Mucinous cystadenocarcinoma of the breast: a case report of a rare entity and how to recognize it

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Abstract

Mammary mucinous cystadenocarcinoma is a rare primary breast malignancy. First described in 1998 by Koenig and Tavassoli, it was named in the third edition of the WHO International Classification of Tumours (2003) but was only recognized as a distinct entity in the most recent fifth edition (2019). Lack of data impedes our understanding of tumourigenesis and long-term prognosis. No standardized treatment protocol is available. Here we present a case in which this unusual diagnosis was suggested on core biopsy and confirmed on surgical resection. The purpose of this case report is to add to the data on its long-term behaviour, and illustrate an approach to its diagnosis.

Keywords Breast; carcinoma; cystadenocarcinoma; mammary; mucinous; triple-negative

Case report

A 42-year-old white female was referred to the Breast Service. She had a 2–3 month history of a lump in the left breast. There was a strong family history of breast cancer. Clinical examination of the left breast revealed two masses. The nipple and skin showed no abnormality. The right breast was normal. There was no palpable lymphadenopathy.

Mammography identified multiple well-defined densities and microcalcifications (M5) and ultrasonography revealed hypoechoic densities (U5) within the left breast. Ultrasound-guided core biopsies sampled the upper and lower parts of the lesion (Figure 1). The lower biopsies were extensively involved by invasive carcinoma (B5b) composed of cystic spaces lined by atypical tall columnar cells with stratification and focal papillary formation. Abundant intracellular and extracellular mucin was confirmed by histochemical stains. The lining cells were atypical with brisk mitotic activity and the tumour was assessed as grade 3 in nature. Epithelial cells expressed CK7 but not CK20 or CDX2. Myoepithelial cells were absent at the periphery of the cystic spaces, as confirmed by p63-negativity. GATA3 was negative in the invasive component. The carcinoma was oestrogen receptor (ER)-negative, progesterone receptor (PR)-negative and HER-2 negative. Multiple foci of high grade ductal carcinoma in situ (DCIS) were seen in the upper mass biopsy alongside minor elements of invasive tumour.

A provisional diagnosis of mammary mucinous cystadenocarcinoma was made and this, together with the differential diagnosis of metastatic mucinous carcinoma, were discussed within the multidisciplinary team. No evidence of metastatic disease was found on staging CT scan or skeletal survey. The final diagnosis was therefore that of multifocal primary mucinous cystadenocarcinoma of the breast.

The patient underwent left mastectomy with sentinel lymph node biopsy. Macroscopic examination revealed two variably defined and partly mucinous lesions. Microscopic examination revealed two grade 3 invasive tumours, with the larger tumour measuring 60 mm (Figure 2). Interspersed were foci of ER-positive DCIS. The whole tumour size was estimated at 80 mm. The sentinel lymph node showed no evidence of tumour involvement. All of the resection margins were clear of invasive and in situ disease. The final pathological stage (TNM8) was pT3(m)N0.

Genetic testing did not detect known mutations in any of the following cancer predisposition genes: BRCA1; BRCA2; PALB2; PTEN; STK11; TP53; ATM; CHEK2; RAD51C; RAD51D. Adjuvant radiotherapy and chemotherapy was considered but the patient decided against further treatment and mammography follow-up. Thirty-six months post-treatment the patient is alive and there has been no evidence of recurrence.

Discussion

Primary breast mucinous cystadenocarcinoma is rare. A keyword search including the terms "breast" and "mucinous

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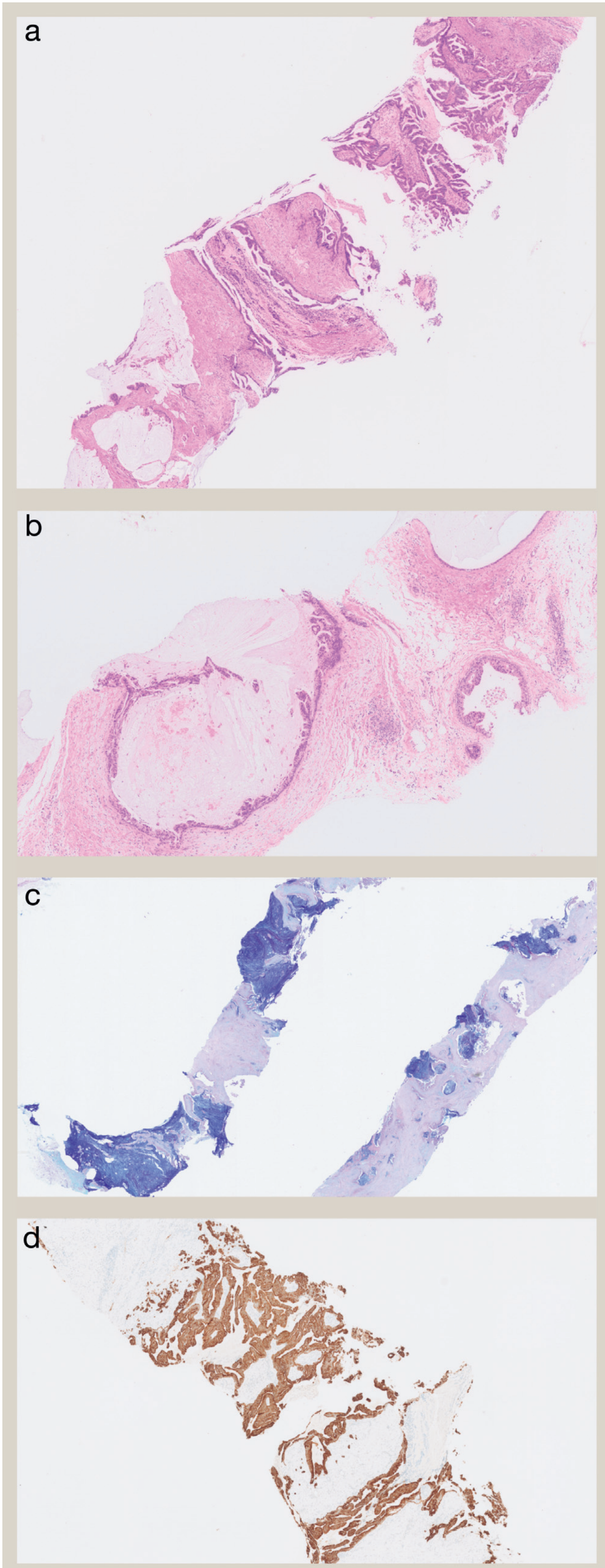

