# Cystic Hypersecretory Carcinoma of the Breast: A Rare Case Report with Review of Literature and Emphasis on Differential Diagnosis

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## Abstract

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Cystic hypersecretory carcinoma (CHC) is a rare subset of in-situ breast carcinoma with or without associated invasive carcinoma. It is part of a spectrum of cystic hypersecretory lesions that includes cystic hypersecretory hyperplasia (CHH), CHH with atypia, CHC in situ, and CHC with invasion. Only 20 cases of CHC with invasion have been reported so far. A 60-year-old female presented with a palpable right breast mass. A core needle biopsy was carried out, which was reported as invasive breast carcinoma with areas of ductal carcinoma in situ (DCIS). Modified radical mastectomy was done post-neo-adjuvant chemotherapy; On microscopy, dilated cystic spaces filled with eosinophilic secretions (thyroid colloid-like), lining neoplastic cells with variable degrees of proliferation and atypia were seen. There were multiple foci of invasion; both skin invasion and axillary lymph node metastasis were present. Immunohistochemistry (IHC) was done with relevant markers; correlating all these findings, a diagnosis of CHC with invasion was made. CHC is a distinct form of DCIS with or without associated invasion. Awareness of this entity is required to rule out other differential diagnoses and to avoid misinterpretation. Little is known about the IHC profile, biological behavior, prognosis, and molecular profile of CHC due to its rarity.

## Introduction

Cystic hypersecretory carcinoma (CHC) of the breast was first described by Rosen and Scott in 1984 as a separate entity due to its unusual and characteristic pathological findings.[1] Multiple studies have documented CHC as a separate variant of ductal carcinoma in situ (DCIS) having a characteristic appearance with or without associated invasive carcinoma.[2–4] While grossly CHC shows multiple cystic spaces filled with gelatinous to colloid-like material, microscopy shows dilated ducts and cystic spaces lined by flat to micropapillary patterned epithelium with atypia and characteristic colloid-like luminal secretion with scalloping. It is considered a part of a spectrum of cystic hypersecretory lesions, which also

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includes cystic hypersecretory change/cystic hypersecretory hyperplasia (CHH) and CHH with atypia (atypical CHH). CHC is extremely rare. Approximately 70 cases of CHC and only about 20 cases of CHC with invasive carcinoma have been reported in the current literature to date.[4] It is not included in the World Health Organization (WHO) classification of breast tumors till date (WHO classification 2019).

Because of its rarity, immunohistochemical (IHC) characterization, molecular profile, behavior, and prognosis data for CHC are lacking. We herein report a case of CHC with invasion, review the literature till now, and discuss its differential diagnosis.

## Case Report

A 60-year-old female presented with a large right breast mass gradually increasing in size for the past 6 months. On computed tomography of the thorax, presence of a $72 \times 53 \times 88$ mm sized heterogeneously enhancing soft tissue density lesion was noted involving the upper quadrants of the right breast, extending into the retroareolar region and involving the overlying skin with internal cystic areas and internal necrosis. Presence of a few necrotic nodes was also noted in the right axilla.

Biopsy was done from the lesion that was reported as invasive breast carcinoma, no special type (IBC-NST) along with focal DCIS. On IHC (with positive internal and external controls), estrogen receptor (ER) and progesterone receptor (PR) were negative and HER2 was equivocal (2+). However, fluorescent in-situ hybridization (FISH) was done using HER 2 neu (ERBB2)/CEP 17 dual color probe in which HER2/CEP17 ratio was 1.75 and average HER2 copy number was 4.3 signals/cell. Based on these findings, HER-2 FISH was reported as negative.

The patient was then proceeded with eight cycles of neoadjuvant chemotherapy that included four cycles of doxorubicin + cyclophosphamide followed by four cycles of docetaxel. Following this, modified radical mastectomy was done considering the size of the tumor and nodal status.

On gross examination, a tumor was found in the upper quadrants of the breast measuring 8 cm in maximum dimension. It was ulcerating and reaching till the overlying skin. The cut surface of the tumor was ill-defined, gray-white to brownish with multiple cystic to microcystic spaces ranging in size from 0.1 to 1 cm having gelatinous to colloid-like material within. No obvious necrosis was noted (►Fig. 1).

