Apocrine Carcinoma of the Breast

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Abstract: Apocrine carcinoma is a rare variant of breast carcinoma, and accounts for 0.3 to 1.0% of all breast cancers. A 55-year-old Japanese female patient presented with a right breast tumor, which had been detected by mass-screening, and she was admitted to our hospital. The physical examination revealed an elastic hard lump in the upper lateral quadrant of the right breast. The tumor size was approximately 1.0 cm in diameter, and the border was clear. There were no palpable axillary lymph nodes nor supraclavicular nodes. Fine-needle aspiration cytology revealed invasive ductal carcinoma. The patient underwent a partial resection of the right breast (breast conserving therapy) and a right axillary lymphadenectomy. Macroscopically, the resected specimen revealed a white tumor measuring 1.2×1.2×1.0 cm. The TNM classification was diagnosed as T1cN0M0 stage I. Histopathologically, the tumor revealed a proliferation of atypical epithelial cells with apocrine differentiation, arranged in a papillotubular or cribriform growth pattern with stromal invasion. The tumor cells showed irregular round-shaped nuclei often containing prominent nucleoli, and had particularly abundant eosinophilic granular cytoplasm. In the immunohistochemical analysis, these carcinoma cells were positive for Gross Cystic Disease Fluid Protein 15 and the androgen receptor, whereas they were negative for the estrogen and progesterone receptors. Immunohistochemical staining for Her2 using the HercepTest was found to be negative (score 0). Thus, the pathological diagnosis was apocrine carcinoma. There were no metastases in the axillary lymph nodes. The patient has had no recurrence in 8 years after surgery.

Key words: apocrine carcinoma, breast cancer, surgical resection, breast conserving therapy.

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Introduction

Apocrine carcinoma is a rare breast carcinoma variant that accounts for approximately 0.3 to 1% of all breast cancers [1-4]. The inconsistencies in the pathologic criteria of apocrine carcinoma may have resulted in the variety of the reported incidences. The histological appearance of apocrine epithelium in breast cancer was first noted by Krompecher in 1916 [5]. The WHO histological classification of breast tumors indicates that it is a special type of carcinoma [6]. The tumor cells show marked amounts of eosinophilic cytoplasm, and have large nuclei and sharp cell borders. Apocrine carcinomas of the breast have cytological or immunohistochemical features of apocrine differentiation in more than 75-90% of the tumor cell population [7]. The morphological characteristics of apocrine carcinoma are essential points for the pathological diagnosis. We herein report a patient who underwent a surgical resection for apocrine carcinoma of the breast.

Case Report

A 55-year-old Japanese female patient presented with a right breast tumor, which was detected by mass-screening, and the patient was admitted to our hospital. There was no remarkable family history. The physical examination revealed an elastic hard lump with a smooth surface and clear margins in the upper lateral quadrant of the right breast. The tumor size was approximately 1.0 cm in diameter. No skin changes or dimpling were observed. There were no palpable axillary lymph nodes or supraclavicular nodes. All laboratory data were unremarkable, and the tumor markers were within the normal ranges. Mammography (MMG) revealed no findings of a primary tumor. Ultrasonography (US) indicated a hypoechoic lesion measuring 1.1×0.9 cm in diameter. The tumor was nearly oval in shape with a partially lobulated, slightly indistinct surface (Fig. 1). The internal echoic pattern of the tumor was heterogeneous. Contrast-enhanced computed tomography (CT) showed a well-enhanced tumor with an irregular form (Fig. 2). Enhanced magnetic resonance imaging (MRI) revealed a mass of high intensity in the right breast, and intraductal spread was not detected (Fig. 3). The tumor was quickly enhanced following the injection

Fig. 1. The results of the ultrasonographic study. A hypoechoic lesion (*) measuring 1.1×0.9 cm was observed in the right breast with a regularly-shaped, slightly indistinct surface.
Fig. 2. Computed tomography (CT). The contrast-enhanced CT image showed a well-enhanced tumor with an irregular form.

Fig. 3. Enhanced magnetic resonance imaging (MRI). MRI revealed a mass of high intensity. The time-intensity curve shows a peak-and-plateau pattern.

of gadolinium diethylenetriamine-pentaacetic acid, and the time-intensity curve showed a peak-and-plateau pattern. This diagnostic imaging suggested an invasive ductal carcinoma, especially solid-tubular carcinoma. Fine-needle aspiration cytology suggested a malignant tumor.

