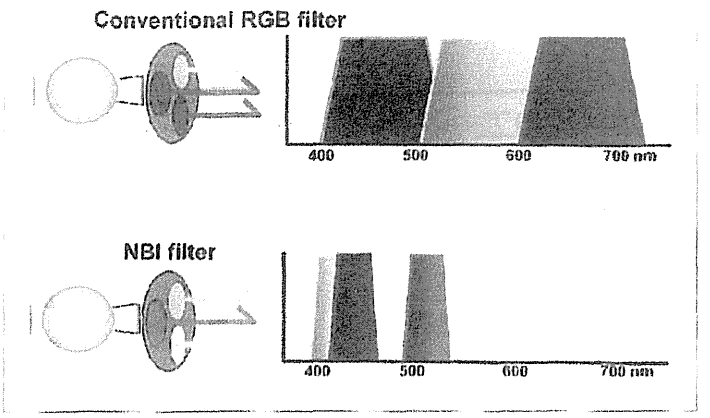

図 1. Narrow band imaging(NBI)システムの観察光
通常光観察では赤，緑，青の光を照射し，白色光としている．NBI では長い波長をカットし，狭帯域化された光を照射している

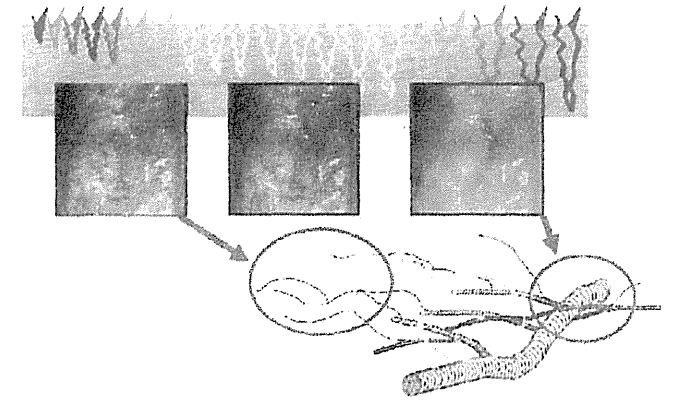

図 2. 観察光の波長による深達度
血液中のヘモグロビンに吸収されやすい狭帯域化された波長の光を照射することにより，粘膜表層の毛細血管，粘膜微細模様の強調表示を行っている

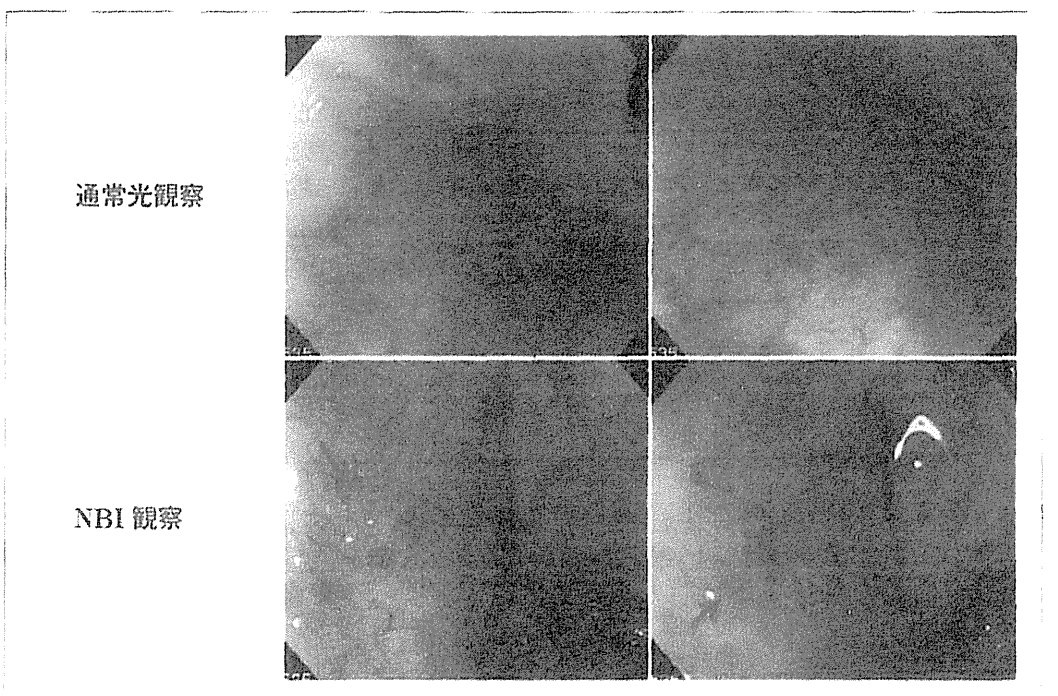

図 3.
下咽頭左梨状陥凹の微小扁平上皮癌の症例
通常光ではわかりにくいが，NBI では血管異型が茶褐色の粘膜領域(brownish area)として明瞭に描出される

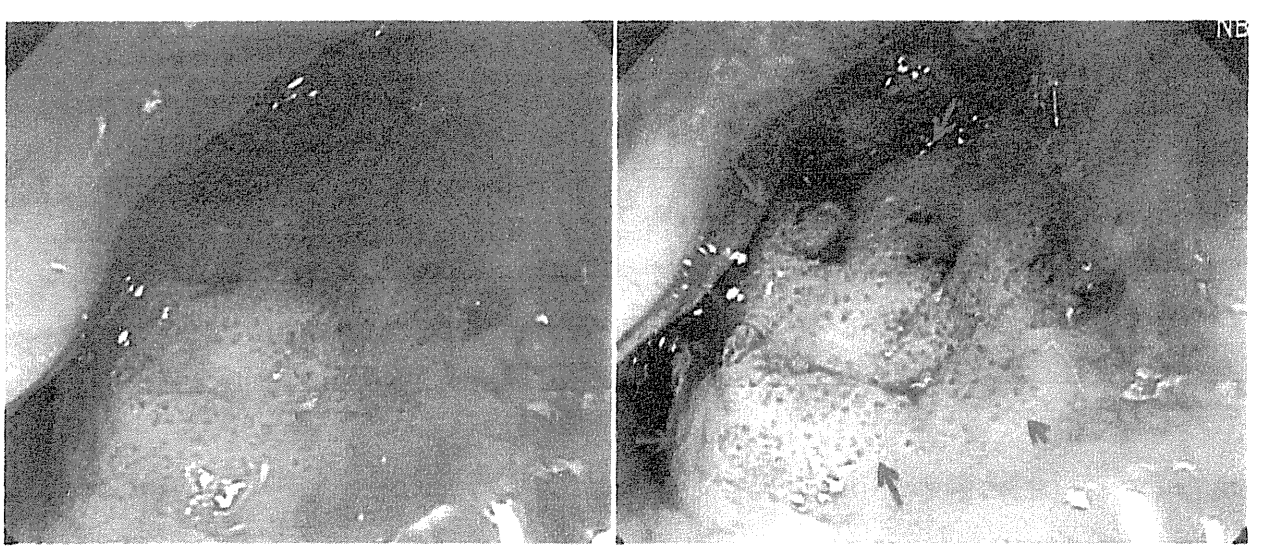

図 4. 喉頭蓋谷の扁平上皮癌
厚みのある病変であり，通常光でも認識は可能 NBI による観察で明瞭に描出される

表 1. オリンパス社製 NBI 対応ファイバー
ENF-VQ, V2, VT2 は経鼻で挿入可能である

	ENF-VQ	ENF-V2	ENF-VT2	GIF-H260Z
視野角	90°	90°	90°	WIDE140° TELE75°
観察深度	5～50 mm	5～50 mm	2～40 mm	WIDE 7～100 mm TELE 1.5～3 mm
先端外形	3.9 mm	3.2 mm	4.8 mm	10.8 mm
挿入部外形	3.6 mm	3.4 mm	4.9 mm	10.5 mm
弯曲角	UP130°/DOWN130°	UP130°/DOWN130°	UP130°/DOWN130°	UP210°/DOWN90° RIGHT100° LEFT100°
有効長	300 mm	300 mm	365 mm	1,030 mm
鉗子チャンネル径	—	—	2.0 mm	2.8 mm
レーザー対応／高周波対応	—	—	○	○

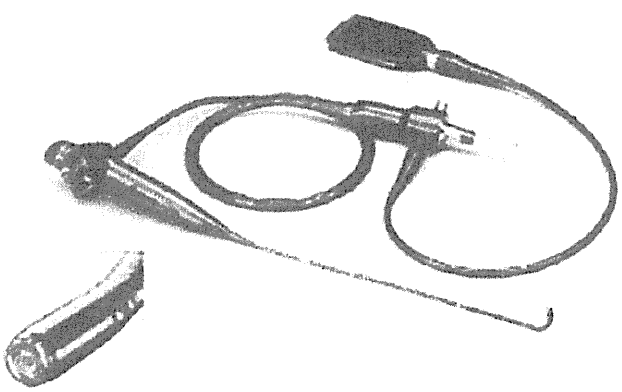

図 5. 経鼻型 NBI 対応ファイバー(オリンパス製)

