Table 1
Source, dilution, pretreatment and cutoff values of antibodies used

Antibody, clone	Dilution	Source	Pretreatment	Cutoff values
ER [1D5]	1:400	IMMUNOTECH	Autoclaved	≥10% (positive)
PR [636]	1:2000	DAKO	Autoclaved	≥10% (positive)
HER2 [HercepTest]	NA*	DAKO	None	NA
HER1 [2-18C9]	NA	DAKO	Proteinase K	≥10% (positive)
CK 5/6 [D5/16134]	1:100	DAKO	Autoclaved	≥10% (positive)

*Not assessable.

Table 2
Prevalence of intrinsic subtypes and clinico-pathological characteristics in Japanese breast cancer patients

	All cases	Luminal A	Luminal B	HER2+/ER−	Basal-like	Unclassified	*P* value*
No. of cases	793	502 (63)†	155 (20)	55 (7)	67 (8)	14 (2)	
Age, median (range), years-old	54 (19–88)	53 (27–88)	53 (19–85)	60 (31–84)	54 (30–79)	50 (36–66)	0.025
AJCC stage							<0.001
I	289	213	48	4	18	6	
II	360	208	70	39	38	5	
III	68	36	17	4	8	3	
IV	40	19	15	4	2	0	
Missing	36	26	5	4	1	0	
Histology							0.142
Invasive ductal carcinoma NOS	721	447	149	53	60	12	
Specific types	70	54	5	2	7	2	
Missing	2	1	1	0	0	0	
Histologic grade							<0.001
I	156	131	23	0	1	1	
II	320	235	56	15	11	3	
III	197	61	48	33	49	6	
Missing	120	75	28	7	6	4	
LVI							0.018
Positive	345	212	69	32	27	5	
Negative	373	249	62	20	36	6	
Missing	75	41	24	3	4	3	
BVI							0.026
Positive	126	82	18	10	14	2	
Negative	570	267	105	40	49	9	
Missing	97	53	32	5	4	3	
Nodal status							0.572
Positive	303	184	62	25	27	5	
Negative	437	286	78	25	29	9	
Not applicable or missing	53	32	15	5	1	0	
Outcome							
Follow-up, median (range), months	46.5 (1–84)						
5-year DFS	85.5%	90.3%	82.9%	62.1%	77.1%	81.8%	<0.001‡
5-year OS	92.8%	96.9%	86.6%	86.9%	86.2%	83.3%	<0.001‡

*Comparing five subtypes using χ^2 test or Fisher's exact test.
†In %.
‡Log-rank test.

Survival by IHC subtypes

Survival data on 786 of 793 patients with invasive breast cancer were available from three hospitals. The duration of follow-up was 1–84 months (median, 46.5). During this period, recurrence was observed in 91 patients, and 48 patients died of any causes.

Breast cancer subtypes significantly differed in 5-year disease-free survival (DFS, $P<0.001$): luminal A (90.3%), luminal B (82.9%), HER2+/ER− (62.1%), basal-like

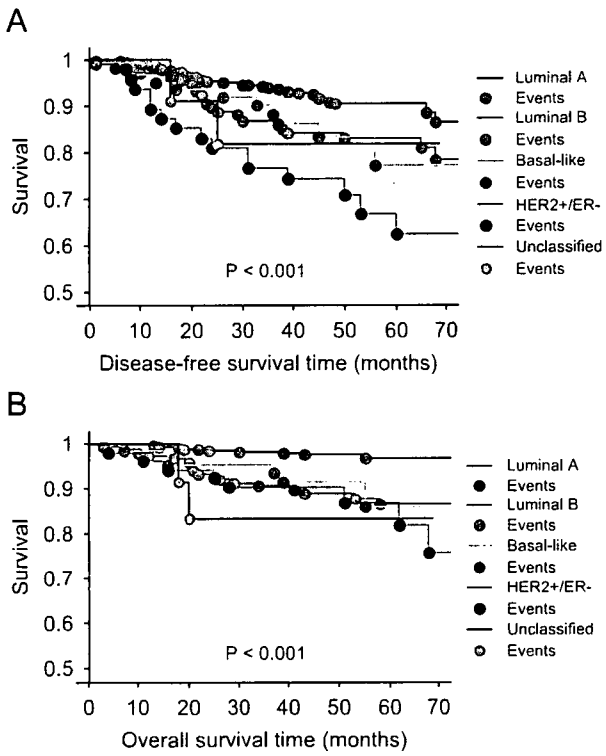

Fig. 1. DFS (A) and OS (B) curves in breast cancer patient groups divided by IHC intrinsic subtypes.