The patient underwent a partial resection of the right breast (breast conserving therapy) and a right axillary lymphadenectomy. Macroscopically, the resected specimen revealed a white tumor measuring 1.2 × 1.2 × 1.0 cm. Histopathologically, the tumor lesion revealed a proliferation of atypical epithelial cells with marked apocrine differentiation, arranged predominantly in a papillotubular or cribriform growth pattern with stromal invasion, associated with occasional comedo necrosis and desmoplastic fibrosis. The tumor cells showed irregular, round-shaped nuclei containing prominent nucleoli, and had sharply distinct cell borders and characteristically abundant eosinophilic cytoplasm (Fig. 4A, B). In the immunohistochemical analysis, these carcinoma cells were positive for gross cystic disease fluid protein 15 (GCDFP-15) and the androgen receptor (AR) (Fig. 5A, B). Based on these features, the pathological diagnosis was apocrine carcinoma of the breast. Both the estrogen and progesterone receptors were negative in the tumor. An immunohistochemical analysis of HER2 expression using the Hercep Test Ventana Medical Systems, Inc. was found to be negative (score 0). There were no metastases in the axillary lymph nodes. The TNM classification was diagnosed as T1cN0M0 stage I. The surgical margin was pathologically negative. Postoperatively, the patient was administered radiation therapy for the right breast with a total dose of 50 Gy, and adjuvant chemotherapy (5-FU) was administered for 2 years after surgery. The patient has since remained well for 8 years without any evidence of recurrence.
Fig. 4. The histological findings of the tumor. The microscopic findings revealed a proliferation of atypical epithelial cells with irregular and large round-shaped nuclei containing prominent nucleoli, arranged in a papillotubular or cribriform growth pattern with stromal invasion, associated with occasional comedo necrosis and desmoplastic fibrosis. The tumor cells with characteristic apocrine differentiation showed sharply distinct cell borders and abundant eosinophilic granular cytoplasm. A: H. E. staining, B: H. E. staining.

Fig. 5. Immunohistochemical staining of the resected tumor. The tumor cells were positive for gross cystic disease fluid protein 15 (GCDFP-15), and also positive for the androgen receptor (AR). A: GCDFP-15, B: AR.

Discussion

Apocrine carcinoma is a very rare and unique neoplasm of the breast. It is a morphologically distinct type of invasive ductal carcinoma, and accounts for 0.3 to 1% of all breast cancers [1-4]. Apocrine carcinoma is classified as a specific histological type of breast carcinoma according to the 2003 World Health Organization classification [6], and also in the General Rules for Clinical and Pathological Recording of Breast Cancer produced by the Japanese Breast Cancer Society [8]. The apocrine glands are tubular glands which function as scent glands, and normally are found
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at only a few sites like the axilla, anogenital region, and mammary glands. When apocrine carcinoma occurs in the breast, it is also known as sweat gland carcinoma of the breast because of the morphological similarity. Haagensen has used two criteria for identifying apocrine carcinoma of the breast: 1) there is a tendency of the individual tumor cells to extrude their cell cytoplasm into the glandular lumens as secretory snouts, and 2) there are myofibrils identifiable at the base of the peripheral duct cells [9]. The interpretation of the criteria for apocrine carcinoma depends on the report [2].

Apocrine epithelium is observed in a broad spectrum of tissues from benign lesions to invasive carcinoma. Fibrocystic changes, fibroadenomas, hamartomas, papillomas, atypical apocrine hyperplasia, apocrine change in sclerosing adenosis (apocrine adenosis) and apocrine adenoma are all benign breast lesions showing apocrine changes. Controversy remains regarding the relative risk of subsequent carcinoma development from these benign lesions. The origin of apocrine carcinoma has also been debated. For example, the invasive ductal carcinomas often obtain morphological differentiation with the features of obvious apocrine metaplasia [10]. Meanwhile, the apocrine epithelium, such as sclerosing adenosis and atypical cells, is known to be at some risk for developing breast carcinoma [11].

The cytological appearance of apocrine carcinoma differs from that of invasive ductal carcinoma. The tumor cells with apocrine differentiation have sharply distinct cell borders and abundant eosinophilic cytoplasm, with large round or oval nuclei containing prominent macronucleoli [1, 7, 12]. They show nuclear overlapping, more frequent nuclear pleomorphism, increased nuclear/cytoplasmic ratios (N/C ratio) and occasional mitotic figures in comparison to the benign apocrine epithelium [13]. Apocrine carcinomas of the breast have cytological or immunohistochemical features of apocrine differentiation in more than 75–90% of the tumor cell population. Microscopically, apocrine carcinomas are composed of cords, sheets, and occasionally tubules of neoplastic cells, and have the same growth pattern as that of invasive ductal carcinoma [7]. The differential diagnosis of apocrine carcinoma includes histiocyteid carcinoma, oncocytic carcinoma, squamous (metaplastic) carcinoma, granular cell tumors, lipid-rich carcinoma, and apocrine metaplasia seen in ductal adenoma, apocrine change in sclerosing adenosis (apocrine adenosis). The tumor cells in our case showed microscopically stromal invasion as basement membrane-uncovered lesions. Sclerosing adenosis is defined as a benign lobulocentric lesion of disordered acinar, myoepithelial, and connective tissue elements, which can mimic infiltrating carcinoma, and we could not find these proliferative lesions as sclerosing adenosis.

