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Case Report

Invasive Cystic Hypersecretory Ductal Carcinoma of Breast: Challenges in Diagnosis and Management

Noof Alshaibani[a] Janaki Krithika Chandramohan[a] Sara Salah Khairi[a]
Fatima Al-Hashimi[b] Aysha Anwar Aljawder[b]

[a]Department of General Surgery, King Hamad University Hospital, Busaiteen, Kingdom of Bahrain;
[b]Department of Pathology, King Hamad University Hospital, Busaiteen, Kingdom of Bahrain

Keywords
Invasive cystic hypersecretory carcinoma · Cystic hypersecretory hyperplasia · Invasive ductal carcinoma of breast · Cystic breast tumour

Abstract
Cystic hypersecretory lesions of the breast are a spectrum of conditions ranging from cystic hypersecretory hyperplasia with atypia and invasive cystic hypersecretory carcinoma (CHC). It is a subtype of ductal carcinoma of the breast. The tumour is very infrequent and hence, extensive literature is limited. This culminates in the fact that it does not feature as part of the WHO classification of breast tumours. However, a good knowledge about its distinct pathological features can avert misdiagnosis and help differentiate CHC from other conditions. Thus far, only 22 cases of invasive CHC have been reported, of which 3 were microinvasive. Only 7 cases of axillary lymph node metastasis have been documented. We report a case of invasive CHC of the breast that was metastatic to the axilla and refractory to neoadjuvant chemotherapy. Our case report aims to add to the literature on the disease, aiming to support large-scale studies in the future in order to elaborate on its clinical and biological characteristics.

Introduction

Invasive cystic hypersecretory carcinoma (CHC) is a member of the spectrum of cystic hypersecretory lesions of the breast. It is a rare subtype of ductal carcinoma of the breast and is not studied extensively due to the limited number of cases reported and lack of follow-up

Correspondence to:
Noof Alshaibani, noof.alshaibani@khuh.org.bh

data. They are usually low-grade lesions but have a potential for metastasis. These lesions have a characteristic gross appearance of multiple, aggregated cysts filled with a gelatinous colloid-like material. Microscopically, the cysts are lined by pseudostratified epithelium with papillaroid folds or tufts [1]. Invasion is portended by the lining epithelium becoming poorly differentiated, losing the secretory property, and forming nests or nodules [2]. Herein, we report a case of invasive CHC with axillary metastasis. The clinical course of this patient and the tumour's insensitivity to chemotherapy served as hints for the final diagnosis and led us to review the literature on this disease. With the advent of chemoimmunotherapy and newer immune checkpoint inhibitors and antibody drug conjugates showing promising results for triple-negative breast cancers, more studies are warranted to evaluate their usefulness in this particular subgroup of patients [3, 4]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533441).

Case Presentation

This 37-year-old female presented in December 2021 with complaints of right breast lump for several months that was increasing in size, alongside pain. On examination, she had a huge cystic mass occupying the entire right breast with no palpable axillary nodes. The contralateral breast and axilla were normal. On ultrasound, there was a 11 × 10 × 8 cm cystic mass over her central and upper outer quadrant with nodular wall thickening, and it was abutting the chest wall muscles. CT thorax and MRI breast confirmed the ultrasound findings and revealed suspicious chest wall involvement on the posterior medial aspect. They also showed bilateral enlarged sub pectoral and axillary nodes.

Aspiration of the cyst and examination of the aspirate revealed the presence of mixed inflammatory cells and macrophages with a few clusters of malignant cells. Core biopsy of the mass was performed, and it showed grade 3 invasive ductal carcinoma with a triple-negative hormone receptor status (oestrogen receptors, progesterone receptors, and HER-2 neu receptors) and a tumour proliferation index of 60–70%. PET CT for staging revealed hypermetabolic right breast primary neoplasm and low-grade metabolically active right axillary nodes. Guided biopsy of the right axillary node revealed the presence of metastatic ductal carcinoma.

