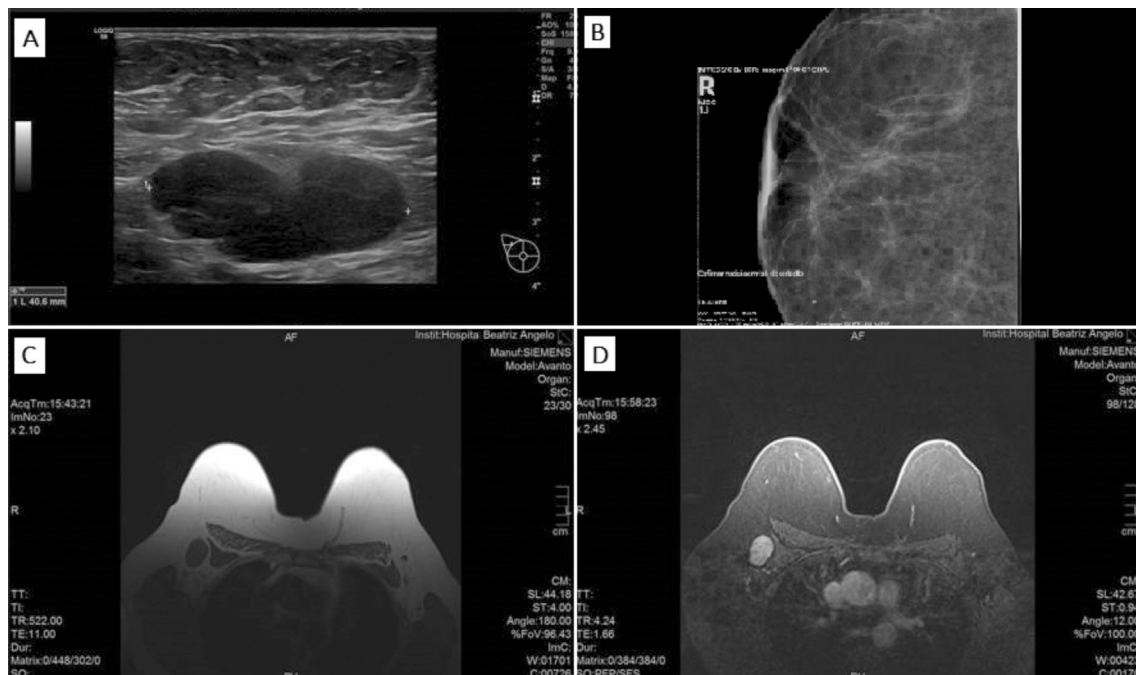


Figure 1 Radiologic work-up: axillary node on ultrasound, before puncture (A), mammogram of the right breast (B), breast MRI with T1 (C) and T1 – fat saturation (D) techniques.

