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CASE REPORT

Intracystic invasive papillary carcinoma of the male breast with analyses of loss of heterozygosity on chromosome 16q

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Abstract A 64-year-old man noticed a right subareolar mass in May 2005. On physical examination, an oval-shaped, well-circumscribedthe tumor (6.0 × 5.5 cm in size) was located just beneath the right nipple. The tumor was elastic, firm and freely movable. Neither axillary nor supraclavicular lymph nodes were palpable. Mammography demonstrated a 5 × 5-cm, relatively distinct and dense mass without microcalcifications or spiculations. There were no findings of concurrent gynecomastia. Ultrasonography revealed a large multilocular cyst with a mural hypoechoic protruding lesion exhibiting wide-based morphology with an irregular margin. On contrast-enhanced computed tomography, the inner lesion enhanced, but direct invasion of the tumor to the major pectoral muscle was not found. An intracystic papillary lesion, possibly papillary carcinoma, was suspected. In December 2007, wide excision of the tumor was performed. On histopathological examination, the tumor had a papillary pattern with a small cribriform component in the cystic wall with microinvasion of the stroma. Marginal status was negative. The final diagnosis of the disease was a microinvasive intracystic papillary carcinoma of low grade without axillary lymph node metastases. Immunohistochemically, estrogen receptor and progesterone receptor were both positive, but negative for HER-2 protein. No LOH on 16q could be detected. The prognosis of the disease was unclear; however, the malignant potential of this condition may be more clearly determined by studying the LOH on chromosome 16q.

Keywords Intracystic papillary carcinoma · Male breast cancer · Loss of heterozygosity

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Introduction

Intracystic papillary tumors of the breast account for less than 1% of all breast lesions biopsied [1], whereas the majority of male papillary carcinomas are intracystic, and approximately 40–50% of the cases are noninvasive. Invasive intracystic carcinomas in male patients are extremely rare. In addition, most cases of intracystic papillary carcinoma of the male breast have a single cystic lesion with a malignant intracystic component. In order to differentiate papillary carcinomas from papillomas in females, analysis of loss of heterozygosity (LOH) on 16q has been reported to be a useful tool for correct diagnoses [2]. We report a case of intracystic invasive papillary carcinoma with analyses of LOH on 16q in a male patient.

Case report

A 64-year-old man noticed a right subareolar mass in May 2005. The patient consulted the family doctor and was

diagnosed as having right gynecomastia. A regular check-up was scheduled, but in August 2007 the tumor enlarged rapidly and become painful. He did not notice any nipple discharge. He was referred to our hospital for further examination.

The patient had a history of hypertension, hyperlipemia, diabetes mellitus and brain infarction. There was no family history of breast malignancy.

On physical examination, the tumor (6.0 × 5.5 cm in size) was located just beneath the right nipple with an oval-shaped, smooth surface and clear margins (Fig. 1). The tumor was also elastic, firm and freely movable. Neither axillary nor supraclavicular lymph nodes were palpable. The left breast was unremarkable. Mammography demonstrated a 5 × 5-cm, relatively distinct and dense mass without microcalcifications or spiculations (Fig. 2). There were no findings of concurrent gynecomastia. Ultrasonography revealed a large multilocular cyst with a mural protruding lesion exhibiting wide-based morphology with an irregular margin (Fig. 3). On contrast-enhanced computed tomography, a large irregular mass with an inner enhanced lesion was detected on the right chest wall (Fig. 4). Direct invasion of the tumor to the major pectoral muscle was not found. Aspiration showed bloody fluid, but cytological examination of this fluid failed to reveal malignancy. Three tumor markers of the serum, including CEA, NCC-ST-439 and CA15-3, were all within normal ranges.

From these findings, the tumor was suspicious for being an intracystic papillary lesion, possibly papillary carcinoma. In December 2007, a wide excision of the lump was performed. Grossly, the size of the lesion was 5.0 × 4.0 cm. The small protruding lesion was 1.5 × 1.0 cm. On histopathological examination, the tumor had a papillary or cribriform pattern in the cystic wall. The cellular composition of the tumor was monomorphic with prominent nucleoli. Microinvasion (less than 0.1 cm) of the stroma was found; the final diagnosis of the disease was a microinvasive intracystic papillary carcinoma (Fig. 5). Marginal status of the resected specimen was negative. Axillary dissection was added later, but there were no lymph node metastases. Estrogen receptor (ER) and progesterone receptor (PgR) were both positive. On immunohistochemical staining, the cancer cells were