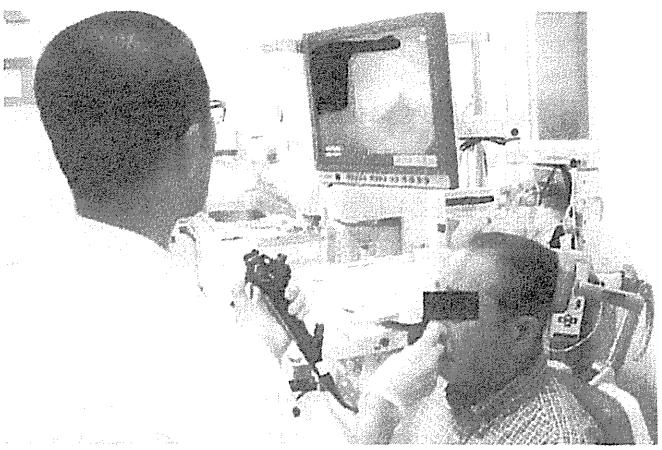

図 6. 外来で NBI を用いた観察を行っている．鼻腔内および咽喉頭のリドカイン噴霧(±アトロピン筋注)で行っている

に観察される．拡大観察によって異型血管が不規則に増生している所見を確認することができる(図 3，4)．

臨床で使用している NBI

現在市販されている耳鼻咽喉科向け NBI システムでは通常の経鼻咽喉頭ファイバーと同様のタイプと経口で使用する上部消化管内視鏡タイプのものがある(表 1)．手元のスイッチで通常光と狭域光の切り替えが可能である．経鼻タイプのもの(外径 3.4～4.9 mm)はこれまでの鼻咽腔・咽喉頭ファイバーに慣れている耳鼻咽喉科医であれば違和感なく使用できる(図 5，6)．

経鼻ファイバーは上咽頭・軟口蓋裏面や舌根の観察を容易に行うことができ，バルサルバ法を行うこともできるが，咽頭後壁が接線方向になるため観察し難い．ファイバーによって太さや解像度，吸引・生検チャンネルの有無などが異なるため症例によって使い分けている．吸引・生検用のチャンネルがないタイプでは唾液や喀痰によって十分に観察できないことがある．唾液の除去のために飲水させたり，アトロピンを使用することがある．出血によって粘膜表面に血液が付着すると NBI では血液が黒色に描出されてしまうため，操作は愛護的に行い，生検は最後に行うようにしている．

上部消化管内視鏡タイプのものは太めであるが，拡大機能や吸引・生検用のチャンネルがついている．唾液の吸引が容易に行え，拡大機能があるため詳細な観察が可能である．経口で挿入することにより咽頭後壁の観察が容易であるが，舌根の観察がやや困難である．耳鼻咽喉科のファイバーと操作が異なり，当院では消化器内科医と連

携して行っている.

目的とする観察部位や患者の条件(鼻腔の狭さ,咽頭反射の強さ,唾液や喀痰などの分泌量)によって使い分けている.

実臨床での使用

当院では,原発不明癌の原発部位の検索,重複癌の検索に多用している.さらに喉頭や咽頭の部分切除術を検討している症例に対して病変の広がりを評価するのに有用である.

原発不明癌の検索

頭頸部粘膜の表在性病変に対するNBIの有用性については2004年に当院の武藤らがNBIを用いて18症例34病変の中下咽頭上皮内癌を検出したことを報告している[2].渡邊らは食道癌患者217例にNBIを用いた頭頸部の観察を行い,6例の上皮内癌患者を検出したと報告している[3].さらに,渡邊らはNBIを用いた観察は通常光と比較して感度,特異度,正診率いずれも優れていたと報告している[4].当院から鵜久森らがNBIを用いた観察が通常光による観察と比較して血管異型の検出および病変境界の描出に優れていると報告している[5].堅田らは口腔癌の検出においてもNBIが有用であると報告している[6].

我々は2006年6月～2009年7月の間に原発不明扁平上皮癌頸部リンパ節転移で当院を受診し,通常光ファイバーで原発巣を検出できなかった19例に対してNBIおよびPETで精査を行った.

表2. NBIによる原発巣の検出
初診時に通常光ファイバーで原発不明と診断された扁平上皮癌頸部リンパ節転移19症例に対してNBIとPETで精査した.NBIによって2例に扁平上皮癌を検出することができた.そのうち1例は下咽頭原発扁平上皮癌,頸部リンパ節転移と診断された

初診時通常光ファイバーで原発不明と診断された扁平上皮癌頸部リンパ節転移19症例
- NBIで下咽頭1例と中咽頭1例を確認(PET陰性)
  - 下咽頭は梨状陥凹の厚みのある病変からscc.原発巣と考えられた.
  - 中咽頭は表在病変からsccを認めたが原発巣との断定には至らず.
- 上部消化管内視鏡で食道癌1例
- PETで肺癌1例,皮膚癌1例
- 全麻生検で舌根癌1例
- 14例は原発不明→1例のみ2年後に口蓋扁桃からscc

NBIによる観察によって19例中2例で病変を検出している(表2).下咽頭の一例は梨状陥凹先端近くに厚みのある病変が存在していた.NBIによって病変を認識し,生検で扁平上皮癌を確認した.中咽頭の1例は口蓋扁桃付近の表在性の扁平上皮癌であった.頸部リンパ節転移の原発巣とは断定できない小さな病変である.この2例はいずれもPETでは原発巣に集積を認めていない.原発不明扁平上皮癌に対してはPETのみならず,NBIを用いた検索は有用といえる.

切除範囲の決定

当院では咽喉頭の表在癌に対して消化器内科と連携して経口内視鏡による切除を行っている(図7,8).全身麻酔下に咽喉頭を観察し,表在性のものは内視鏡で,深部浸潤があるものは外切開を併用している.NBIも併用するが,出血によって所

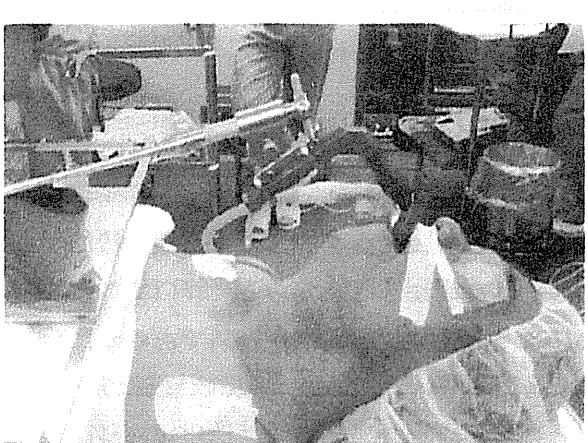

図7. 全身麻酔下に弯曲型喉頭鏡で咽喉頭を展開

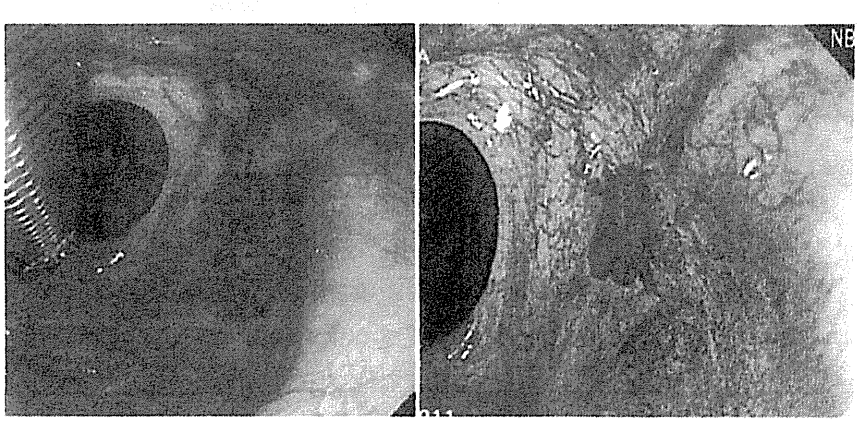

図8. 全身麻酔下にNBIで下咽頭を観察.右梨状陥凹に表在癌を認める.内視鏡で切除した

見が十分に取れなくなることがあるため，ルゴール散布による切除範囲の決定を行っている．堅田らは化学放射線療法後の症例においてもNBIによる病変範囲の確認が有効と報告している[7]．今後増加するであろう放射線治療の評価や再発診断の1つとして期待される．

まとめ

頭頸部領域でのNBIの有用性について述べた．NBIは原発巣の検出や病変範囲の確認に有用である．

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CLINICAL TRIAL

Phase III randomized adjuvant study of tamoxifen alone versus sequential tamoxifen and anastrozole in Japanese postmenopausal women with hormone-responsive breast cancer: N-SAS BC03 study

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Abstract Clinical trials conducted in Western countries have shown that aromatase inhibitors are associated with better disease-free survival (DFS) than tamoxifen in postmenopausal early breast cancer. Because pharmacogenetic differences in drug-metabolizing genes may cause ethnic differences, assessment of the efficacy and tolerability of aromatase inhibitors in non-white women is warranted. This open-label, randomized clinical trial included 706 postmenopausal Japanese women with hormone-receptor-positive breast cancer, who had received tamoxifen for 1 to 4 years as adjuvant therapy. This study was closed early after entry of ~28% of the initially planned patients. They were randomly assigned to either switch to anastrozole or to continue tamoxifen for total treatment duration of 5 years. Primary endpoints were DFS and adverse events. At a median follow-up of 42 months, the unadjusted hazard ratio was 0.69 (95% confidence interval, 0.42–1.14; $P = 0.14$) for DFS and 0.54 (95% CI, 0.29–1.02; $P = 0.06$) for relapse-free survival (RFS), both in favor of anastrozole. The incidence of thromboembolic events in

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the tamoxifen group and bone fractures in the anastrozole group was not excessively high. Switching from tamoxifen to anastrozole was likely to decrease disease recurrence in postmenopausal Japanese breast cancer patients. Ethnic differences in major adverse events may be attributable to a low baseline risk of these events in Japanese.