On microscopic examination, the tumor showed multiple cystic spaces of varying sizes. These spaces showed a spectrum of lining from a single layer of flat to cuboidal epithelium without atypia to crowded, pseudostratified and stratified epithelium arranged in micropapillary architecture with moderate-to-marked atypia and apical snouts (►Fig. 1). Cyst contents were predominantly homogenous eosinophilic secretions with crackling and scalloped borders. Few cysts showed eosinophilic granular secretions. There were multiple foci of associated invasive carcinoma arranged in trabeculae and nests with high-grade nuclear morphology resembling the cells lining the cyst wall in high-grade areas. The overlying skin was involved by the tumor. Eight out of fifteen axillary lymph nodes showed nodal macro-metastasis (8/15) with few areas showing cystic spaces with eosinophilic secretions similar to the primary tumor. The secretions were periodic-acid-Schiff positive (PAS-positive) and resistant to diastase treatment (PAS-D resistant). PAS-D also highlighted a few intracytoplasmic vacuoles (►Fig. 2).

With this morphology, differential diagnoses can range from in-situ to invasive carcinoma that include micropapillary and comedo-type DCIS with associated IBC, secretory carcinoma of breast, CHC, mucinous cystadenocarcinoma of breast, and metastatic thyroid follicular carcinoma. Considering these differentials, IHC markers were given. On IHC, ER was low positive (1–10% cells; 3/8- Allred score), PR was negative, and HER2 was equivocal (2+) in the invasive component. CK7, EMA(MUC1), and GCDFP-15 were diffusely positive; CK-20 was focal positive. P63, CK5/6, epidermal growth factor receptor (EGFR), thyroglobulin, Thyroid Transcription Factor 1 (TTF-1), S-100, and CDX2 were negative on the tumor cells. P63 and CK5/6 highlighted myoepithelial cells in most of the cystic spaces while they were lost in a few of them (►Fig. 2).

The material within the ducts and cysts was proteinaceous (highlighted with PAS and PAS-D) rather than necrotic. This rules out comedo-type DCIS. Micropapillary DCIS was excluded as the tumor showed predominantly dilated cystic spaces (which is not seen in DCIS). Other points that were against DCIS were absence of mixture of patterns (solid, cribriform, and micropapillary DCIS) and loss of myoepithelial cells in few of the cysts (P63 and CK5/6 negativity on IHC). Even though, both the secretions and intracytoplasmic vacuoles were PAS-positive and resistant to diastase treatment (PAS-D resistant), mucin was not identified both on gross and microscopic examination. This rules out mucinous cystadenocarcinoma. Presence of myoepithelial cells in most of the cysts (highlighted by P63 and CK5/6) also argues against mucinous cystadenocarcinoma. Secretory carcinoma, a uniformly microcystic (honeycomb like) patterned tumor lined by low grade tumor cells, was also ruled out in view of absence of this typical histology. This was also supported by IHC (the tumor cells were negative for S100 and low positive for ER). Both clinical and IHC findings rule out metastatic thyroid carcinoma and point towards a breast primary (the tumor cells were negative for TTF1 and thyroglobin; positive for CK7 and GCDFP-15)

After ruling out other common differential diagnoses, the final diagnosis was CHC of breast (>90%) with focal areas of IBC-NST (<10%) (In view of presence of multiple cysts having colloid like secretions, retraction spaces, retained myoepithelial cells in most of the cysts and a spectrum of changes in lining epithelium of the cysts from CHH to CHC as described above). The patient is on adjuvant chemotherapy with capecitabine following adjuvant radiotherapy without any adverse events, recurrence or metastasis 8 months post-surgery.