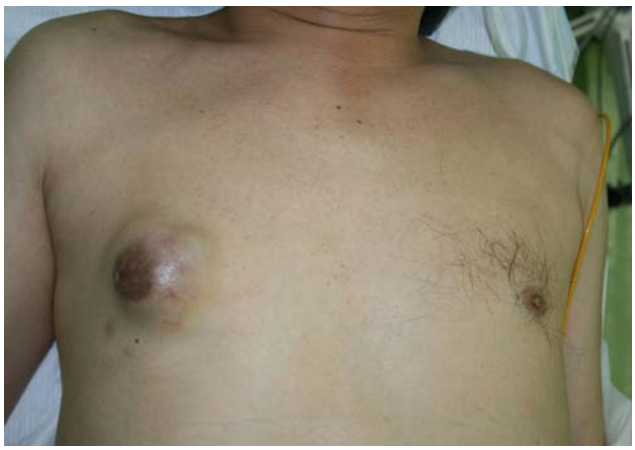

Fig. 1 On physical examination, the tumor (6.0 × 5.5 cm in size) was located just beneath the right nipple with an oval shape, smooth surface and clear margins

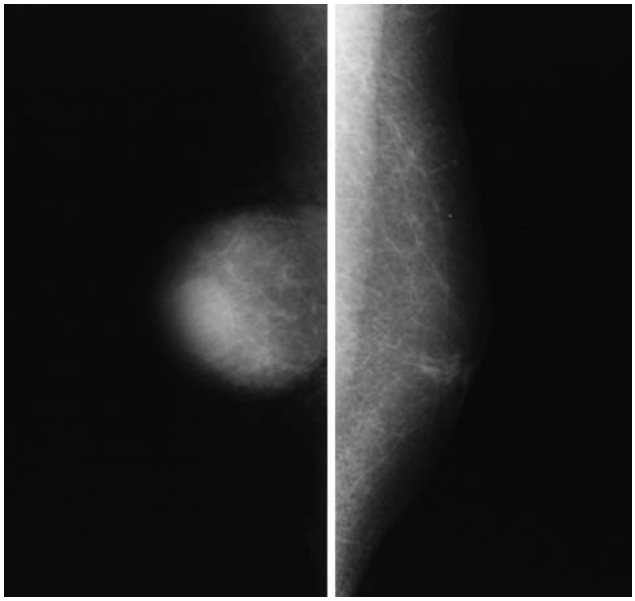

Fig. 2 Mammography demonstrated a 5 × 5-cm, relatively distinct and dense mass without microcalcifications or spiculations

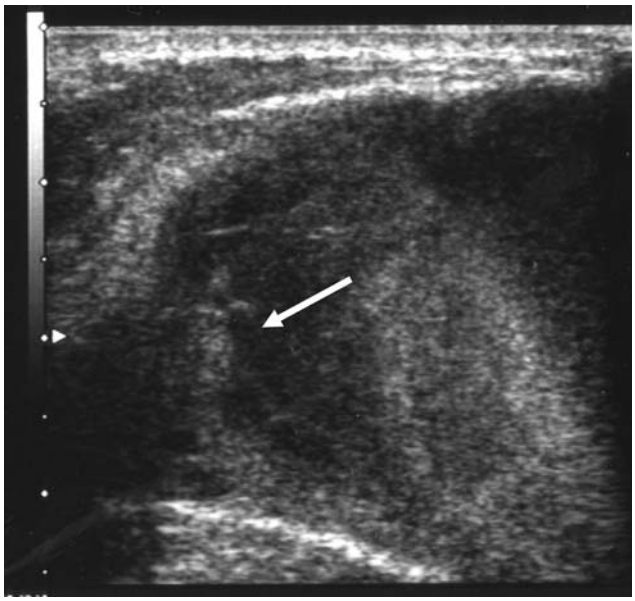

Fig. 3 Ultrasonography revealed a large multilocular cyst with a mural hypoechoic protruding lesion exhibiting wide-based morphology with an irregular margin (*arrow*)

negative for HER-2 protein. Adjuvant hormone therapy with 20 mg/day of tamoxifen was started 2 weeks after the axillary dissection. The patient was disease-free 12 months after surgery.

LOH of 16q

LOH on chromosome 16q has been shown to occur frequently in intracystic papillary carcinoma, but not in intraductal papilloma in the female breast [2]. We conducted LOH analysis in this case in order to determine if the examination of LOH on 16q was helpful for the differential diagnosis of male breast papillary tumors. The details of the procedure have been reported previously [2].