Keywords Adjuvant therapy · Anastrozole · Breast cancer · Ethnic difference · Hormonal therapy · Tamoxifen

Introduction

The incidence of breast cancer in Japanese women is increasing, while it remains much lower than that in Western women [1]. Nonetheless, breast cancer has been the most common type of cancer in Japanese women since the 1990s [1]. Mortality from breast cancer is decreasing in Western countries owing to the increased use of screening mammography and adjuvant therapy [2], but continues to increase in Japan. As for adjuvant therapy, most newly developed drugs are available in Japan, but data from randomized controlled trials in Asian women are often lacking.

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Tamoxifen, classified as a selective estrogen-receptor modulator, for 5 years has been the gold standard for adjuvant hormonal therapy in women with early breast cancer. Although tamoxifen is generally well tolerated, it can cause serious complications such as endometrial cancer or deep venous thrombosis [3]. Tamoxifen significantly decreases disease recurrence and increases overall survival (OS) irrespective of nodal status and age [4], but some patients become resistant to tamoxifen and have recurrence. Therefore, the development of improved strategies is awaited. Randomized controlled trials have compared aromatase inhibitors with tamoxifen for adjuvant treatment in postmenopausal women with hormone-responsive breast cancer. Studies comparing 5 years of treatment with anastrozole or letrozole with 5 years of treatment with tamoxifen showed a 15% improvement in disease-free survival (DFS) at 100 months [5] or an 18% reduction in the risk of an event at 51 months [6]; however, neither study showed a significant improvement in OS. Switching from tamoxifen to aromatase inhibitors has been also compared with tamoxifen for 5 years, given for a total of 5 years. Switching from tamoxifen to anastrozole improved DFS by 65% at 36 months in one study [7] and by 40% at 28 months in another [8]. In another randomized trial, switching from tamoxifen to exemestane improved DFS by 32% at 31 months [9].

These clinical trials were conducted in Western countries and included only small numbers of Asian women. When we apply these results to Asian populations, ethnic differences in drug metabolizing genes such as cytochrome P450 (CYP)2D6 genotype may be appreciable, because CYP2D6 metabolizes tamoxifen into its more potent metabolite, endoxifen. Polymorphisms of the CYP2D6 gene may thus alter the response to tamoxifen [10]. About 10% of whites are classified as inactive metabolizers of tamoxifen, resulting in decreased turnover of tamoxifen into its active metabolite, endoxifen [11]. In contrast, less than 1% of Japanese are inactive metabolizers of tamoxifen, and about 20% are intermediate metabolizers [12]. Such ethnic differences in the CYP2D6 gene may lead to differences between whites and Japanese in the efficacy and safety of tamoxifen, especially when compared with those of aromatase inhibitors. This situation is further complicated by the fact that the distribution of CYP19 gene (aromatase) polymorphisms differs among distinct ethnic populations [13], potentially causing differences between whites and Japanese in the efficacy and safety of aromatase inhibitors. In fact, one placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women with early breast cancer showed that letrozole improved DFS in whites, but not in women from minority groups [14]. Therefore, clinical trials assessing the efficacy and safety of aromatase inhibitors in non-white women are warranted.

Here, we report the results of switching adjuvant therapy from tamoxifen to anastrozole in postmenopausal Japanese women with breast cancer who were enrolled in an open-label, randomized clinical trial, designated the N-SAS BC03 study (UMIN CTRID: C000000056).

Study design

This study was a multi-institutional, open-label, randomized control trial, designed to compare the efficacy and safety of tamoxifen with those of tamoxifen followed by anastrozole in postmenopausal women with hormone-responsive breast cancer, who remained disease-free after having received tamoxifen for 1 to 4 years as adjuvant therapy. The subjects were randomly assigned to continue to receive tamoxifen (20 mg per day) or to switch to anastrozole (1 mg per day). The total duration of treatment was 5 years (Fig. 1). The primary endpoints were DFS and adverse events. The secondary endpoints were relapse-free survival (RFS), OS, and the health-related quality of life (HRQOL). At the time of randomization, treatment assignments were adjusted according to the following factors: clinical stage (I, IIA, IIB/IIIA/IIIB) [15]; the number of metastases to axillary lymph nodes (0/1–3/more than 3); HER2 status (unknown/0, 1+, 2+/3+); tumor size (<3 cm/ ≥3 cm), estrogen receptor (ER) and progesterone receptor (PR) status (ER[+], PR[+]/ER[+], PR[−]/ER[−], PR[+]); type of surgery (breast-conserving surgery/mastectomy); duration of tamoxifen administration (1.0–<2.0 years/2.0–4.0 years); age (younger than 60 years/60 years or older); chemotherapy (performed/not performed); and institution. Menopause in this study was defined as follows: an age of > 60 years, an age of > 45 years with amenorrhea for 1 year or longer without hysterectomy, or bilateral ovariectomy.

Patients and methods

Eligible patients were postmenopausal women who had undergone surgery for histologically confirmed stage I, IIA, IIB, IIIA, or IIIB [15] unilateral primary invasive breast cancer that was positive for estrogen receptor, progesterone receptor, or both; all patients had postoperatively received adjuvant tamoxifen for 1 to 4 years. Patients also had to be younger than 75 years and to have adequate organ functions at the time of enrollment. Diagnostic imaging studies, including chest radiography (or computed tomography), abdominal ultrasonography (or computed tomography), bone scintigraphy (or radiography), and mammography, were performed within 6 months before the day of enrollment and repeated annually thereafter. Adjuvant therapy should have been started within 12 weeks after surgery. Preoperative endocrine therapy with tamoxifen or preoperative chemotherapy was allowed. Patients were excluded if they had any of the following conditions: invasive cancer in other organs for which treatment was not completed within 5 years; a medical history of deep venous thrombosis; or osteoporosis requiring treatment or a medical history of bone fracture due to osteoporosis. Follow-up of the patients was scheduled as follows: physical examination was scheduled every 3 months for 1 year, for every 6 months from year 2 to five, and annually thereafter by year 10. Diagnostic imaging was scheduled annually that included chest X-ray or CT, abdominal ultrasonography or CT, bone X-ray or bone scan.

Data on the following prespecified adverse events were prospectively collected: hot flashes, nausea, anorexia, fatigue/asthenia, mood alteration, headache, arthralgia, leukocytopenia, hepatic dysfunction (aspartate aminotransferase and alanine aminotransferase), ischemic cerebrovascular disorders, ischemic cardiovascular disorders, thrombosis (including all types), genital bleeding, vaginal discharge, bone fracture and endometrial cancer. Data on adverse events were prospectively collected at 3-month intervals for the first year and at 6-month intervals thereafter for a total of 5 years after randomization. Toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. HRQOL was also assessed; the results will be presented elsewhere (Ohsumi S et al., in preparation).

Written informed consent was obtained from all subjects after they had received an explanation of the clinical trial. The protocol was approved by the institutional review board of each participating institution before enrollment began. The trial was conducted in accordance with the Declaration of Helsinki (1996 revision).

Statistics

Eligible patients were randomly assigned to continue tamoxifen or to switch to anastrozole in a ratio of 1:1 according to the allocation adjustment factors described above, using a dynamic allocation method. DFS and RFS were calculated from the date of randomization to the date of confirmation of an initial event. All of the following

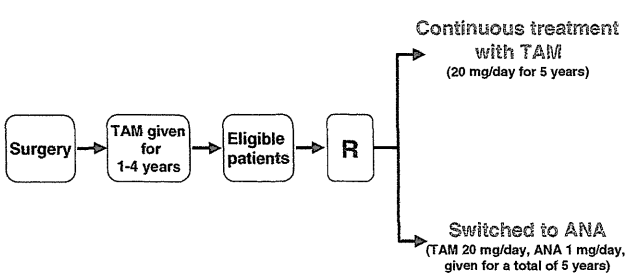

Fig. 1 Study design. *TAM* tamoxifen, *ANA* anastrozole

were considered events for DFS: locoregional relapse, distant metastasis, asynchronous cancer or secondary cancer (except skin basal cell cancer/spinocellular cancer and uterine intraepithelial cancer), and death from any cause. The data were censored on the day on which the above events were last confirmed to be absent or on the day on which survival was last confirmed for survivors. Events for RFS were locoregional relapse and distant metastasis. The data were censored on the day on which the above events were last confirmed to be absent, on the day of occurrence of asynchronous or secondary cancer, or on the day on which none of the above events was confirmed. For patients who died with none of the above events confirmed, data were censored on the date of death.

This study was designed to test the hypothesis that switching to anastrozole from tamoxifen does not worsen outcomes (non-inferiority) or improves outcomes (superiority). Non-inferiority in terms of DFS, OS, and RFS was to be tested at the acceptable upper limit of the hazard ratio (anastrozole group vs. tamoxifen group) of 1.1 and a significance level of 2.5% (one-sided). We initially set the target number of patients at 2,500. Because recruitment was slower than anticipated and the results of other clinical trials comparing tamoxifen with aromatase inhibitors appeared, we decided to terminate accrual at the end of 2005 after an accrual of a total of 706 patients. Statistical considerations were amended in October 2007 on the basis of the following reported hazard ratios of aromatase inhibitors versus tamoxifen: 0.68 in the IES031 [9], 0.60 in the ARNO95/ABCSG8 [8], and 0.35 in the ITA [7]. The numbers of events required to demonstrate the non-inferiority of anastrozole to tamoxifen at a hazard ratio of 1.1 were 51 and 85, respectively, assuming a hazard ratio of anastrozole over tamoxifen of 0.50 or 0.60, an alpha value of 0.025 (unilateral), and a power of 80%, based on the method of Lakatos and Lan [16]. Sixty-five or 120 events were required to demonstrate the superiority of anastrozole over tamoxifen under the same conditions. An interim analysis of efficacy endpoints was planned when the 50% of the estimated events were reached so that the disadvantageous treatment arm would not be continued if the interim results failed to demonstrate non-inferiority of the anastrozole group on the basis of Bayesian predictive power less than 5 to 10% or if the anastrozole group showed remarkable superiority over the tamoxifen group.