 

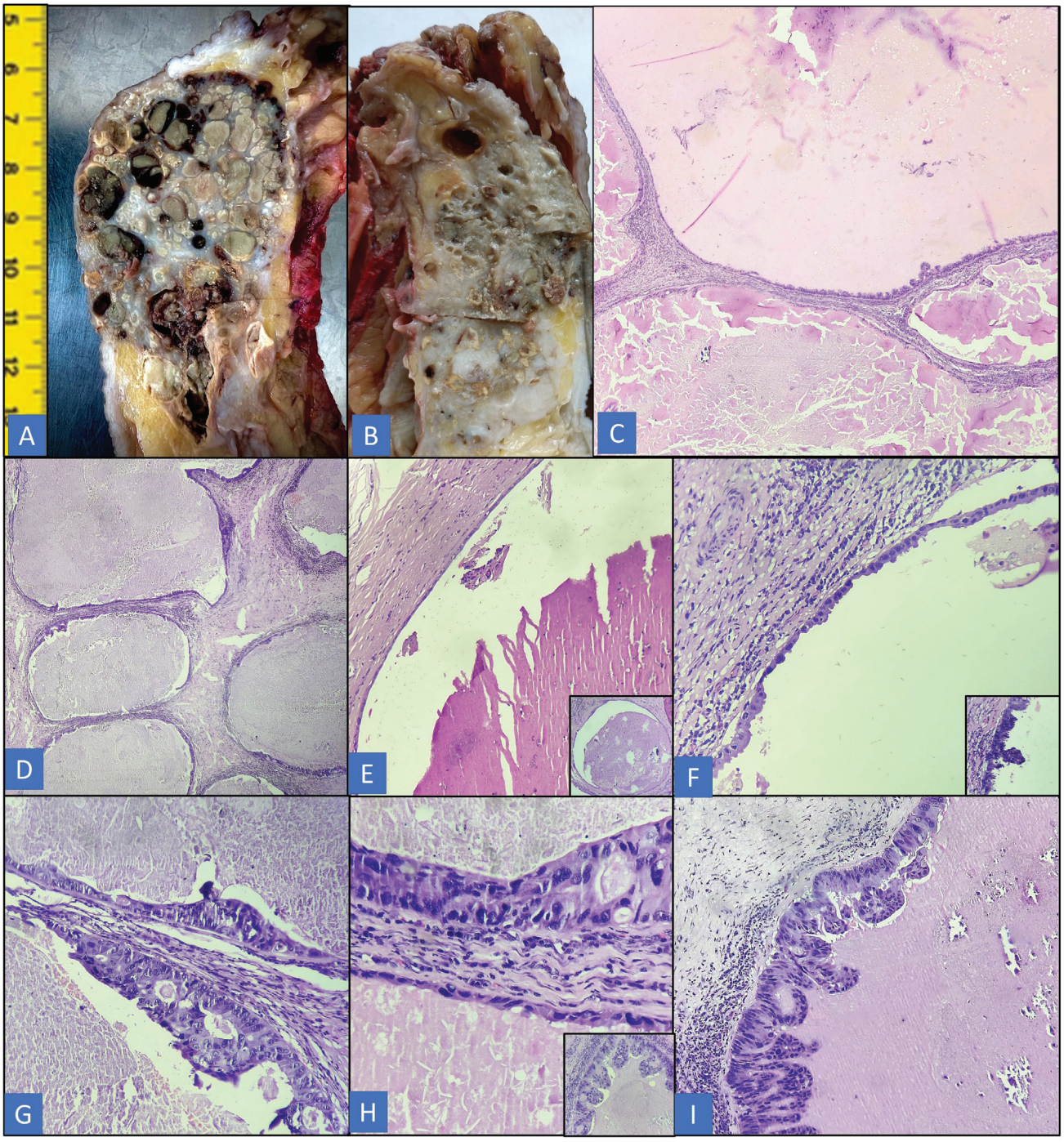


**Fig. 1** (**A**, **B**) Gross appearance of cystic hypersecretory carcinoma (CHC) (A—showing skin involvement); (**C**, **D**) Multicystic spaces with colloid like secretions (hematoxylin and eosin [H and E]; 10x); (**E**) Cystic hypersecretory hyperplasia (CHH) like areas with retracted colloid like material; (**F**) Atypical CHH with micropapillary architecture (H and E; 20x); (**G**, **H**) CHC areas (inset: CHC with micropapillary growth); (**I**) CHC with retracted colloid like material (H and E; 20x).