She was clinically staged as T4b N1 M0 and was planned for neoadjuvant chemotherapy. She was started in January 2022 on adriamycin-cyclophosphamide regimen, and after 2 cycles, she was infected with COVID-19. Reassessment in April 2022 revealed that her tumour had grown in size with inflammation of overlying skin (Fig. 1). Repeat ultrasound and MRI corroborated disease progression and revealed the cystic mass size to be 19.5 × 18.5 × 19 cm with scattered mural-based intra-cystic lesions at the upper outer part (11 o'clock) of size 28 × 10 mm and 2 lesions at the midline-posteriorly at 12 o'clock of sizes 17 × 8.5 mm, 32 × 6.5 mm, respectively.

Since the tumour was unresponsive to chemotherapy, she underwent a right modified radical mastectomy with insertion of expander on April 24, 2022 (Fig. 2). Her post-operative histopathology came out to be grade 3 invasive ductal carcinoma (Fig. 3–5).

The breast tumour was cystic in nature and partially lined by atypical epithelial cells which were pseudostratified columnar with areas showing papillaroid folds and tufts, with underlying solid invasive nests comprising large pleomorphic cells with hyperchromatic nuclei and high nuclear cytoplasmic ratio. The cyst extended over an area of 200 mm; however, the invasive component was seen over an area of 90 mm. The background showed dilated ducts with thick eosinophilic material with focal areas with highly pleomorphic and

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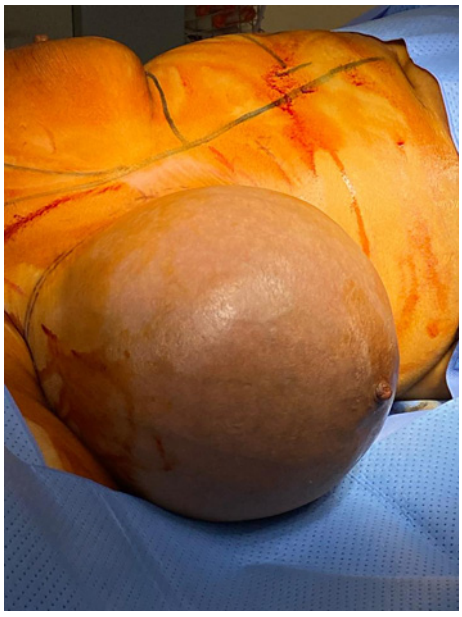

Fig. 1. Preoperative findings of right breast tumour.

spindled cells which showed patchy positivity for SMA and p63 on immunohistochemistry. They were negative for S100 and AE1/3 markers as well. The features were those of a high-grade invasive ductal carcinoma with sarcomatoid areas and were in accordance with a metaplastic carcinoma (Fig. 6.)

The tumour was completely excised with no lympho-vascular invasion. It was triple negative with a proliferation index of 40%. Her axillary dissection showed 19 lymph nodes, all of which were negative for metastasis. Her post-operative course was uneventful. She completed adjuvant chemotherapy with paclitaxel, carboplatin, and pembrolizumab followed by adjuvant radiation.

Discussion

CHC is a rare variant of breast carcinoma and is usually composed of in situ component. It is a member of the spectrum of cystic hypersecretory lesions of the breast which includes cystic hypersecretory hyperplasia (CHH), CHH with atypia, CHC, and CHC with invasion [5]. Invasive CHC is the rarest in the spectrum with only 22 reported cases in the literature till date. It was first described by Rosen and Scott [6] with a series of 10 cases. Guerry et al. [7] elucidated the spectrum of these lesions in 1988. However, it is not part of the WHO classification (5th edition, 2019) due to the rarity of the tumour and lack of large studies on the biological behaviour and prognosis [2].

CHCs are usually indolent breast tumours with slow progression unless they have an invasive component. They are usually confined to the duct but have a potential for local invasion and distant metastasis. 20% of the reported CHC cases were noted to have an invasive component, making this entity infrequent [8].

The age of onset of these tumours was found to be between 32 and 79 years, based on previous case reports with a mean age of 47 years [2]. The commonest clinical presentation was that of a significant palpable breast mass associated with pain. Serous nipple discharge was reported in a few cases [9]. Rarely, the tumour can grow to the point of skin ulceration. Our patient only complained of the mass. She had no pain or nipple discharge.