Tissue microdissection and DNA extraction

Cancerous cells and non-cancerous tissues were microdissected, and the microdissected cells were placed in proteinase K solution and incubated. The proteinase K was inactivated by incubation, followed by standard phenol–chroloform extraction and ethanol precipitation in the presence of glycogen.

PCR and analysis of alleic pattern

PCR amplification of genomic DNA was performed. Non-cancerous DNA samples with two different amplified bands were defined as informative cases for LOH analysis. The presence of LOH was determined in accordance with the manufacturer's criteria. LOH was considered to exist if the ratio of peak heights calculated by the following formula was lower than 0.67 or greater than 1.35: [Peak height of the affected allele (allele A) of the tumor × Peak height of the unaffected allele (allele B) of normal cells]/(Peak height of allele A of normal cells × Peak height of allele B of tumor cells). Results were considered non-informative when the alleles of normal tissue were homozygous, when the tissue lysate failed to be amplified or when the results could not be interpreted unambiguously.

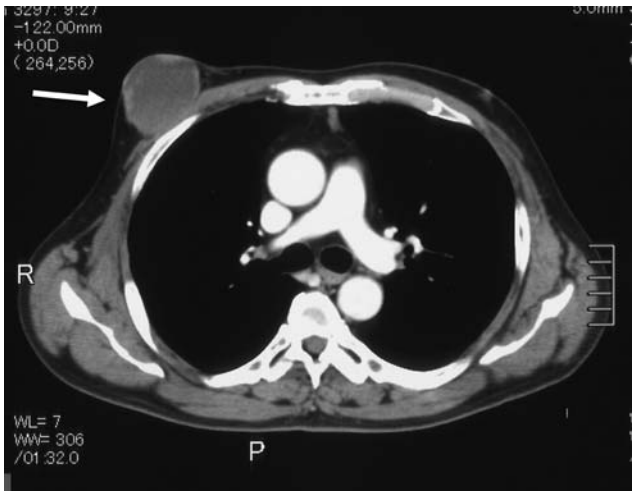

Fig. 4 On contrast-enhanced computed tomography, a large irregular mass with the enhanced inner lesion was detected on the right chest wall (*arrow*). Direct invasion of the tumor to the major pectoral muscle was not found

Results

Using five markers (D16S409: 16q12.1, D16S308: 16q12.1, D16S514: 16q21, D16S508: 16q21, D16S520: 16q24: 16q24, D16S413: 16q24), no LOH on 16q could be detected, even though one marker (D16S413) failed to be amplified (Table 1). The other five markers were all heterozygous (Fig. 6).

Discussion

The clinical findings of intracystic carcinoma were tumors and nipple discharge. Eighty percent of the discharge was bloody.

Mammography is not particularly useful for diagnosing intracystic lesions, whereas ultrasonography can detect intracystic papillary lesions on the wall of the cyst [3].

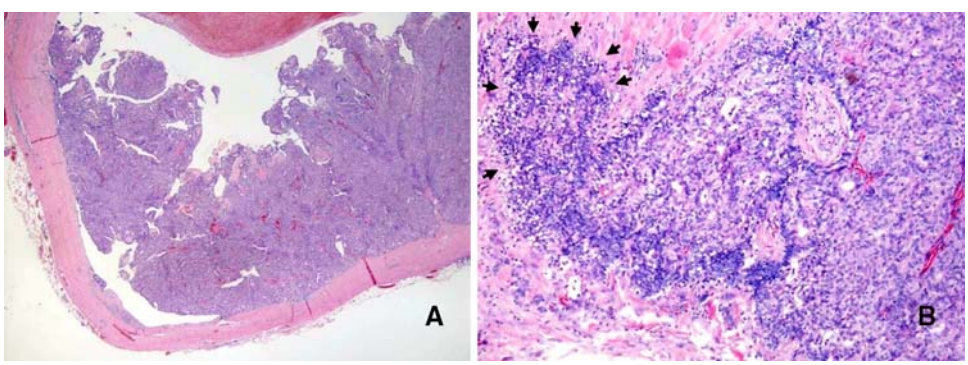

Fig. 5 On histopathological examination, the tumor was found to have a papillary or cribriform pattern in the cystic wall (**a**). Isolated invasive carcinoma cells were obscured by a lymphocytic reaction (*arrow*) in the stroma (**b**)