## Discussion

CHC was first reported by Rosen and Scott in 1984. They described CHC as a low-grade DCIS that has the potential to give rise to invasive carcinoma.[1] The lining epithelium showed a spectrum of changes from flat orderly lining to micropapillary growth with atypia and stratification and the entity was referred to as CHC. Transformation areas of benign to malignant appearing epithelium were noted. Subsequently, in the series of 29 cases by Guerry et al, CHC with cystic areas lined by benign flat to cuboidal epithelial lining were termed CHH and these were proposed to be precursors of CHC.[5] These CHH areas showed transition through atypical CHH showing mild atypia, crowding, and stratification to CHC. Among around 70 cases of CHC published till date,[1–5] all cases showed focal areas of CHH and/or atypical CHH similar to our case supporting the proposal by Guerry et al[5] that these are precursors for CHC. There is a wide age distribution

 

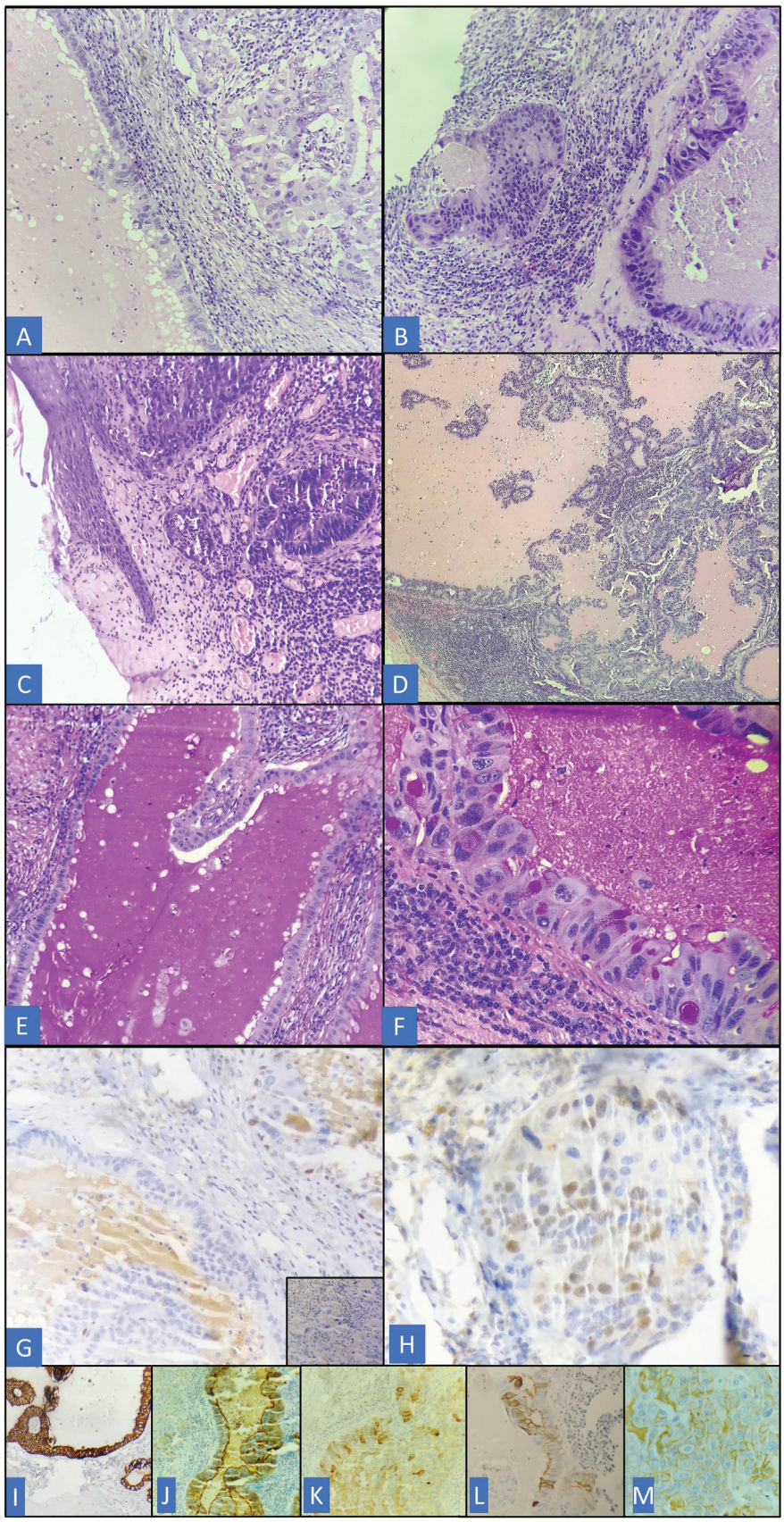


**Fig. 2** (**A**, **B**): Cystic hypersecretory carcinoma (CHC) with invasion (hematoxylin and eosin [H and E]; 20x); (**C**) CHC with skin invasion (H and E; 10x); (**D**) CHC with invasion showing lymph-node metastasis with similar colloid like material (H and E; 20x); (**E**; **F**) PAS-D positive intraluminal secretions and intracytoplasmic globules; (**G**) P63 positivity in CHC (upper right) with focal negative areas(lower left) (inset: P63 negative in invasive areas) (immunohistochemistry [IHC]; 20x); (**H**) Focal estrogen receptor low positive in invasive component (IHC; 40x); (**I**, **J**, **K**, **L**) Tumor cells showing positivity for CK7, EMA, GCDFP-15, and focal CK20 respectively(IHC; 20x); (**M**) Her2- equivocal in invasive areas (IHC;40x).

 

**Table 1** Differential diagnosis of CHC

| Favoring CHC—1. Elderly patient, presence of multiple cysts having colloid like secretions with retraction spaces and retained myoepithelial cells in the cysts; 2. Spectrum of changes in lining epithelium from CHH to CHC | | |
|---|---|---|
| **Lesion** | **Similarity with CHC** | **Difference from CHC** |
| Benign | | |
| PLH | Multiple cystic spaces; Can be associated with adjacent CHC | Overall preserved lobular architecture, minimally dilated cysts with bubbly secretions and cells with vacuolated to clear cytoplasm |