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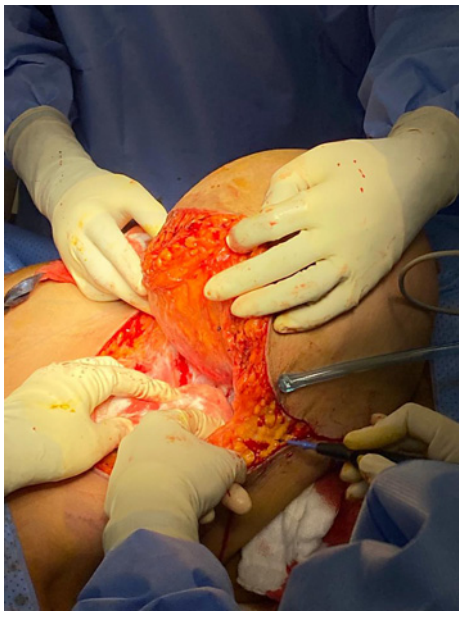

Fig. 2. Intraoperative image of right modified radical mastectomy.

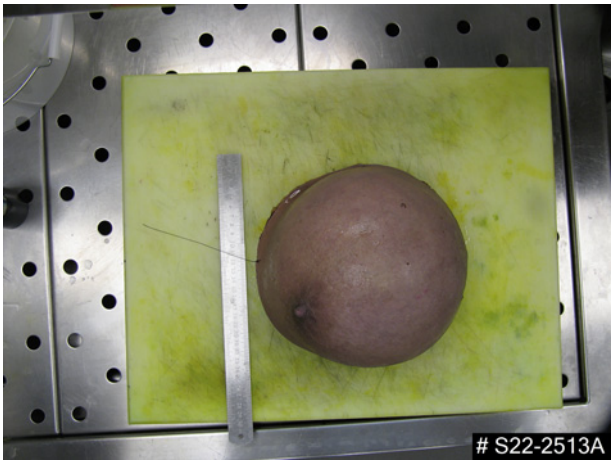

Fig. 3. Anterior aspect of the operative specimen.

Fig. 4. Posterior aspect of the operative specimen.

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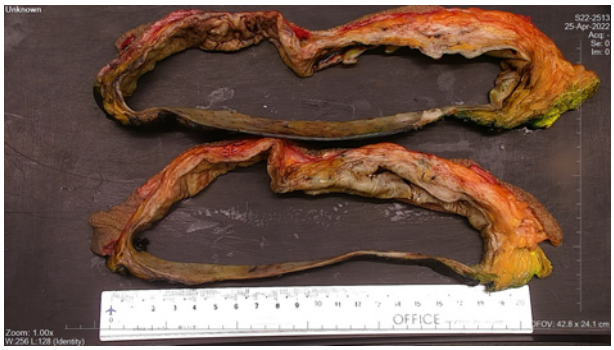

Fig. 5. Gross sections of the excised tumour.

Diagnosis and staging of breast neoplasms depend on radiological and pathological assessment of the tumour. However, there are some diagnostic pitfalls as far as cystic breast lesions are concerned. Due to the cystic nature of the lesion, it is commonly mistaken to be a component of benign fibrocystic breast disease. There have been sonographic reports of aggregated complex cysts, intraductal papilloma and even, breast abscess in such patients [10]. Advanced cases may have a hypoechoic lesion with hyperechoic foci in it associated with smaller cysts and dilated ducts [11]. Our patient had an ultrasound done 6 months before presentation which was reported as a simple breast cyst. During presentation, the repeat ultrasound showed evidence of a malignant cyst with intra-cystic soft tissue lesions and suspicious chest wall involvement with pathological-looking axillary nodes.

Mammography may add value by showing increased breast density or speculations and calcifications [11]. However, microcalcifications have not been reported in many previous studies, and overall mammographic picture is highly variable and insufficient to induce a suspicion of malignancy. MR imaging has been reported to show multiple cystic lesions with segmental enhancement and multifocal washout foci in dynamic studies.