Results

Patients

From November 2002 through December 2005, a total of 706 patients (tamoxifen group, $n = 352$; anastrozole group, $n = 354$) were recruited at 71 institutes in Japan. Three patients in the tamoxifen group and seven in the anastrozole group did not start the allocated treatment and were excluded from analysis. The full analysis set thus consisted of 696 patients (tamoxifen group, $n = 349$; anastrozole group, $n = 347$). The demographic characteristics of the patients are shown in Table 1. Baseline characteristics were well balanced between the two groups.

Table 1 Patients' characteristics

Age (mean ± SD)	TAM ($n = 349$) 60.2 ± 7.4	ANA ($n = 347$) 59.5 ± 7.4	*P* value 0.19
Stage			
I	142 (40.7)	148 (42.7)	0.83
IIA	134 (38.4)	123 (35.4)	
IIB	50 (14.3)	51 (14.7)	
IIIA	12 (3.4)	12 (3.5)	
IIIB	11 (3.2)	13 (3.7)	
Pathological tumor size			
<3 cm	276 (79.1)	276 (79.5)	0.88
≥3 cm	73 (20.9)	71 (20.5)	
Nodal status			
0	210 (60.2)	206 (59.4)	0.82
1–3	99 (28.4)	102 (29.4)	
4–9	30 (8.6)	22 (6.3)	
10–	10 (2.9)	17 (4.9)	
ER			
Positive	325 (93.1)	322 (92.8)	0.87
Negative	24 (6.9)	25 (7.2)	
PR			
Positive	273 (78.2)	272 (78.4)	0.96
Negative	76 (21.8)	75 (21.6)	
Type of Surgery			
Breast-conserving surgery	181 (51.9)	182 (52.4)	0.88
Mastectomy	168 (48.1)	165 (47.6)	
HER2			
0, 1+, 2+	164 (47.0)	165 (47.6)	0.99
3+	13 (3.7)	13 (3.7)	
Unknown	172 (49.3)	169 (48.7)	
Chemotherapy			
+	186 (53.3)	187 (53.9)	0.87
–	163 (46.7)	160 (46.1)	

Values in parenthesis are in percentage

TAM tamoxifen, *ANA* anastrozole

Efficacy endpoints

The present analysis was conducted at a median follow-up period of 42 months (range, 3.2–60 months) according to

the statistical amendment described above. There were 26 DFS-related events in the anastrozole group as compared with 37 in the tamoxifen group, and 15 RFS-related events in the anastrozole group as compared with 28 in the tamoxifen group. The unadjusted hazard ratios were 0.69 (95% CI, 0.42 to 1.14; $P = 0.14$ by the log-rank test) for DFS (Fig. 2) and 0.54 (95% CI, 0.29–1.02; $P = 0.06$ by the log-rank test) for RFS (Fig. 3), both in favor of anastrozole. Distribution of events was shown in Table 2. There was no significant difference in OS ($P = 0.59$). The estimated 3-year rate of DFS was 90.7% (95% CI, 87.5–93.8%) in the tamoxifen group and 94.3% (95% CI, 91.7–96.9%) in the anastrozole group. The estimated 3-year rate of RFS was 93.1% (95% CI, 90.3–95.8%) in the tamoxifen group and 96.6% (95% CI, 94.6–98.6%) in the anastrozole group. There were four deaths in the anastrozole group, including one due to breast cancer, as compared with six deaths in the tamoxifen group, including three due to breast cancer. The estimated 3-year rate of OS was 98.8% (95% CI, 97.5–100%) in the tamoxifen group and 99.6% (95% CI, 98.8–100%) in the anastrozole group. On the basis of these results, the independent data-monitoring committee recommended to make this analysis to be final and to release the data.

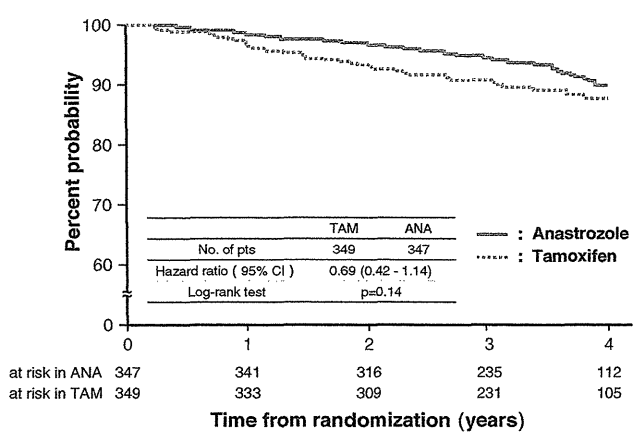

Fig. 2 Kaplan–Meier probability of disease-free survival. *TAM* tamoxifen, *ANA* anastrozole

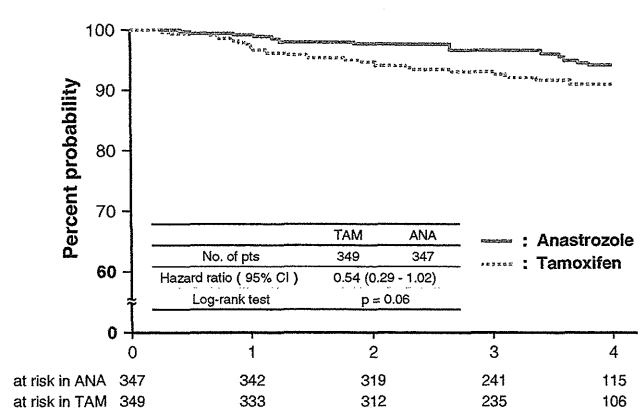

Fig. 3 Kaplan–Meier probability of relapse-free survival. *TAM* tamoxifen, *ANA* anastrozole

Table 2 Distribution of events

Event	TAM ($n = 349$)	ANA ($n = 347$)
Local recurrence	7	4
Distant recurrence	20	11
Primary cancer in the contralateral breast	2	2
Intercurrent death	1	2
Second primary non-breast cancer	7	7
Total	37	26

TAM tamoxifen, *ANA* anastrozole

A subgroup analysis was planned to explore the interactions of anastrozole or tamoxifen with stratified factors on disease-free survival (Fig. 4). The beneficial effect of anastrozole over tamoxifen was suggested in node-positive patients, those who were younger than 60 year old, those who have had mastectomy, those who had tamoxifen administration for 1–2 years or those who have had adjuvant chemotherapy.

Safety endpoints

Predefined adverse events which were collected prospectively are summarized in Table 3. Menopausal symptoms such as hot flashes and vaginal discharge were more common in the tamoxifen group (44.7 vs. 36.3% and 24.4 vs. 16.1%), and arthralgia was more common in the anastrozole group (31.8 vs. 50.4%), of which differences were statistically significant. There were no thromboembolic events in the tamoxifen group, and there was one grade four event in the anastrozole group. The number of patients who had bone fractures was nine in tamoxifen group and five in anastrozole group. Contralateral breast cancer was reported in two patients in the tamoxifen group and two in the anastrozole group. Second malignancies other than contralateral breast cancer were reported in seven patients in the tamoxifen group (including one endometrial cancer) and seven in the anastrozole group (including no endometrial cancer).

Discussion

The role of tamoxifen as the gold standard for adjuvant hormonal treatment in postmenopausal women with early

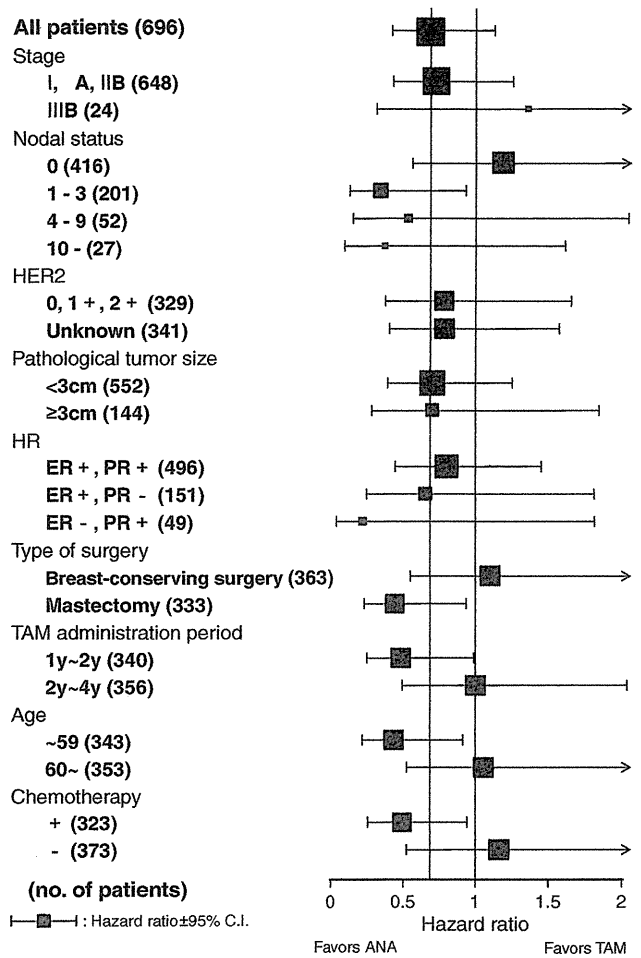

Fig. 4 Subgroup analysis of disease-free survival. The hazard ratio was not able to be estimated in subgroups of stage IIIA and Her2 3+ , because of the lack of event in the anastrozole group. *TAM* tamoxifen, *ANA* anastrozole

breast cancer has been challenged by aromatase inhibitors in several clinical trials. The use of aromatase inhibitors was consistently associated with a modest decrease in disease recurrence as compared with tamoxifen. There are three basic treatment strategies for aromatase inhibitors: aromatase inhibitors can be given from the start of adjuvant treatment for 5 years (initial strategy); aromatase inhibitors can be given after initial treatment with tamoxifen for a combined total of 5 years (switch strategy); or aromatase inhibitors can be given after 5 years of treatment with tamoxifen.