| JP | Similar gross appearance; multiple dilated cystic spaces with lining showing variable atypia | Younger age; absence of colloid like secretions, presence of combination of papillary lesions, hyperplasia, adenosis and duct ectasia |
| Mucocele like lesion | Multiple dilated cysts | Secretions are basophilic and pale blue (mucin) with calcifications and extravasation of mucin in the stroma |
| Malignant | | |
| DCIS (comedo and micropapillary) | Dilated ducts, micropapillary growth, stratification and similar grade nuclei | Other patterns of DCIS often present. Ducts are filled with granular necrotic material rather than colloid like secretions |
| Secretory carcinoma | Multiple cysts with secretions | Younger age; uniform microcystic (Honeycomb) appearance with eosinophilic secretions and vacuolated cytoplasm; ER −ve and S100 +ve |
| Mucinous cystadenocarcinoma | Elderly patient with multicystic tumor | Multiple mucin-filled cysts; absence of myoepithelial cells in the lining of all the cysts, both on morphology and by IHC (p63 and CK5/6–ve). |
| Metastatic thyroid follicular carcinoma | Multiple cysts with thyroid colloid like luminal secretions. | TTF1, thyroglobin positivity on IHC |

Abbreviations: CHC, cystic hypersecretory carcinoma; CHH, cystic hypersecretory hyperplasia; DCIS, ductal carcinoma in-situ; JP, juvenile papillomatosis; PLH, pregnancy-related hyperplasia.

from 34 to 79 years. They have variable clinical presentations ranging from mass forming lesion to mammographic calcification and nipple discharge.[4]

CHC has characteristic microscopic findings showing cystic spaces filled with colloid-like luminal secretions with retraction and lined by a spectrum of epithelium ranging from flat, cuboidal to columnar, monolayered to stratified micropapillary and atypia ranging from nil to marked with apical luminal snouts as seen in our case. Invasion, as seen in our case, is usually in the form of nests of poorly differentiated cells with similar morphology to CHC areas.[3,6] Among the reported 70 CHC cases, only 20 showed invasive carcinoma associated with them and only eight of these showed axillary lymph-node metastasis (2 among them were micrometastasis).[1,4,5] As seen in our case, Sun et al also have documented that axillary lymph-node metastatic foci had cystic spaces containing eosinophilic secretion analogous to CHC.[2] All these underscore that even though CHC behaves in a low-grade fashion, it, nevertheless, has a potential for invasive growth and can be associated with invasive carcinoma and axillary lymph-node metastasis.