The cystic nature of these lesions entails fine needle aspiration cytology, which is often ambiguous for malignancy. Aspirate from our patient showed inflammatory cells with few clusters of malignant cells. It is not unusual to end up with negative findings in FNAC, and this makes core needle biopsy the most crucial investigation in the work up [12]. Core biopsy can show the nests of atypical cells lining the cyst wall and foci of invasion, if any.

The evidence on clinical response to chemotherapy for these tumours is very sparse. Mohamed et al. [13] have documented poor response to neoadjuvant and disease progression during ongoing chemotherapy in their case report. Our patient had a similar clinical course and decision was made to proceed with surgery for this reason. Almost all previous studies have reported either modified radical mastectomy or a simple mastectomy in such patients [14]. Our patient underwent a modified radical mastectomy due to her axillary lymph node metastasis.

Grossly, these lesions have a characteristic appearance of multiple cysts of different sizes filled with gelatinous material. Microscopically, the ducts show cystic dilatation, sometimes exhibiting a honeycomb appearance [15]. The lining epithelium is proliferative with areas of papillaroid folds. In CHH, the epithelium is orderly, but when invasion occurs, the cyst wall may thicken with the epithelium forming solid nests or nodules [5]. The cyst, itself, is filled with amorphous, colloid-like material which may retract from the cyst wall resulting in scalloping of its margins. Occasionally, cyst rupture may cause spillage of the contents eliciting an inflammatory response in the surrounding stroma [2, 12].

As for immunohistochemistry, the data from previous studies provide variable pictures. The tumour may or may not be positive for oestrogen and progesterone receptors. However, most cases reviewed have a HER-2 neu positive status [16]. Although the data on hormonal