In this study, we compared tamoxifen for 5 years with tamoxifen for 1 to 4 years, followed by anastrozole for a total treatment period of 5 years in Japanese population (switch strategy). The unadjusted hazard ratio was 0.69 (95% CI, 0.42–1.14) for DFS and 0.54 (95% CI, 0.29–1.02) for relapse-free survival (RFS), both in favor of anastrozole. The range of the 95% CI was large because of the relatively small number of events, but the hazard ratio of 0.69 for DFS in our study was in line with the results of previous clinical trials in which tamoxifen was switched to aromatase inhibitors [7–9, 17, 18]. Therefore, our study provides the first evidence that switching to aromatase inhibitor from tamoxifen is as effective in Asian women as in Western women irrespective of ethnic differences in polymorphisms of the CYP2D6 or CYP19 genes, and also suggests that aromatase inhibitors would also be effective in the initial strategy.

A planned subgroup analysis suggested that progesterone receptor status did not influence the efficacy of anastrozole. Benefit of anastrozole seen in patients with node positive, those who have had mastectomy or adjuvant chemotherapy suggested that the superiority of anastrozole was evident in patients with more advanced disease. We could assess the better timing to switch to anastrozole by this subgroup analysis which has not been reported previously, because the duration of tamoxifen therapy in the present study was allowed between 1 and 4 years.

Data on predefined adverse events were prospectively collected to monitor the safety profile of anastrozole as compared with that of tamoxifen. Overall, the safety profile was similar to that obtained in studies of Western women in terms of menopausal symptoms and arthralgia, but there were some differences. Hot flashes and vaginal discharge were more common in the tamoxifen group. Arthralgia was more common and more severe in the anastrozole group. In contrast to the studies conducted in Western countries, the fracture rate was lower in the anastrozole group ($n = 5$) than in the tamoxifen group ($n = 9$), also this difference was not statistically significant. Vertebral fractures occurred in one patient in the anastrozole group and three in the tamoxifen group. Hip fractures occurred in zero patients in the anastrozole group and one in the tamoxifen group. The reason for the lower frequency of fractures in the anastrozole group is unclear. This might have happened by chance, or because patients who required medication for osteoporosis were excluded, or because Japanese women who receive anastrozole are less likely to have bone fractures. The last hypothesis is supported by the presence of ethnic differences in the baseline fracture risk, with Asian populations having the lowest risk [19]. Further studies are needed to draw firm conclusions, but this issue is important because the risk of bone fractures, one of the most serious adverse effects of anastrozole, might be negligible in Japanese women. Another important finding of our study was that the incidence of thromboembolic events was very low in both groups, i.e., only one patient in anastrozole group or 0.14% of the entire study group. Because the baseline risk of idiopathic deep venous thrombosis in Asians is much lower than that in whites [20], our results suggest that the risk of deep venous thrombosis, one of the most serious toxic effects of tamoxifen, may be negligible in Japanese women.

Table 3 Adverse events

	TAM (n = 349)					ANA (n = 347)					P value
	G1	G2	G3	G4	G1-4	G1	G2	G3	G4	G1-4	
Leukopenia	67	9	0	0	76 (21.8)	60	13	0	0	73 (21.0)	0.91
AST, ALT	87	10	2	0	99 (28.4)	95	8	4	1	108 (31.1)	0.34
Anorexia	19	1	0	0	20 (5.7)	18	1	0	0	19 (5.5)	0.89
Nausea and vomiting	20	2	0	0	22 (6.3)	24	1	0	0	25 (7.2)	0.77
Hot flash	142	14	0	0	156 (44.7)	114	12	0	0	126 (36.3)	0.04
Fatigue	86	3	0	0	89 (25.5)	86	5	1	0	92 (26.5)	0.55
Mood fluctuations	61	2	0	0	63 (18.1)	56	3	0	0	59 (17.0)	0.81
Headache	55	1	0	0	56 (16.0)	60	2	1	0	63 (18.2)	0.33
Joint pain (arthralgia)	100	9	2	0	111 (31.8)	140	27	8	0	175 (50.4)	<0.01
Genital bleeding	28	0	0	0	28 (8.0)	28	4	0	0	32 (9.2)	0.31
Vaginal discharge	84	1	0	0	85 (24.4)	54	2	0	0	56 (16.1)	0.01
Heart disease	0	0	0	3	3 (0.9)	0	0	0	2	2 (0.6)	0.66
Thrombosis/embolism	0	0	0	0	0 (0.0)	0	0	0	1	1 (0.3)	0.32
Bone fracture	9				9 (2.6)	5				5 (1.4)	0.29
Endometrial cancer	n.a.	n.a.	n.a.	1	1 (0.3)	n.a.	n.a.	n.a.	0	0 (0.0)	0.32

Values in parenthesis are in percentage

TAM tamoxifen, *ANA* anastrozole

In conclusion, our study provided additional evidence that switching to anastrozole from tamoxifen for a total treatment period of 5 years is likely to be of benefit for postmenopausal Japanese women with early breast cancer actually being treated with tamoxifen than continued treatment with tamoxifen for 5 years. The toxicity profile of this regimen in Japanese women differed in some respects with that previously reported in Western women.

Acknowledgments We are indebted to all women who participated in the study. We thank all physicians contributing to this trial. We thank Mizuki Yamauchi and Yumiko Nomura for data management, and Hitoshi Masuda for his editorial assistance. This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html). The pharmaceutical manufacturer/distributor who had provided financial contribution as a corporate sponsor took no part in this study other than providing information relevant to proper use of the study drugs. All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

Appendix

The list of participants is shown in Table 4.

Table 4 Participating institutions

Participating institution	Investigator	Participating institution	Investigator
NHO Shikoku Cancer Center	K. Aogi	Toho University Sakura Medical Center	Y. Park
Jichi Medical University Hospital	Y. Hozumi	Seirei Hamamatsu General Hospital	M. Yoshida
National Cancer Center Hospital East	S. Imoto	Nagoya City University Hospital	H. Iwase
Kansai Rosai Hospital	T. Aihara	Kinki University Hospital	M. Watatani
Aichi Cancer Center Hospital	H. Iwata	Osaka Koseinenkin Hospital	E. Shiba
National Cancer Center Hospital	T. Watanabe	Yodogawa Christian Hospital	K. Wakita
Shizuoka General Hospital	K. Nakagami	Miyoshi Central Hospital	Y. Kai
Hokkaido Cancer Center	M. Tamura	NHO Kure Medical Center	M. Koseki
Rinku General Medical Center	T. Ito	NHO Tokyo Medical Center	T. Hojo
Osakahu-Saiseikai Tondabayashi Hospital	N. Ogino	Kanagawa Cancer Center	T. Asaga
Hiroshima City Asa Hospital	K. Hisamatsu	Aichi Medical University Hospital	S. Nakano
Kitakyushu Municipal Medical Center	S. Mitsuyama	Shimane Prefectural Central Hospital	H. Hikino
Shiga University of Medical Science Hospital	H. Abe	Okayama University Hospital	H. Doihara

Table 4 continued

Participating institution	Investigator	Participating institution	Investigator
NHO Osaka National Hospital	E. Shin	NHO Sendai Medical Center	T. Watanabe
Ashikaga Red Cross Hospital	H. Tokura	The Institute of Medical Science, The University of Tokyo	H. Tahara
NHO Nagasaki Medical Center	Y. Tokunaga	Osaka Medical Center for Cancer and Cardiovascular Diseases	H. Inaji
Sakai Municipal Hospital	N. Masuda	Kochi Prefectural Hata Kenmin Hospital	S. Ozaki
NHO National Kyushu Cancer Center	S. Ohno	Asahikawa Medical College Hospital	K. Yamazaki
St. Luke's International Hospital	S. Nakamura	Tokyo Metropolitan Komagome Hospital	M. Toi
Yokohama Rosai Hospital	H. Arioka	Kanazawa University Hospital	K. Tsugawa
Toyokawa City Hospital	Y. Ito	Fukui Red Cross Hospital	F. Tanaka
Matsuyama Red Cross Hospital	S. Tsutsui	Yurin Koseikai Fuji Hospital	N. Sonoda
Mitsui Memorial Hospital	T. Nishi	Nagoya Kyouritsu Hospital	A. Naito
Kochi Medical School Hospital	T. Sugimoto	Minoh City Hospital	H. Yamamoto
Akita City Hospital	T. Hashizume	Kinki Central Hospital	K. Kobayashi
Chiba Cancer Center	N. Yamamoto	Kyushu University Hospital	Y. Maehara
Fukuroi Municipal Hospital	T. Tamauchi	Tochigi Cancer Center	J. Ando
Hiroshima University Hospital	A. Osaki	Kyorin University Hospital	H. Fukushima
Saitama Cancer Center	K. Suemasu	Yamato Municipal Hospital	A. Suto
Saitma Red Cross Hospital	T. Saito	West Medical Center Jouhoku Municipal Hospital City of Nagoya	T. Yamashita
Tokai University Hospital	Y. Tokuda	Kyoto First Red Cross Hospital	T. Ri
Niigata Prefectural Sakamachi Hospital	H. Makino	Okayama Saiseikai General Hospital	H. Kimura
Osaka-hu Saiseikai Senri Hospital	K. Yamazaki	Uwajima City Hospital	K. Okada
Kumamoto Municipal Hospital	R. Nishimura	Iizuka Hospital	M. Hashimoto
Hirosaki University School of Medicine and Hospital	Y. Hirao	Sasebo Municipal General Hospital	S. Hara
Sakata Medical Center	Y. Asato		

NHO National Hospital Organization

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DIAGNOSTIC PATHOLOGY

CASE REPORT Open Access

Two cases of breast carcinoma with osteoclastic giant cells: Are the osteoclastic giant cells pro-tumoural differentiation of macrophages?