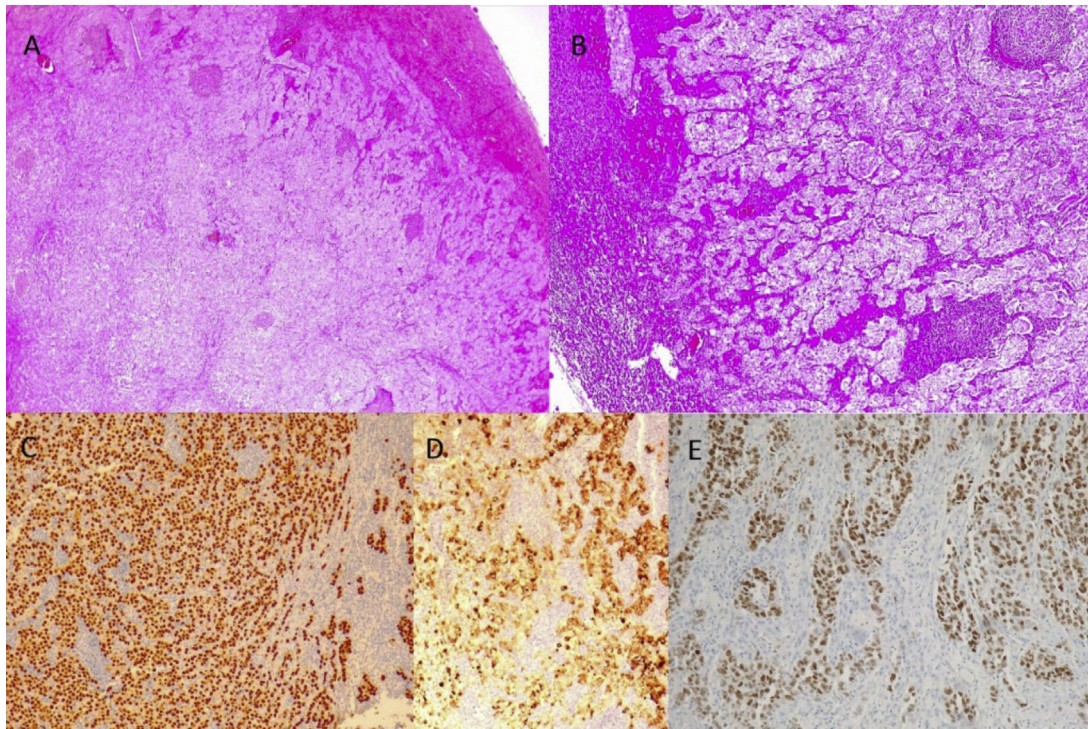


Figure 3 Paraffin sections from the lymph node with metastasis, stained with H&E in A ($\times 2$) and B ($\times 5$). IHC results included RE(+) (C), GCDFP15(+) (D) and TTF1(–) (E).

On physical examination, a right, hard, mobile, painless 3 cm nodule was identified in the right axilla. No lumps in the left axilla, breasts or supraclavicular areas bilaterally were identified.

A bilateral mammogram (Fig. 1B) and a breast ultrasound were recently done in an imaging center outside the hospital, that were normal. Images were reviewed and a needle biopsy was performed (Fig. 1A). Pathological examination revealed a right axillary metastasis (Fig. 2). Immunohistochemical (IHC) results were: ER(+), CK7(+), CK20(–), RCC(–), GCDFP15(+), HER2(–), TTF1(–). Primitive breast cancer was the suspected etiology. She had recently done a colonoscopy and underwent breast MRI (Fig. 1C and D), whole body CT and bone scintigram – no other lesions were found.

The patient was diagnosed with OBC and underwent right Axillary Lymph Node Resection (ALND). Pathological examination showed 1/9 dissected lymph nodes with metastasis, ER 90%, PrR 30%, remaining IHC results confirmed (Fig. 3). The tumor-node-metastasis classification was TON1a(1/9)M0, stage IIA.

Surgery was followed by chemotherapy with anthracyclines and taxanes, whole breast radiation therapy (WBRT) and HT with letrozole.

She has now 3 years of surveillance since surgery, maintains letrozole and mammography every year. No recurrence or distant metastasis was observed so far.

Discussion

A cancer of unknown primary site accounts for 4–5% of all invasive cancers.⁹ Despite generally having a poor prognosis,^{3,10} improvements have been made in treating

some subgroups, namely OBC.¹⁰ Its peak incidence is 55 years old.¹¹

Due to its low prevalence, studies tend to include diagnosis made throughout broad periods of time, when technological limitations hampered the identification of small breast carcinomas with a falsely increased diagnosis of OBC.¹² Its incidence may be decreasing with more sensitive techniques, namely MRI.¹¹

An isolated axillary lymphadenopathy relates more often to benign disorders.³ However, in women, when malignant, breast is the most common primary tumor site.³

IHC staining is an extremely useful tool for diagnosing the primary site but usually a broad panel is needed. Breast cancer usually expresses CK7 but does not express CK20, and rarely TTF1.³ ER and PrR supported the diagnosis of an occult breast primary.³ However, staining negatively would not exclude breast cancer^{2,4}; in fact, hormonosensitivity is lower than in non-occult breast cancer.⁷ HER2 is generally not useful for differential diagnosis but may help in treatment decision.³ GCDFP15 is breast cancer specific in 65–80% of the cases³ and supports the diagnosis of OBC in our case.