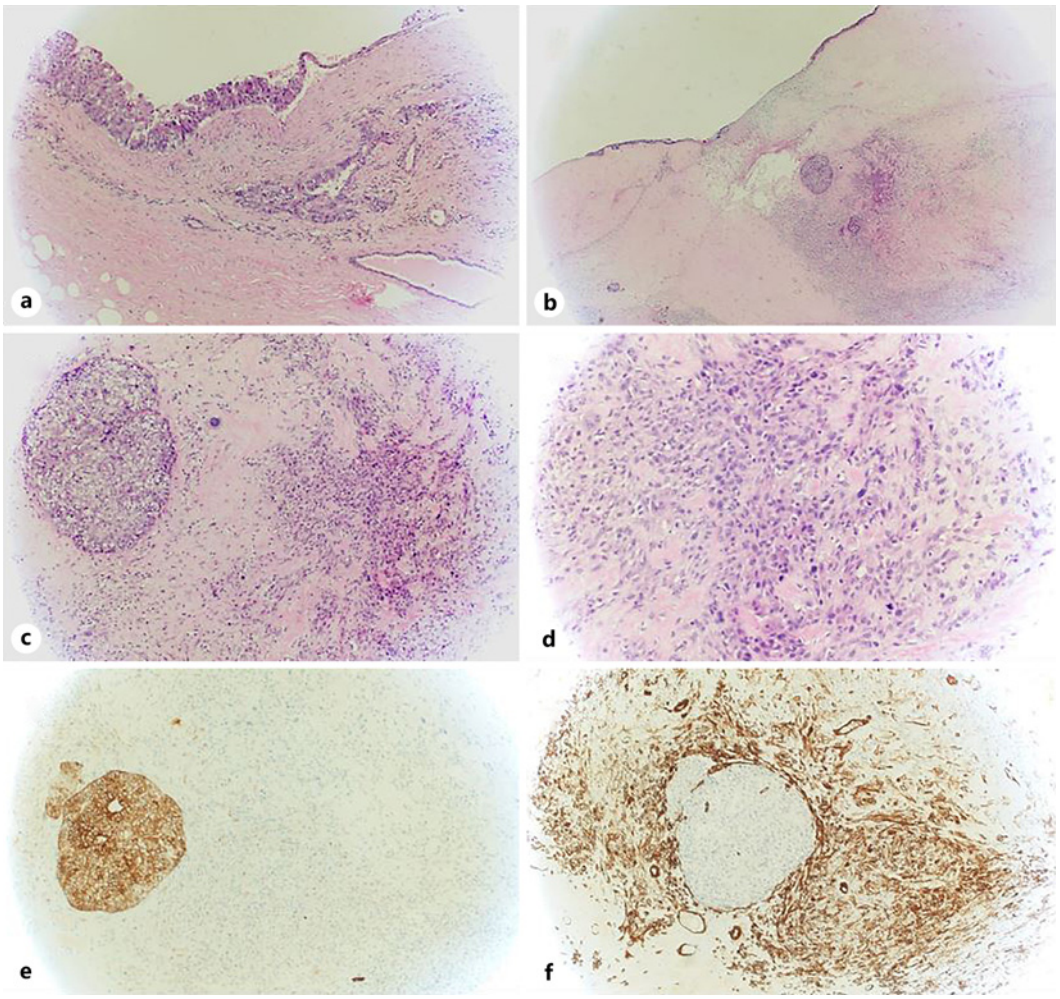

Fig. 6. a Cystic area of the invasive tumour. **b** Low magnification of invasive epithelial component with metaplastic area. **c** Higher magnification of the area. **d** Higher magnification of the pleomorphic and atypical spindled cells with frequent mitotic figures. **e** Epithelial component of the invasive carcinoma highlighted by immunohistochemistry for AE1/AE3. **f** Spindle cell component highlighted by immunohistochemistry for SMA, confirming smooth muscle differentiation in the metaplastic tumour.

profile of the tumours are limited, we could find 4 cases reported by Skalova et al. [17], Sahoo et al. [9], Gupta et al. [8], and Mohamed et al. [13] that were triple negative, like in our case. The data available are however, insufficient to study the impact of the hormonal profile of the tumour on its behaviour, response to neoadjuvant chemotherapy, and prognosis.

The differential diagnosis of these tumours includes secretory carcinoma, micropapillary ductal carcinoma in situ, mucocele-like lesions, mucinous cystadenocarcinoma, and metastatic papillary thyroid carcinoma. They are all usually differentiated by the distinction in their gross and microscopic features and immunohistochemistry [2, 5]. The picture in core biopsy may be a confounding factor which makes clinical suspicion highly necessary for the diagnosis of such tumours. Misdiagnosis of this tumour can act as a major impediment in deciding the appropriate treatment comparable to other clinical scenarios, like the CUP syndrome from occult breast carcinoma [18].

The patient in our case study presented to us with the breast mass for several months. Simple aspiration of the cyst revealed malignant cells instigating further evaluation. Had she

presented to us earlier, the tumour could have been tackled at a less invasive stage. Lack of studies on the effect of neoadjuvant chemotherapy on CHC served as a knowledge gap in the management of this patient. However, poor response to chemotherapy was identified early and safe surgical removal was carried out. More studies in the future with respect to appropriate neoadjuvant chemotherapy including chemoimmunotherapy, use of immune checkpoint inhibitors and antibody drug conjugates in these tumours will aid clinicians to pursue the right course of treatment for different stages of presentation of CHC.

Conclusion

Cystic hypersecretory lesions of the breast, albeit rare, have distinct gross and microscopic features. A clear knowledge about the pathology can help minimize the underdiagnosis of these conditions. Invasive CHC is a rare variant of ductal carcinoma and can be diagnosed with a good index of clinical suspicion. Timely diagnosis can benefit the patient by planning appropriate surgery instead of simple excision. Prospective studies with larger group of patients and longer follow-up duration need to be conducted to be able to analyse the tumour behaviour, molecular characteristics, response to chemotherapy, and to predict the prognosis of this disease.