Yukiko Shishido-Hara[1], Atsushi Kurata[1], Masachika Fujiwara[1], Hiroki Itoh[2], Shigeru Imoto[2], Hiroshi Kamma[1*]

Abstract

Breast carcinoma with osteoclastic giant cells (OGCs) is characterized by multinucleated OGCs, and usually displays inflammatory hypervascular stroma. OGCs may derive from tumor-associated macrophages, but their nature remains controversial. We report two cases, in which OGCs appear in common microenvironment despite different tumoural histology. A 44-year-old woman (Case 1) had OGCs accompanying invasive ductal carcinoma, and an 83-year-old woman (Case 2) with carcinosarcoma. Immunohistochemically, in both cases, tumoural and non-tumoural cells strongly expressed VEGF and MMP12, which promote macrophage migration and angiogenesis. The Chalkley count on CD-31-stained sections revealed elevated angiogenesis in both cases. The OGCs expressed bone-osteoclast markers (MMP9, TRAP, cathepsin K) and a histiocyte marker (CD68), but not an MHC class II antigen, HLA-DR. The results indicate a pathogenesis: regardless of tumoural histology, OGCs derive from macrophages, likely in response to hypervascular microenvironments with secretion of common cytokines. The OGCs have acquired bone-osteoclast-like characteristics, but lost antigen presentation abilities as an anti-cancer defense. Appearance of OGCs may not be anti-tumoural immunological reactions, but rather pro-tumoural differentiation of macrophage responding to hypervascular microenvironments induced by breast cancer.

Background

Breast carcinoma with osteoclastic giant cells is a rare entity that falls under the WHO classification of invasive ductal carcinoma, not otherwise specified [1]. This tumor is characterized by the presence of osteoclastic giant cells (OGCs), the nature of which remains controversial. OGCs accompany a variety of breast tumors, including invasive ductal carcinoma and cribriform, tubular, mucinous, papillary, lobular, squamous, and other metaplastic patterns. Despite divergent tumor histology, most cases present a well-demarcated mass with characteristic inflammatory and hypervascular stroma [2].

OGCs are agreed to be of histiocytic origin, and are hypothesized to derive from macrophages [3]. Macrophages display marked plasticity with both pro-tumoural and anti-tumoural activities [4-6]. Their classical anti-tumoural roles include promotion of specific immunity by inducing T cell activation via antigen presentation. Recent studies have also focused on their direct or indirect pro-tumoural functions: enhancement of angiogenesis and cancer cell growth and spread [4,6]. Macrophages secrete growth factors such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF), and produce proteases including matrix metalloproteinases (MMPs). Both VEGF and MMP12 enhance macrophage migration [7,8], and VEGF also regulates angiogenesis and lymphangiogenesis through different types of receptors. Microenvironments, with secretion of cytokines, seem to affect progression of breast cancer [9,10], and may also determine whether OGCs are formed. However, in current thinking, the prognosis of breast carcinoma with OGCs is considered to be related to the tumoural histology, and not influenced by the presence of OGCs [1].

Here, we report two cases of breast carcinoma with OGCs associated with invasive ductal carcinoma (Case 1) or carcinosarcoma (Case 2). Despite different tumoural histology, two cases displayed common microenvironments with expression of VEGF and MMP12, suggesting enhanced macrophage migration and

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angiogenesis. The OGCs presented phenotypic resemblance to the osteoclasts in the bone, and lacked antigen presentation abilities. Macrophage plasticity responding microenvironments is discussed, in relation to prognosis of breast carcinoma.

Case Presentation

Case 1: A 44-year-old woman presented with a lump in the lower inner quadrant of her right breast. Physical examination revealed a well-demarcated firm tumor with good mobility. Mammography and ultrasonography revealed a well-circumscribed tumor of 30 × 20 × 25 mm, and magnetic resonance imaging (MRI) showed rich vascularity, especially in the periphery. Fine-needle aspiration and core needle biopsy demonstrated invasive ductal carcinoma with multi-nucleated OGCs. Partial mastectomy was performed following sentinel lymph node biopsy. There was no metastasis to the sentinel lymph nodes, and the postoperative stage was pT2 N0 M0, stage IIA.

Case 2: An 83-year-old woman presented with a painful lump in the upper inner quadrant of her right breast. Ultrasonography revealed a well-defined mass of 19 × 16 × 10 mm. Both mammography and MRI suggested malignancy. As the specimen of aspiration cytology did not contain enough epithelial cells for diagnosis, an intraoperative frozen section was examined, leading to diagnosis of malignant tumor. Partial mastectomy was performed, and the final pathologic diagnosis was beast carcinoma with OGCs. The postoperative stage for this patient was also pT2 N0 M0, stage IIA.

Materials and methods

For histological analysis, the surgical specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. For immunohistochemical analysis, the sections were deparafinized and reacted with primary antibodies, followed by the immunoperoxidase method with a commercial kit (DakoCytomation Co Ltd, Glostrup, Denmark). The primary antibodies used in this study are as follows: ER (1D5, 1:100, Dako), PgR (PgR636, 1:400, Dako), HER2 (polyclonal, 1:1, Dako), CKAE1/AE3 (AE1/AE3, 1:100, Dako), Vimentin (V9, 1:2, Nichirei), VEGF (A-20, 1:400, Santacruz), MMP9 (polyclonal, 1:5000, Abcam), MMP12 (polyclonal, 1:100, Abcam), CD31 (JC70A, 1:50, Dako), CD68 (PGM-1, 1:100, Dako), HLA-DR (TAL1B5, 1:100, Dako), TRAP (26E5, 1:100, Novocastra), Cathepsin K (182-12G5, 1:10000, Dai-ichi fain chemical).

Results

Gross and microscopic findings

Case 1 grossly showed a well-circumscribed solid tumor, measuring 3.5 × 2.5 cm on the maximum cut plane. The tumor appeared gray to white in the center, but hemorrhagic dark brown at the periphery (Figure 1A). Microscopically, the tumor was surrounded by hyperemic blood vessels (Figure 1B). The ductal carcinoma cells, which had relatively small and round nuclei with mild atypia and infrequent mitosis, formed distinct glandular and cribriform structures, equivalent to invasive ductal carcinoma, grade 1 (well-differentiated) (Figure 1C, D). The hypervascular stroma contained numerous inflammatory cells and multinucleated giant cells (Figure 1E). Some giant cells showed a polarized cell body resembling activated osteoclasts (Figure 1F). Immunohistochemically, strong staining for cytokeratin (CK) AE1/AE3 was observed in all tumor cells, but not in OGCs (Figure 1G). About 40% of tumor cells were positive for estrogen receptor (ER) (Figure 1H) and progesterone receptor (PgR), but negative for HER2, phenotypically corresponding to Luminal A type. Following the WHO classification, the diagnosis was breast carcinoma with OGCs.

The tumor in Case 2 also showed a well-circumscribed gross appearance, measuring 2.2 × 1.5 cm on the maximum cut plane. The tumor was rather whitish, but contained a small (5 mm) hemorrhagic area (Figure 1I). Microscopically, the main part of tumor consisted of spindle-shaped sarcomatous cells with frequent mitotic figures, and there were also foci of ductal carcinoma cells with an intraductal component (Figure 1J-L). Inflammatory cells and multinucleated OGCs were seen in the hypervascular stroma (Figure 1M, N). Immunohistochemically, the ductal carcinoma cells were positive for CK AE1/AE3 (Figure 1O) but not ER, PgR, or HER2. The spindle-shaped tumor cells constituting most of the tumor were not reactive for CK AE1/AE3, but instead were strongly positive for vimentin (Figure 1P). Thus, the case was diagnosed as breast carcinoma with OGCs, and the tumor was equivalent to metaplastic carcinoma with mesenchymal component, corresponding to so-called carcinosarcoma.