During imagiologic work-up, a breast MRI is essential. It is able to detect a primary breast cancer up to 75–86% of women who present with axillary adenocarcinoma and a negative clinical examination and mammogram $\pm$ ultrasound.^{1,3,7,12,13} Despite having a high false positive rate,³ MRI is now considered standard approach for evaluation of breasts in OBC patients.^{11,14}

Other exams are less consensual: bone scan may be reserved for symptomatic women or those with elevated alkaline phosphatase³ and PET scanning is not indicated in stage II disease but may be helpful where standard staging studies are suspicious/equivocal.¹⁴

There is no clear consensus about optimal management – studies are usually small and retrospective^{3,12} and bigger ones comprise long period of data accrual with inevitable changes in clinical practice.^{12,15}

Standard approach used to be a modified radical mastectomy, likely driven by the high percentage of patients whose primary tumor was found upon histological analysis.^{6–8} Nevertheless, rates have been decreasing.^{11,12}

Mastectomy showed lower rate of local recurrence and superior disease free and overall survival than no local therapy.^{4,6} However, surgery became more conservative^{12,13} as studies demonstrated that mastectomy did not improve survival outcomes, locoregional recurrence or distant metastasis⁵ compared to breast conservative surgery (BCS). An upper-outer quadrantectomy (it was believed to represent the most likely primary site location¹⁵) and ALND (Sohn et al.⁸ showed no difference in overall survival between performing ALND alone, plus BCS or plus mastectomy) were described.

Radiotherapy also gained an important role in the treatment of OBC.^{1,2,4} ALND plus WBRT showed favorable locoregional recurrence,^{1,8,12} distant metastasis,^{8,12} survival⁴ and breast cancer-specific survival^{1,8,12} rates compared to ALND alone. Recent NCCN guidelines recommend either mastectomy plus ALND or ALND plus WBRT, with or without nodal irradiation for TON1MO disease.¹⁴

Regarding adjuvant systemic therapy, NCCN recommends systemic chemotherapy, endocrine therapy and biologic therapy (anti-HER2 monoclonal antibody) according to the same indications as for stage II and III disease.^{2,6,8,14}

Based on the diagnostic and stage work-up, we believe this to be an OBC case. ALND plus WBRT, chemotherapy and HT were performed but anti-HER2 monoclonal antibody was not suitable considering IHC profile.

OBC has a five-year survival rate averaging 75%³ and axillary lymph node status (number of positive nodes) was pointed as the most important prognostic factor.¹² With one positive node, we believe this patient has a good prognosis.

Despite obvious need for prospective randomized controlled trials, they will unlikely be performed,¹² as low incidence makes it challenging.⁶ With time, probably there will be more homogeneous and larger retrospective studies with diagnosis of true OBC based on negative MRI.¹¹

Meanwhile, other approaches may be established – some studies defend the use of neoadjuvant systemic therapy, sentinel lymph node biopsy⁷ or systemic and axillary treatment, with no need for mastectomy or WBRT¹¹ (Terada et al.¹¹ suggested that some cases may be a primary tumor arising from ectopic breast tissue in axillary lymph nodes).