The characteristic steroid receptor expression of these apocrine cells is important for the diagnosis. The immunohistochemical profile of the apocrine differentiation in benign and malignant breast lesions is characterized by positive staining for the AR and consistently negative staining for the estrogen receptors (ERs) and progesterone receptor (PgR) [14]. The apocrine carcinomas tend to express low levels of ER and PgR receptor proteins [3, 15]. AR expression was observed in up to 60–70% of breast carcinomas, and apocrine breast carcinoma was also characterized as being consistently positive for the expression of the AR [14]. Increased testosterone metabolism may be another feature of apocrine differentiation in mammary carcinomas. The Her2 protooncopgene is overexpressed in 10–30% of invasive breast carcinomas [16], and the Her2 status of
apocrine carcinoma was reported to be positive in 40–50% of cases [17]. The apocrine differentiation marker, called gross cystic disease fluid protein-15 (GCDFP-15), is a unique glycoprotein initially isolated from the fluid of the breast cysts. The GCDFP-15 protein is expressed in 75% of apocrine carcinomas and 23% of non-apocrine breast carcinomas [18]. Using the immunoperoxidase technique, GCDFP-15 has been found to localize predominantly to the normal apocrine epithelium. It is also present in apocrine glands at all sites, including metaplastic apocrine epithelium and carcinoma in the breast. However, positive staining has been found to decrease in infiltrating, larger, or metastasizing apocrine carcinomas of the breast [19]. Therefore, the GCDFP-15 staining was frequently negative for advanced cases, and the combined use of another technique with the B72.3 monoclonal antibody (MAb) was recommended to confirm the diagnosis of apocrine carcinoma, especially for advanced tumors [20]. However, Tavassoli et al [21] reported that MAb B72.3 is neither specific nor sensitive for the differential diagnosis of malignant breast lesions, because a positive reaction was observed in 23 of 24 cases of apocrine metaplasia (96%) and 17 of 18 cases of apocrine carcinoma (94%).

Most of the clinicopathological features of apocrine carcinoma don't seem to differ from those of invasive ductal carcinomas. Matsuo et al. reported findings based on the clinicopathological analysis of 12 cases of apocrine carcinoma. In patients with apocrine carcinoma, older age and postmenopausal status were observed more frequently than in those with invasive ductal carcinoma [22]. The percentages of apocrine carcinomas with axillary nodal metastasis and lymphatic invasion were significantly lower in the invasive apocrine carcinoma group than in the invasive ductal carcinoma group ($P = 0.03$ and $0.02$, respectively) [23]. Mossler et al. reported that the prognosis and clinical behavior of apocrine carcinoma was almost the same as that of invasive ductal carcinoma [3]. In contrast, Japeze et al. reported that a significantly better outcome was observed in patients with apocrine carcinoma after adjustment for the tumor grade and axillary status [7]. Matsuo et al. reported three histopathological classifications of apocrine carcinoma according to the pattern of local extension: type I, intraductal spreading type; type II, adenosis-associated type; and type III, infiltrating type. The intraductal spreading type and adenosis-associated type are associated with a favorable prognosis, however, the clinical behavior of the infiltrating type is aggressive, and frequently leads to lymph node metastasis [22]. Our case was characterized by a local spreading pattern mainly involving stromal invasion, thus categorized into the infiltrating type (type III). The tumor cells were associated with lymphatic permeation, however, lymph node metastasis was not observed in this case. Consequently, the clinical behavior of our case was favorable. The histological grade of apocrine carcinoma generally seems to be low, and this low histological grade is consistent with a favorable prognosis. These studies, however, were based on small numbers of patients, and analyses of multi-institutional surveys are therefore needed.

In our case, the carcinoma cells were positive for the AR, GCDFP-15, and negative for the ER and PgR, indicating that the tumor was a pure apocrine carcinoma. The histological grade was relatively low (grade 1), and there was no lymph node metastasis. The patient has remained well for 8 years after treatment without any evidence of recurrence.
References

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乳腺アポクリン癌の1切除例

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要旨：乳腺アポクリン癌は、全乳腺悪性腫瘍のうち0.3〜1%の頻度と稀である。症例は55歳女性。乳癌確定で右乳房の腫瘤を指摘され、精査加療目的で来院された。右乳房C領域に約1cm大の可動性良好な弾性硬腫瘤を触知した。腋窩、鎖骨上窩リンパ節腫大を認めたかった。術前の穿刺細胞診にてinvasive ductal carcinomaと診断し、右乳房温存術および腋窩リンパ節郭清を施行した。腫瘍径は1.2×1.2×1.0cmであった。最終病理組織検査では、核小体が目立つ核と好酸性顆粒状の細胞質をもつ異型細胞が腺管状から腺管状に増殖しており、右乳癌(invasive carcinoma, special type: apocrine carcinoma T1cN0M0 stage I)と診断した。ER(-), PgR(-), Hercep test score 0でTNBC (triple negative breast cancer)であった。術後8年経過しているが、無再発生存中である。

キーワード：アポクリン癌, 乳癌, 手術, 乳房温存療法。

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