Statement of Ethics

This study protocol was reviewed, and the need for approval was waived by the KHUH IRB committee. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.A., J.K.C., and S.S.M. conducted patient review, medical follow-ups, and performed the main surgery. Histopathological findings were reported by F.H. and A.A. Literature review, the consolidation of references, and the manuscript write-up were performed by N.A., J.K.C., S.S.M., F.H., and A.A.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Sun J, Wang X, Wang C. Invasive cystic hypersecretory carcinoma of the breast: a rare variant of breast cancer: a case report and review of the literature. BMC Cancer. 2019;19(1):31.
2 Chitti S, Misra S, Ahuja A, Gupta N, Yelamanchi R. Invasive cystic hypersecretory carcinoma of the breast. Autops Case Rep. 2022 Apr 28;12:e2021375.
3 Rizzo A, Cusmai A, Acquafredda S, Rinaldi L, Palmiotti G. Ladiratuzumab vedotin for metastatic triple negative cancer: preliminary results, key challenges, and clinical potential. Expert Opin Investig Drugs. 2022 Jun;31(6):495–8.
4 Rizzo A, Ricci AD, Lanotte L, Lombardi L, Di Federico A, Brandi G, et al. Immune-based combinations for metastatic triple negative breast cancer in clinical trials: current knowledge and therapeutic prospects. Expert Opin Investig Drugs. 2022 Jun;31(6):557–65.
5 Lee JS, Lee YJ. Invasive cystic hypersecretory carcinoma of the breast: a case report. J Korean Med Sci. 2004;19(1):149–51.
6 Rosen PP, Scott M. Cystic hypersecretory duct carcinoma of the breast. Am J Surg Pathol. 1984;8(1):31–41.
7 Guerry P, Erlandson RA, Rosen PP. Cystic hypersecretory hyperplasia and cystic hypersecretory duct carcinoma of the breast. Pathology, therapy, and follow-up of 39 patients. Cancer. 1988;61(8):1611–20.
8 Gupta P, Dhingra S, Musa O, Srivastava AN. Lnvasive cystic hypersecretory carcinoma of the breast associated with papillary pattern: a rare and poorly recognised variant of ductal carcinoma of the breast. Ecancermedicalscience. 2014;8:477.
9 Sahoo S, Gopal P, Roland L, Pile N. Cystic hypersecretory carcinoma of the breast with paget disease of the nipple: a diagnostic challenge. Int J Surg Pathol. 2008 Apr;16(2):208–12.
10 Song SW, Whang IY, Chang ED. Cystic hypersecretory ductal carcinoma of the breast: a rare cause of cystic breast mass. Jpn J Radiol. 2011;29(9):660–2.
11 Park C, Jung JI, Lee AW, Cheon HM, Hahn ST, Lee JM. Sonographic findings in a patient with cystic hypersecretory duct carcinoma of the breast. J Clin Ultrasound. 2004 Jan;32(1):29–32.
12 Resetkova E, Padula A, Albarraccin CT, Sneige N. Pathologic quiz case: a large, ill-defined cystic breast mass. Invasive cystic hypersecretory duct carcinoma. Arch Pathol Lab Med. 2005 Mar;129(3):e79–80.
13 Mohamed G, Elmahs A, Ahmed H. A rare case of invasive cystic hypersecretory carcinoma of the breast post neoadjuvant therapy: case report and literature review. J Histol Histopathol. 2021;8(1):2.
14 Herrmann ME, McClatchey KD, Siziopikou KP. Invasive cystic hypersecretory ductal carcinoma of breast: a case report and review of the literature. Arch Pathol Lab Med. 1999;123(11):1108–10.
15 Bi R, Cheng Y, Yu B, Shui R, Yang W, Xu X. Clinicopathologic features of cystic hypersecretory lesion of the breast. Chin J Pathol. 2014;43(1):25–9.
16 D'Alfonso TM, Ginter PS, Liu YF, Shin SJ. Cystic hypersecretory (in situ) carcinoma of the breast: a clinicopathologic and immunohistochemical characterization of 10 cases with clinical follow-up. Am J Surg Pathol. 2014;38(1):45–53.
17 Skalova A, Ryska A, Kajo K, Di Palma S, Kinkor Z, Michal M. Cystic hypersecretory carcinoma: rare and poorly recognized variant of intraductal carcinoma of the breast. Report of five cases. Histopathology. 2005;46(1):43–9.
18 Barbieri E, Anghelone CAP, Gentile D, La Raja C, Bottini A, Tinterri C. Metastases from occult breast cancer: a case report of carcinoma of unknown primary syndrome. Case Rep Oncol. 2020 Sep 28;13(3):1158–63.