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Confidentiality of data

The authors declare that they have followed the protocols of their center on the publication of patient data.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- Masinghe SP, Faluyi OO, Kerr GR, Kunkler IH. Breast radiotherapy for occult breast cancer with axillary nodal metastases – does it reduce the local recurrence rate and increase overall survival? *Clin Oncol*. 2011;23:95–100, <http://dx.doi.org/10.1016/j.clon.2010.10.001>.
- Wang X, Fan L, Yan W, Zhang Q, Bao S, Wang Y, et al. Axillary lymph node metastasis as the first manifestation of male occult breast cancer: a case report. *Medicine (Baltimore)*. 2018;97, <http://dx.doi.org/10.1097/MD.00000000000013706>, 50(e13706).
- Kaklamani V, Gradishar WJ. Axillary node metastases with occult primary breast cancer; 2019. <http://www.uptodate.com> [accessed 20.12.19].
- Wang X, Zhao Y, Cao X. Clinical benefits of mastectomy on treatment of occult breast carcinoma presenting axillary metastases. *Breast J*. 2010;16:32–7, <http://dx.doi.org/10.1111/j.1524-4741.2009.00848.x>.
- Ge L, Liu XY, Xiao Y, Gou ZC, Zhao S, Jiang YZ, et al. Clinicopathological characteristics and treatment outcomes of occult breast cancer: a SEER population-based study. *Cancer Manag Res*. 2018;10:4381–91, <http://dx.doi.org/10.2147/CMAR.S169019>.
- Hessler LK, Molitoris JK, Rosenblatt PY, Bellavance EC, Nichols EM, Tkaczuk KHR, et al. Factors influencing management and outcome in patients with occult breast cancer with axillary lymph node involvement: analysis of the national cancer database. *Ann Surg Oncol*. 2017;24:2907–14, <http://dx.doi.org/10.1245/s10434-017-5928-x>.
- McCartan DP, Zabor EC, Morrow M, Van Zee KJ, El-Tamer MB. Oncological outcomes following treatment for MRI occult breast cancer (pT0N+). *Ann Surg Oncol*. 2017;24:3141–7, <http://dx.doi.org/10.1245/s10434-017-5965-5>.
- Sohn G, Son BH, Lee SJ, Kang EY, Jung SH, Cho SH, et al. Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: a nationwide retrospective study. *J Surg Oncol*. 2014;110:270–4, <http://dx.doi.org/10.1002/jso.23644>.
- Hainsworth JD, Greco FA. Overview of the classification and management of cancers of unknown primary site; 2019. <http://www.uptodate.com> [accessed 20.12.19].
- Toss A, Moschetti L, Cascinu S. Occult breast cancer: the uncommon presentation of a common disease. *Chin Clin Oncol*. 2019;8(S1):S10, <http://dx.doi.org/10.21037/cco.2019.01.06>.
- Terada M, Adachi Y, Sawaki M, Hattori M, Yoshimura A, Naomi G, et al. Occult breast cancer may originate from ectopic breast tissue present in axillary lymph nodes. *Breast Cancer Res Treat*. 2018;172:1–7, <http://dx.doi.org/10.1007/s10549-018-4898-4>.
- Macedo FIB, Eid JJ, Flynn J, Jacobs MJ, Mittal VK. Optimal surgical management for occult breast carcinoma: a meta-analysis. *Ann Surg Oncol*. 2016;23:1838–44, <http://dx.doi.org/10.1245/s10434-016-5104-8>.
- Couder F, Schmitt C, Treilleux I, Tredan O, Faure C, Carra-N N, et al. Envahissement ganglionnaire axillaire sans tumeur primitive mammaire retrouvée: à propos de 16 cas issus d'une cohorte de 7770 patients. *Gynécol Obst Fertil*. 2015;43:588–92, <http://dx.doi.org/10.1016/j.gyobfe.2015.06.010>.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – Breast Cancer. Version 1; 2019. <http://www.nccn.org>.
- Wild JB, Thrush S, Vidya R. What can National Registry data tell us about occult breast cancer? *Chin Clin Oncol*. 2019;8(S1):S15, <http://dx.doi.org/10.21037/cco.2019.02.03>.