Table 1 Results of heterozygosity on 16q

Locus	Marker	F-primer	R-primer	LOH analysis
16q12.1	D16S409	TGAATCTTACATCCCATCCC	AGTCAGTCTGTCCAGAGGTG	Heterozygous
16q12.1	D16S308	CAGCCAGGGTAGTAAGGCTAGACCT	TGGGTGGCAGAGTGAGACCCTGTCT	Heterozygous
16q21	D16S514	CTATCCACTCACTTTCCAGG	TCCCACTGATCATCTTCTC	Heterozygous
16q21	D16S508	CAGGAAAATAAATCTAACACACATA	CCTGTGGGCACTGATAAATA	Heterozygous
16q24	D16S520	GCTTAGTCATACGAGCGG	TCCACAGCCATGTAAACC	Heterozygous
16q24	D16S413	ACTCCAGCCCGAGTAA	GGTCACAGGTGGGTTC	Not amplified

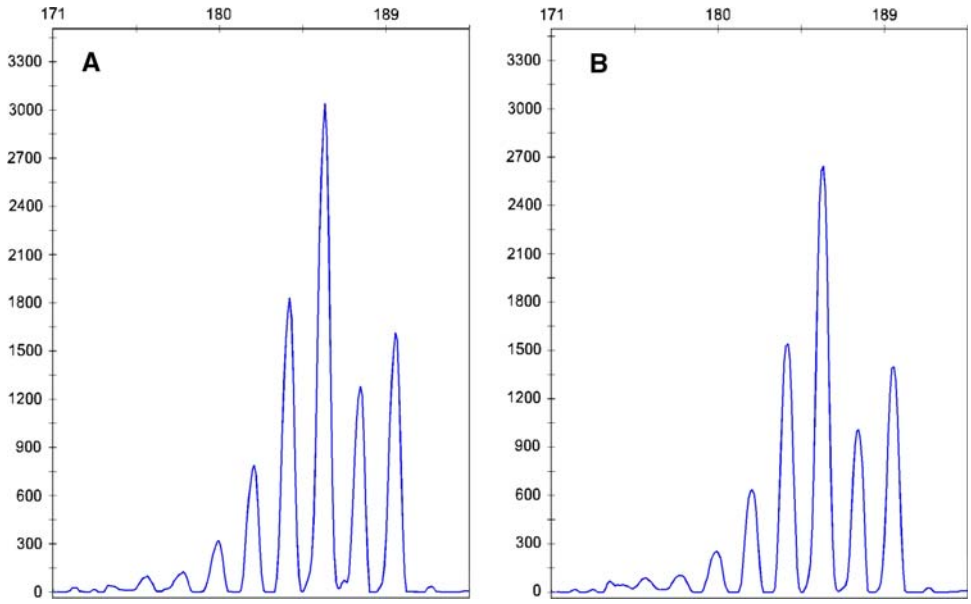

Fig. 6 No LOH on 16q could be detected (D16S520). **a** Cancer tissue DNA. **b** Non-cancerous tissue DNA. In both **a** and **b**, alleles 1 and 2 were preserved

Aspiration biopsy cytology made a correct diagnosis in 35% of the cases [4]. For the cytological feature revealed by aspiration biopsy, cytology might be misleading because cellular atypia is slight in intracystic papillary lesions. The diagnosis should be made by core needle biopsy [5]. Ultrasound-guided core needle biopsy is therefore the most valuable method for a correct preoperative diagnosis. Excisional biopsy is sometimes needed to confirm the diagnosis, because invasive cases have been reported previously [6–8].

In the Japanese literature reviewed, the average age of the patients with intracystic male breast carcinoma was 69 years (range 41–91), suggesting that the patients with the disease were older than for the common-type breast cancers. The mean tumor diameter was 3.0 cm (range 1.7–7.0) [7, 9]. There is no consensus regarding the surgical procedure of intracystic papillary carcinoma. Approximately 90% of the patients were treated with mastectomy; however, excisional biopsy with a negative margin can be also recommended in this condition [7–10]. However, the etiology still remains unknown.

Examination of LOH on 16q could be helpful for the differential diagnosis of intracystic papillary tumors, because such LOH was detected in approximately 70% of the cases. In addition, the incidence of LOH on chromosome 16q is high in intracystic carcinomas, regardless of their low histological grade of atypia and of no or only relatively limited extent of invasion in general. In this case, however, no LOH on 16q could be detected.

The prognosis of the disease is also unknown except for non-invasive cases; however, the malignant potential of the disease may be more clearly determined by studying the LOH on chromosome 16q. In this case, it is possible that another LOH, such as LOH on 17p or 11p, is also related to intracystic papillary carcinoma.

To our knowledge, this is the first report to analyze LOH on 16q in intracystic male papillary breast carcinoma. Further studies will be required to clarify the etiology and biological behavior of this condition.

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