Figure 1 Features of mucinous cystadenocarcinoma seen on core biopsy. (**a**) Multiple cystic spaces with mucin and lining cells with complex architecture (H&E stain, 2x magnification). (**b**) DCIS is interspersed between large mucin-filled cystic spaces lined by atypical columnar cells (H&E stain, 5x magnification). (**c**) Abundant extracellular and intracellular mucin (ABPAS stain, 1xx magnification). (**d**) Atypical columnar cells lining cystic spaces are CK7-positive, CK20-negative on immunohistochemical stains (CK7, 2x magnification).

cystadenocarcinoma" in PubMed to 3 October 2024 yielded fewer than 40 cases.[1] Rarer still are multifocal lesions. To the best of our knowledge this is the third such case.[2] However, reports of the entity appear to be increasing. In the two decades that followed publication of the first cases (1998–2018) only 19 case reports were found in our search. In contrast, 5 years after recognition in the WHO Classification (2019) there have been at least 18 reports.[3]

When the pathologist encounters mucin on a breast core biopsy, there is a broad differential diagnosis that includes many common as well as rare entities.[4] Benign mucin-rich lesions include non-neoplastic nodular mucinosis and mucocoele-like lesion. DCIS can show mucin extravasation. Several primary breast carcinomas can be associated with mucin: mucinous carcinoma; mucinous cystadenocarcinoma; invasive lobular carcinoma; invasive solid papillary carcinoma. Metastatic mucinous tumours should also be considered in the differential diagnosis.

If metastatic disease is excluded and the essential histological features are present, a diagnosis of primary mucinous cystadenocarcinoma of breast can be made. According to the WHO International Classification of Tumours, the essential criteria are cystic spaces containing mucin lined by atypical columnar cells with intracytoplasmic mucin. Adjacent DCIS and ER- and PR-negativity in tumour cells are desirable criteria. Primary breast mucinous cystadenocarcinoma is CK7-positive, CK20-negative and CDX2-negative (Table 1). This can help to distinguish it from a pancreatobiliary carcinoma metastasis, which usually expresses CK20 and CDX2, with variable CK7 expression. Metastatic mucinous ovarian carcinoma is frequently immunoreactive for CK7, but can show variable expression of CK20 and CDX2. Radiological correlation is required to exclude metastasis.

Most cases of mucinous cystadenocarcinoma share a 'triple-negative/basal-like' molecular profile, defined by absent expression of ER, PR and HER2. Histological subtype in triple negative breast cancer is an important determinant of survival and disease recurrence.[5] Mucinous cystadenocarcinoma subtype has a relatively favourable prognosis. Reports of lymph node metastasis and of late recurrence are rare. No patient is known to have died as a result of their disease. A comparison of limited data in reported cases shows follow up duration ranges from three to 108 months (median 12 months.) Twenty-eight out of 38 patients (including our case) are alive with no evidence of recurrence at follow up. Two died due to unrelated causes. One patient experienced local recurrence after 96 months.[1]

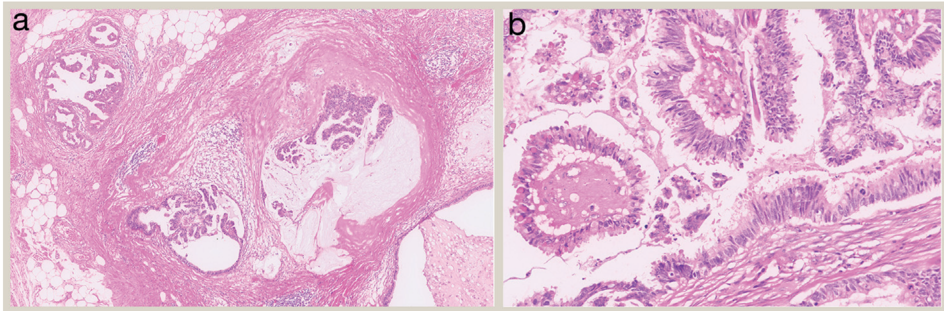

Figure 2 Features of mucinous cystadenocarcinoma seen on surgical excision. (**a**) DCIS (bottom right) adjacent to mucinous cystadenocarcinoma (H&E stain, 5x magnification). (**b**) Tumour cells lining cystic spaces show marked nuclear pleomorphism and brisk mitotic activity (H&E stain, 20x magnification).