subtype (77.1%), and unclassified (81.8%). They also differed in 5-year overall survival (OS, $P<0.001$): luminal A (96.9%), luminal B (86.6%), HER2+/ER− (86.9%), basal-like subtype (86.2%), and unclassified (83.3%). Kaplan–Meier survival curves are presented in Fig. 1. Both DFS and OS were significantly worse among basal-like and HER2+/ER− breast cancer patients compared with luminal A patients.

Differences in DFS and OS by IHC subtypes were seen among lymph node-positive patients ($P = 0.006$ for DFS and $P<0.001$ for OS) but not lymph node-negative patients; however, the number of patients after stratifying by lymph node status was limited and these data should be interpreted with caution. Five-year DFS within lymph node-positive patients by subtype was as follows: luminal A (79.3%), luminal B (71.2%), HER2+/ER− (35.2%), basal-like subtype (68.1%), and unclassified (50.0%). Five-year OS within lymph node-positive patients was as follows: luminal A (96.3%), luminal B (75.6%), HER2+/ER− (84.1%), basal-like subtype (83.9%), and unclassified (60.0%).

Discussion

Carey et al. have recently reported for the first time the population-based prevalence of intrinsic subtypes of breast tumors. They refined an IHC-based assay to identify breast tumor intrinsic subtypes instead of gene expression profiling.[15] This IHC-based assay has been verified against gene expression profiles to estimate the prevalence of intrinsic subtypes.[15,20] Additionally, large-scale subtyping using gene expression profiling from formalin-fixed, paraffin-embedded samples is not currently feasible; therefore, we conducted this cohort study to investigate the prevalence of intrinsic subtypes using the IHC-based assay in Japanese breast cancer patients.

According to Carey et al.,[15] the prevalence of basal-like and luminal A tumors in the Carolina Breast Cancer Study was 27% and 47% in AA patients and 16% and 54% in non-AA patients, respectively. Since breast cancer-specific survival was significantly worse in patients with basal-like tumors than with luminal A tumors, the higher prevalence of a basal-like subtype could contribute to a worse prognosis in AA patients. Moreover, the prevalence of basal-like and luminal A tumors was 39% and 36% in premenopausal AA patients, respectively. In contrast, the prevalence of basal-like and luminal A tumors was 8% and 63% in Japanese breast cancer patients, respectively, in the present study. The prevalence of basal-like tumors was 2–3 times lower in Japanese patients than in non-AA patients or AA patients. In addition, the prevalence of luminal A tumors was 9–16% higher in Japanese patients than in non-AA patients or AA patients. Breast cancer patients with basal-like tumors had a poorer prognosis in terms of DFS and OS than those with luminal A tumors in the present study (Fig. 1) as previously indicated in the report by Carey et al.[15] These findings have suggested that the lower prevalence of basal-like tumors and higher prevalence of luminal A tumors in Japanese patients could contribute to their better prognosis.

A limited number of studies have investigated the prevalence of intrinsic subtypes by the IHC-based assay in different races. On the other hand, the prevalence of triple-negative breast tumors has recently become available. Triple-negative tumors include both basal-like and unclassified tumors. The prevalence of basal-like tumors was reported to be approximately 70% in triple-negative tumors[15]; it was 78% in the present study. The prevalence of triple-negative tumors was 22% in the Carolina Breast Cancer Study,[15] 16% in a large series of patients in the UK,[21] 26% in conservatively managed patients in the USA,[22] and 31% in consecutive patients in Korea.[23] In the present study, the prevalence of triple-negative tumors was only 10%, 1.6–3 times lower in Japanese patients than in patients of other races. These findings also support the lower prevalence of basal-like tumors in Japanese patients.