As seen in our case, studies have documented PAS-D highlighting the luminal secretions and intracellular globules in CHC.[4,6] Myoepithelial and basal markers (CK5/6, P63, SMA) have been documented to be preserved in the basal layer of the cystic spaces in CHC. However, recent case series by D'Alfonso et al documented an absence of myoepithelial stains in a single case of CHC even in areas showing CHH.[4] In addition, they documented androgen receptor positivity in 3/10 cases. They argued that the loss of myoepithelial markers in that single case similar to focal areas seen in our case may be due to a phenomenon similar to those seen in benign apocrine lesions that can show loss or reduction in myoepithelial cells as documented by Tramm et al.[7]

Few case reports have examined the hormonal receptor status and Her2 status on IHC in CHC. Results of ER and PR status were variable; both ER and PR were positive in four and were negative in six studies.[2–4,8–10] Her2 was negative in most of the cases reported; nonetheless, it was positive (3 +) in 3/5 cases and 2/2 cases reported by Skalova et al and Yami et al, respectively.[3,9] In a recent series by D'Alfonso et al, predominant cases were ER-positive (8/10), while PR was variable. None of their cases (0/10) showed Her2 positivity.[4] Our case showed ER-low positive (1-10% cells), PR-negative with equivocal HER2(2 +) IHC and negative Her2 on FISH. Discordance of ER between biopsy (negative; Allred score: 0/8) and specimen (low positive; Allred score: 3/8) in our case can be attributed to intratumoral heterogeneity.[11]

 

Due to its rarity, IHC profile is not yet clearly established in CHC. Few case reports, as seen in our case, have documented positivity for CK-7 and GCDFP-15 (supporting breast origin) and negativity for high molecular weight keratin (CK5/6), EGFR, and P63 in the tumor cells.[4]

Excision of the tumor with negative margins is recommended for CHC; post-surgery, based on ER/PR and HER2 status, hormonal therapy can be given for CHC similar to treatment for DCIS. For patients with associated invasive carcinoma, adjuvant chemotherapy is recommended.[4] However, in view of rarity of this tumor, a standardized treatment protocol has not yet been established.

CHC must be distinguished from other mimickers that range from benign to malignant. Among benign lesions, mucocele like lesion, juvenile papillomatosis (JP), pregnancy like hyperplasia (PLH), and fibrocystic changes must be distinguished from CHC. Overall preserved lobular architecture with minimally dilated glands in PLH, absence of characteristic colloid like secretions, absence of spectrum of changes from CHH, atypical CHH to CHC help differentiate both JP and PLH from CHC.[4,6] In our case, overall architecture (presence of pseudostratification and micropapillae in the cyst wall with multiple invasive tumor nests) and cytology (marked cytological atypia of the tumor cells) rule out these above-mentioned benign entities.

Other in situ and invasive carcinomas that can mimic CHC are micropapillary and comedo-type DCIS, secretory carcinoma of breast, mucinous cystadenocarcinoma of breast, and metastatic thyroid follicular carcinoma. Each differential diagnosis along with their similarities and differences from CHC is discussed in detail in ►Table 1.

In summary, our case adds an extremely rare case of CHC with invasion, of which only 20 cases so far have been documented, to the existing literature. CHC is a histologically distinct form of DCIS with or without associated invasive carcinoma. Coexisting invasive component is poorly differentiated but with similar nuclear grade to that of adjacent CHC. Though this tumor has unique gross and microscopic features, due to its rarity, IHC profile, molecular features and standardized treatment have not yet been established. To disclose the biological behavior of this rare tumor, studies with larger sample size and follow-up data are needed. More common differential diagnosis that includes both benign and malignant entities is to be excluded before considering CHC.

Conflict of Interest
None declared.

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