Comparison of features of malignant mucinous lesions of the breast

	Invasive breast carcinomas with mucin	Mucinous cystadenocarcinoma	Metastatic mucinous cystadenocarcinoma (ovary; pancreas; appendix)
Clinical features...	5th to 7th decades Palpable mass	Median age 61 years Cystic-solid, lobulated mass	Wide age range Alternative primary tumour
DCIS	+/−	+/−	−
ER	+	−	−
CK7	+	+	+/−
CK20	−	−	+/−
CDX2	−	−	+/−

Table 1

Conclusion

Mucinous cystadenocarcinoma is a rare primary breast neoplasm. Whilst understanding of its natural history is incipient, it often shows a triple-negative/basal-like molecular profile. Reported cases, including that presented here, suggest mucinous cystadenocarcinoma shows an indolent behaviour. It is incumbent upon pathologists to recognize and report these cases in the literature so that appropriate risk stratification and treatment protocols can be developed. ◆

REFERENCES

1 Vegni F, D'Alessandris N, Santoro A, et al. Primary mucinous cystadenocarcinoma of the breast intermixed with pleomorphic invasive lobular carcinoma: the first report of this rare association. *J Pers Med* 2023; **13:** 948. https://doi.org/10.3390/jpm13060948.

2 Sun M, Su S, Liu Q, et al. Mammary synchronous mucinous cystadenocarcinoma and columnar cell mucinous carcinoma: a case report. *Int J Clin Exp Pathol* 2020; **13:** 2381−6. PMID: 33042347; PMCID: PMC7539871.

3 Koenig Christopher MD, Tavassoli Fattaneh AMD. Mucinous cystadenocarcinoma of the breast. *Am J Surg Pathol.* 1998; **22**(6)**:** 698−703.

4 Joneja Upasana, Palazzo Juan. The spectrum of mucinous lesions of the breast. *Arch Pathol Lab* 2023; **147:** 19−29. https://doi.org/10.5858/arpa.2022-0054-RA.

5 Grosse C, Noack P, Grosse A, et al. Prognostic impact of histological subtyping in triple-negative breast cancer. *Hum Pathol* 2024; **152**. https://doi.org/10.1016/j.humpath.2024.105640.x. 2024.

Practice points

- Mucinous cystadenocarcinoma is a rare primary breast malignancy, newly recognized in the fifth edition of the WHO International Classification of Breast Tumours
- On immunohistochemistry tumour cells express CK7 but not CK20 or CDX2, which can help distinguish it from metastatic disease, in addition to clinical and radiological correlation
- Mammary mucinous cystadenocarcinoma frequently shows a triple negative molecular profile (ER-negative, PR-negative, HER-2-negative)
- Mucinous cystadenocarcinoma appears to have a low incidence of lymph node metastasis and late recurrence, however data is limited

Self-assessment questions

1. Mucinous cystadenocarcinoma of breast exhibits these morphological features

- [a] Epithelial cell clusters with low-to-intermediate grade atypia free-floating in extracellular mucin
- [b] Intraductal neoplastic epithelial proliferation with cribriform architecture and mucin extravasation
- [c] Mucin-filled cystic spaces lined by tall columnar cells with intracytoplasmic mucin and variable atypia
- [d] Dyscohesive rounded tumour cells with intracytoplasmic lumina and signet-ring appearance in association with extracellular mucin pools
- [e] Mucin filled cystic spaces lined by cuboidal-to-columnar epithelial cells without atypia

2. The purported molecular subtype of mammary mucinous cystadenocarcinoma is

- [a] Luminal A (hormone receptor-positive, HER-2-negative)
- [b] Luminal B (hormone receptor-positive, HER-2 positive or negative)
- [c] HER-2/neu (HER-2-positive, hormone receptor positive or negative)
- [d] Triple-negative/basal-like (hormone receptors ER- and PR-negative, HER-2-negative)
- [e] Unclassified (hormone receptor and HER-2 status not relevant)

3. Mammary mucinous cystadenocarcinoma can be distinguished from a metastasis to breast by radiological exclusion of an alternative primary tumour and supported by a panel of immunohistochemistry including

- [a] CK7, CK20, CDX2
- [b] CK7, CK20, PAX8
- [c] CK7, CDX2, WT1
- [d] CK7, ER, GATA3
- [e] CK7, CK20, MUC2

Answers: 1=c 2=d; 3=a.