Topography of CD68-positive cells and expression of chemotactic agents

Despite the different histological features of the breast carcinoma cells, the OGCs in both cases showed similar morphology, and large OGCs contained 20-30 nuclei. In both cases, OGCs preferentially appeared in hypervascular stroma, but the topography of OGCs and blood vessels differed between Case 1 and Case 2. In Case 1, CD31 immunostaining demonstrated that the smaller blood vessels were relatively evenly distributed within the tumor; in contrast, numerous enlarged blood vessels were seen in the periphery (Figure 2A). Large OGCs with over 20 nuclei showed concentric topography; they were mainly seen in the central invasive lesion, while

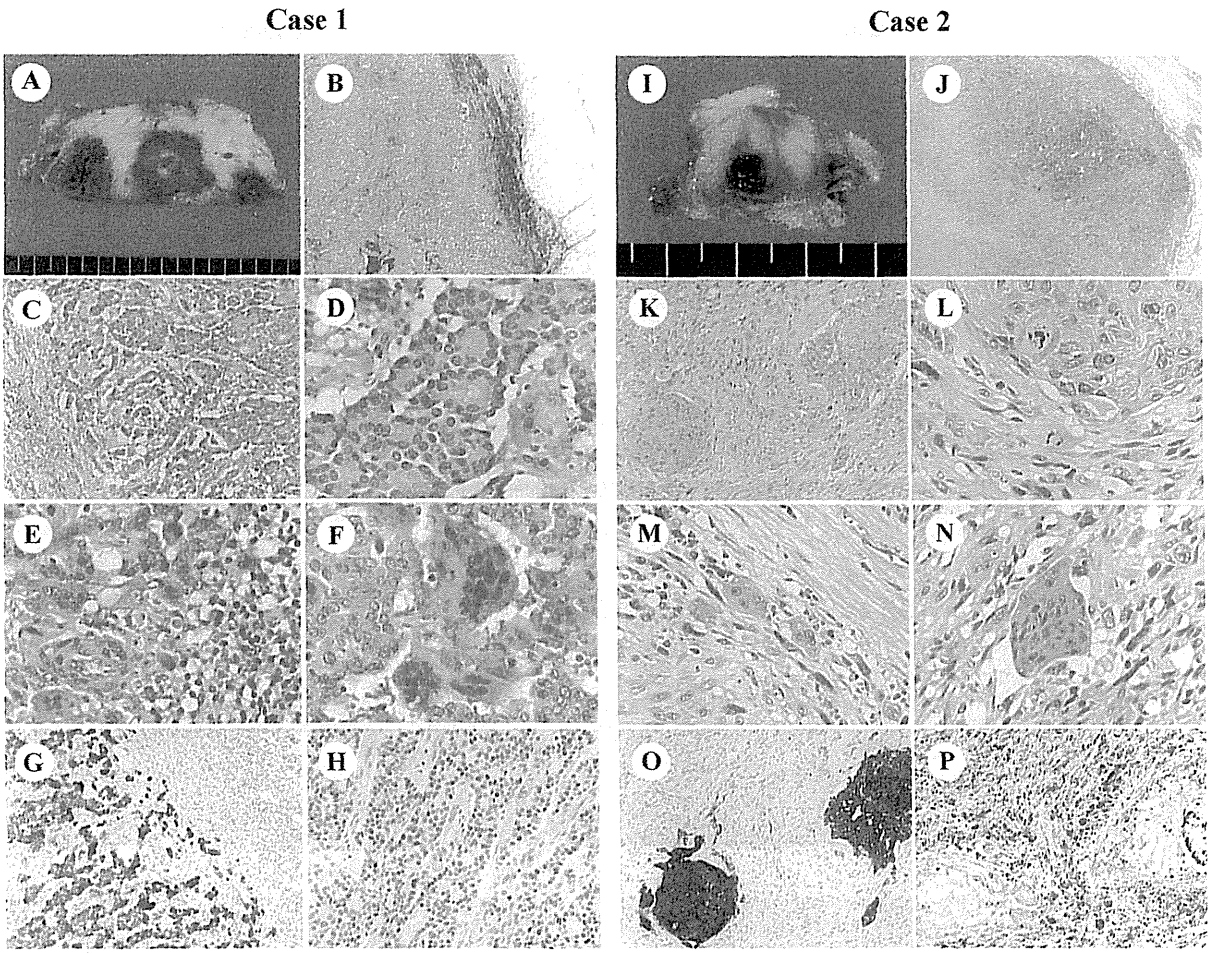

Figure 1 Gross and microscopic findings of breast carcinoma with OGCs. OGCs in Case 1 appeared associated with invasive ductal carcinoma, grade 1, and in Case 2 with carcinosarcoma. **A-H**: Case 1. **A**: Gross appearance. **B**: Low power view of the tumor. **C, D**: High power views of the tumor. **E, F**: Bi-, tri-, tetranucleate cells were observed as well as OGCs in hypervascular inflammatory stroma. **G**: CK AE1/AE3 staining. **H**: ER staining. **I-N**: Case 2, corresponding to A-F in Case 1. **O**: CK AE1/AE3 staining. **P**: Vimentin staining.

mono-, bi-, tri-, or oligonucleate CD68-positive cells were usually observed in the periphery (Figure 2B). Typical OGCs containing more than 20 nuclei were scarcely detected in the intraductal components, although some CD68-positive cells, including mono-, bi- or trinucleate cells, were seen within the ducts (Figure 2C). In Case 2, unlike Case 1, the distribution of OGCs and blood vessels was irregular, not concentric. OGCs were usually clustered in irregularly distributed hypervascular areas (Figure 2D). Mono-, bi-, tri-, or oligonucleated cells were also observed around the OGCs (Figure 2E). However, CD68-positive cells, regardless of the number of the nuclei, were scarcely seen within the minor intraductal lesions (Figure 2F).

To assess the microenvironment of the tumors, we examined the expression of two chemoattractants for macrophage migration and angiogenesis, VEGF and MMP12. Prominent expression of VEGF and MMP12 was observed in most tumor cells, most inflammatory cells, and even neighboring normal mammary glands both in Case 1 and Case 2 (Figure 2G-R). The OGCs, in both cases, also displayed marked expression of VEGF and MMP12.

Statistic evaluation of microvessel density

In hypervascular stroma of both cases, microvessel density was evaluated according to the Chalkley count on CD-31-stained sections, as described earlier. The mean values of the three most vascular areas (hot spot) were 9.6 for Case 1 and 10.7 for Case 2, respectively. These counts were much higher than the average Chalkley count of a total 330 invasive breast carcinoma cases, 5.75 (range 2.33 - 10.67, median 5.67, SD 1.54), reported in a previous study[11,12].

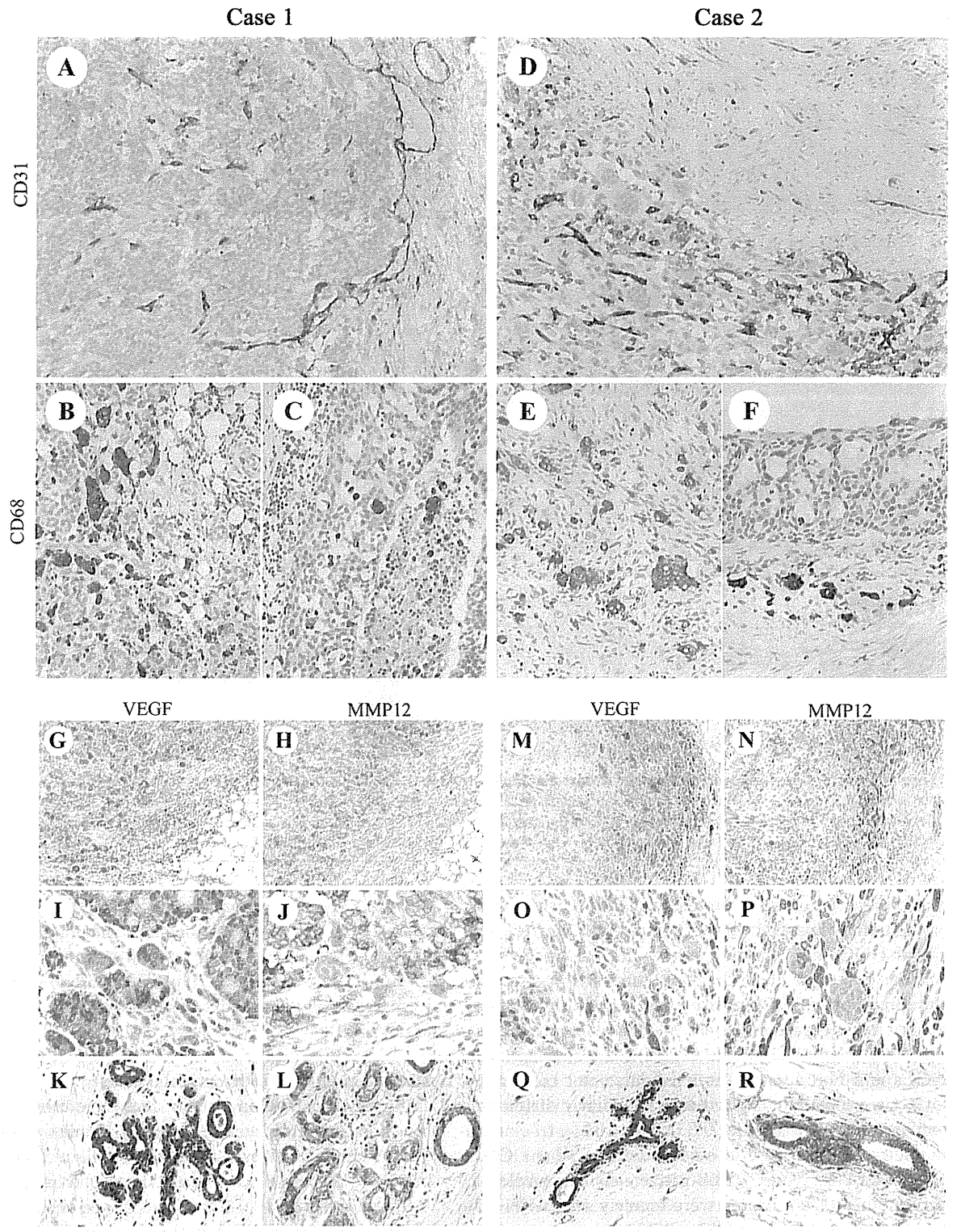

Figure 2 Topography of CD68-positive cells and expression of VEGF and MMP12. Case 1 and Case 2 showed distinct vascular patterns, but in both cases OGCs preferentially appeared in hypervascular stroma. Marked expression of VEGF and MMP12 was evident. **A**: Distribution of blood vessels marked with CD31 in Case 1. **B, C**: CD68-positive cells in Case 1. **D**: Distribution of blood vessels marked with CD31 in Case 2. **E, F**: CD68-positive cells in Case 2. **G-R**: VEGF and MMP12 expression in Case 1 (G-L), and Case 2 (M-R).

Phenotype of the OGCs in the breast

Phenotypic characteristics of OGCs in the two cases were evaluated and compared with those of osteoclastic cells in fibrous dysplasia of the rib bone (from a 45-year-old woman) and foreign-body giant cells in re-operated breast tissue (a 42-year-old woman). CD68, a histiocytic marker, was detected on all macrophage lineage cells, including OGCs and oligonucleated giant cells in both Case 1 and Case 2, osteoclastic cells in the bone sample, and foreign-body giant cells (Figure 3A-D). MMP9 is a broad marker for macrophage-osteoclast lineage cells, including mononuclear precursors, fused polykaryons, and mature osteoclasts in bone. MMP9 expression was distinctly detected in the osteoclastic cells (Figure 3E) and the OGCs in Case 1 (Figure 3F), but markedly weaker in Case 2 (Figure 3G) and foreign-body giant cells (Figure 3H). TRAP and cathepsin K, lytic enzymes for bone resorption, are functional markers for osteoclast-lineage cells. Their expression was distinct in the osteoclastic cells and the OGCs in both Case 1 and Case 2 (Figure 3I-K, M-O). Unexpectedly, foreign body giant cells were also strongly positive for

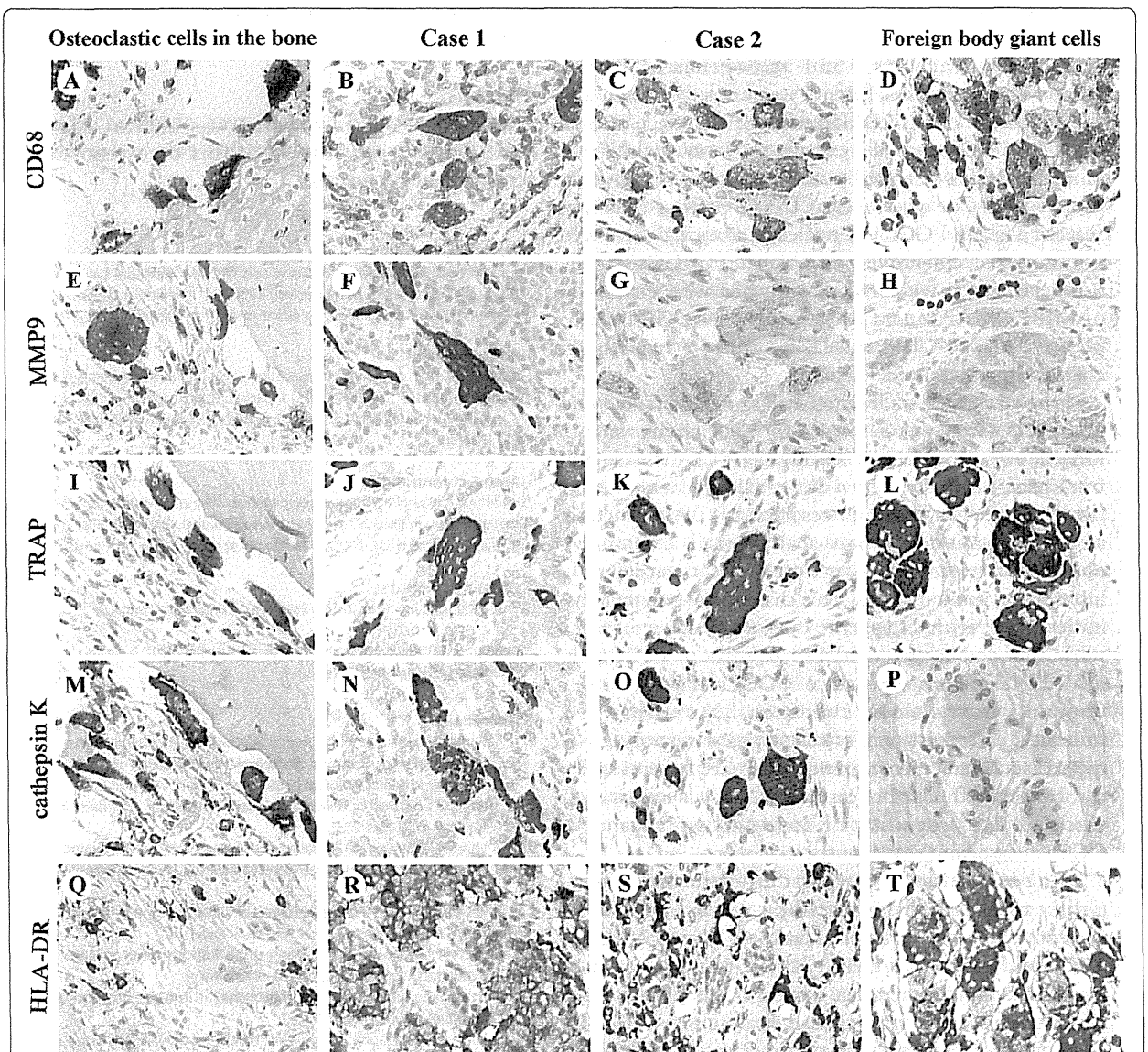

Figure 3 Expression of phenotypic markers of OGCs. Phenotypes of OGCs in the breast (center panels) were compared those of osteoclastic cells in the bone (far left) and foreign body giant cells (far right). OGCs in the breast displayed both osteoclastic and histiocytic characteristics but lacked antigen presentation abilities. **A-D**: CD68, a phenotypic marker for histiocytes. **E-H**: MMP9, a broad marker for macrophage-osteoclast lineage cells. **I-L**: TRAP. **M-P**: Cathepsin K. **Q-T**: HLA-DR.

TRAP (Figure 3L), although they were negative for cathepsin K (Figure 3P). HLA-DR, an MHC class II antigen, is generally expressed in antigen-presenting cells including macrophages and peripheral blood mononuclear cells. Only foreign body giant cells were positive for HLA-DR; the bone osteoclasts and OGCs were negative (Figure 3Q-T).

Discussion

In this study, we demonstrated that the OGCs appear in relation to inflammatory hypervascular stroma around breast carcinoma regardless of histology. Abundant VEGF and MMP12 were secreted from both tumoural and non-tumoural cells, and these cytokines promote macrophage migration and angiogenesis. Notable increase of microvessel density was actually shown by the Chalkley count in inflammatory stroma of both cases. The OGCs are likely generated by syncytial fusion of macrophages, but not by mitosis without cell division. Thus, bi-, tri-, or oligo-nuclear CD-68 positive cells were scattered around OGCs, but nuclear mitotic figures were not observed. Phenotypic resemblance of OGCs to the osteoclasts in the bone was confirmed with expression of MMP9, TRAP, and cathepsin K. The OGCs were negative for HLA-DR, and lacked antigen presentation abilities as anti-cancer defence.

Macrophages are multifunctional, showing marked phenotypic plasticity in response to microenvironments. Indeed, tumor-associated macrophages (TAMs) isolated from breast cancer *in vitro* differentiated into multinucleated giant cells with bone resorption [3]. A characteristic inflammatory and hypervascular stroma is commonly observed in breast carcinoma with OGCs, regardless of histology of tumoural cells. This characteristic stroma may indicate secretion of specific cytokines, and we, in this study, first demonstrated marked expression of VEGF and MMP12. Therefore, appearance of OGCs may not be anti-tumoural immunological reactions, but rather pro-tumoural differentiation of macrophage responding to hypervascular microenvironments induced by breast cancer. However, the further case series study is necessary to elucidate the prognostic or biological significance of OGCs in association with breast carcinoma.

In the bone tissue, osteoclast differentiation seems tightly associated with signaling related to RANKL (receptor activator of nuclear factor-κB ligand) [13], or VEGF and its receptor Flt-1 [14]. Flt-1, expressed on human monocyte/macrophage lineage cells [15], also regulates macrophage migration in response to VEGF [7]. To test for such differentiation signaling in the OGCs in the breast, we also examined expression of RANKL and Flt-1. Weak but distinct expression of Flt-1 was detected in the OGCs of both Case 1 and Case 2, but expression of RANKL was not clear (data not shown). Thus, it is still uncertain if osteoclast differentiation signaling function in the breast, mimicking in the bone.

Conclusion

The OGCs likely develop from macrophages in response to pro-tumoural microenvironment defied by cytokines, favoring macrophage migration and angiogenesis. The OGCs have acquired bone-osteoclast-like characteristics, but no more have antigen presentation abilities as anti-cancer defence. Macrophages and angiogenesis may imply the poor prognosis of the breast cancer [16,17]. Therefore, the appearance of OGCs is not merely histiocytic reactions, but better taken as a part of pathology of breast tumours.

Consent

Written informed consent was obtained from both patients for publication of this case report and any accompanying images.

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Authors' contributions

YS-H, AK, MF and HK participated in conception of the idea and writing of the manuscript. HI and SH provided the clinical data and edited the clinical case presentation. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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