Differences in genetic influences or lifestyle may explain the prevalence of intrinsic subtypes among different races. Differences in the distribution of breast cancer risk factors, such as breast cancer family history, age at menarch, age at first birth, body mass index, and hormone replacement therapy, have been extensively investigated, and these differences may explain differences in breast caner incidence rates among different races.[5] However, the investigation of causative factors leading to differences in the prevalence of intrinsic subtypes in different races remains

to be investigated. Because of a close correlation between the prevalence of intrinsic subtypes and the prognosis of breast cancer patients indicated by us and others,[15,20] nutritional or environmental factors influencing the prevalence may provide hints for developing new intervention strategies to reduce breast cancer mortality rates. It has been indicated that the intake of green tea or soy beans relates to a reduction in breast cancer incidence rates.[24,25] Furthermore, the consumption of green tea was suggested to correlate with not only a reduction in breast cancer incidence but also improved outcome of breast cancer patients in Japanese women.[26] In addition, it is suggested that breast cancer patients with a high intake of green tea tend to have less aggressive and hormone-responsive breast tumors.[27] Interestingly, recent experimental studies have revealed that green tea extracts such as (−)-epigallocatechin gallate have significant anti-tumor activity in breast cancer cells with basal-like phenotypes.[28–30] These findings suggest that green tea intake may modify the biological characteristics of breast tumors and the prevalence of intrinsic subtypes. Further epidemiologic and experimental studies are warranted to investigate the role of green tea intake in breast cancer development and progression.

In conclusion, the present study suggests for the first time that a lower prevalence of basal-like breast tumors and a higher prevalence of luminal A breast tumors could contribute to a favorable prognosis of Japanese breast cancer patients. Taken together with the worse prognosis of AA patients having a higher prevalence of basal-like tumors and a lower prevalence of luminal A tumors, it could be concluded that the prevalence of intrinsic subtypes differs among different races and such a difference may explain differences in the prognosis of breast cancer patients of different races. From the clinical point of view, the prevalence of intrinsic subtypes should be taken into account when analyzing survival data in a multi-racial/international clinical study. In addition, causative factors influencing the prevalence of intrinsic subtypes should be explored to develop intervention strategies to reduce breast cancer incidence and the mortality rate.

Conflict of Interest Statement

None declared.

Acknowledgments

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References

1. Boyle P. Breast cancer control: signs of progress, but more work required. *Breast* 2005;**14**:429–38.
2. Blackman DJ, Masi CM. Racial and ethnic disparities in breast cancer mortality: are we doing enough to address the root causes? *J Clin Oncol* 2006;**24**:2170–8.
3. Li CI, Malone KE, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. *Cancer Epidemiol Biomarkers Prev* 2002;**11**: 601–7.
4. Porter PL, Lund MJ, Lin MG, et al. Racial differences in the expression of cell cycle-regulatory proteins in breast carcinoma. *Cancer* 2004;**100**:2533–42.
5. Chlebowski RT, Chen Z, Anderson GL, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst* 2005;**97**:439–48.
6. Polednak AP. Racial differences in mortality from obesity-related chronic diseases in US women diagnosed with breast cancer. *Ethn Dis* 2004;**14**:463–8.
7. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA* 2005;**294**:1765–72.
8. Smith-Bindman R, Miglioretti DL, Lurie N, et al. Does utilization of screening mammography explain racial and ethnic differences in breast cancer? *Ann Intern Med* 2006;**144**:541–53.
9. Sassi F, Luft HS, Guadagnoli E. Reducing racial/ethnic disparities in female breast cancer: screening rates and stage at diagnosis. *Am J Public Health* 2006;**96**:2165–72.
10. Gwyn K, Bondy ML, Cohen DS, et al. Racial differences in diagnosis, treatment, and clinical delays in a population-based study of patients with newly diagnosed breast carcinoma. *Cancer* 2004;**100**: 1595–604.
11. Gorin SS, Heck JE, Cheng B, Smith SJ. Delays in breast cancer diagnosis and treatment by racial/ethnic group. *Arch Intern Med* 2006; **166**:2244–52.
12. Joslyn SA. Racial differences in treatment and survival from early-stage breast carcinoma. *Cancer* 2002;**95**:1759–66.
13. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med* 2003; **163**:49–56.
14. Bickell NA, Wang JJ, Oluwole S, et al. Missed opportunities: racial disparities in adjuvant breast cancer treatment. *J Clin Oncol* 2006; **24**:1357–62.
15. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 2006;**295**: 2492–502.
16. Braun KL, Fong M, Gotay C, Pagano IS, Chong C. Ethnicity and breast cancer in Hawaii: increased survival but continued disparity. *Ethn Dis* 2005;**15**:453–60.
17. Elston EW, Ellis IO. Method for grading breast cancer. *J Clin Pathol* 1993;**46**:189–90.
18. Rosen PP. *Rosen's breast pathology*. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 325–64.
19. Jacobs TW, Gown AM, Yaziji H, Barnes MJ, Schnitt SJ. Specificity of HercepTest in determining HER-2/neu status of breast cancers using the United States Food and Drug Administration-approved scoring system. *J Clin Oncol* 1999;**17**:1983–7.
20. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res* 2004;**10**:5367–74.
21. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. *Cancer* 2007;**109**:25–32.
22. Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol* 2006;**24**:5652–7.
23. Kim MJ, Ro JY, Ahn SH, Kim HH, Kim SB, Gong G. Clinicopathologic significance of the basal-like subtype of breast cancer: a comparison with hormone receptor and Her2/neu-overexpressing phenotypes. *Hum Pathol* 2006;**37**:1217–26.

24. Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis* 2006;**27**:1310–5.
25. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. *J Natl Cancer Inst* 2006;**98**:1275–84.
26. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. *Integr Cancer Ther* 2005;**4**:144–55.
27. Nakachi K, Suemasu K, Suga K, Takeo T, Imai K, Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res* 1998;**89**:254–61.
28. Roy AM, Baliga MS, Katiyar SK. Epigallocatechin-3-gallate induces apoptosis in estrogen receptor-negative human breast carcinoma cells via modulation in protein expression of p53 and Bax and caspase-3 activation. *Mol Cancer Ther* 2005;**4**:81–90.
29. Bigelow RL, Cardelli JA. The green tea catechins, (−)-epigallocatechin-3-gallate (EGCG) and (−)-epicatechin-3-gallate (ECG), inhibit HGF/Met signaling in immortalized and tumorigenic breast epithelial cells. *Oncogene* 2006;**25**:1922–30.
30. Kim J, Zhang X, Rieger-Christ KM, et al. Suppression of Wnt signaling by the green tea compound (−)-epigallocatechin-3-gallate (EGCG) in invasive breast cancer cells. Requirement of the transcriptional repressor HBP1. *J Biol Chem* 2006;**281**:10865–75.

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Case Report

Brain Metastases after Achieving Local Pathological Complete Responses with Neoadjuvant Chemotherapy

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Background: We encountered two patients with inflammatory breast carcinoma who developed symptomatic brain metastases after achieving local pathological complete responses (pCR) with neoadjuvant chemotherapy (NAC).

Case presentations: The first patient is a 39-year-old woman (Case 1), who underwent NAC with AC (doxorubicin + cyclophosphamide) followed by weekly paclitaxel. After achieving a clinical CR (cCR), we conducted a modified radical mastectomy. Pathological evaluation confirmed no residual malignant cells within the breast tissue or lymph nodes. However, she developed neurological symptoms from brain metastases one month postoperatively. The second patient is a 44-year-old woman (Case 2). Again, no residual malignant cells were detected within the breast tissue or lymph nodes following NAC, but the patient developed symptomatic brain metastases eight months postoperatively. When primary breast tumors are locally advanced, it may be worthwhile to rule out brain metastases even if pCR is obtained after NAC.

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Key words: Brain metastasis, Pathological complete response, Breast cancer

Introduction

Neoadjuvant chemotherapy (NAC) is a standard treatment option for patients with locally advanced and/or inflammatory breast cancers. The outcomes of patients achieving pCR of their primary tumors are significantly better than those with residual disease[1-3]. Here, we introduce two patients who developed symptomatic brain metastases shortly after documented pCRs following NAC and surgery.

Case Report

Case 1

A 39-year-old premenopausal woman sought medical attention for erythematous induration of her left breast. With a working diagnosis of inflammatory breast cancer, fine needle aspiration cytology revealed adenocarcinoma. The patient was referred to the National Cancer Center Hospital for further treatment in February 2005. Physical examination revealed an indistinct 12 cm mass in the upper area of the left breast, and the surface of this lesion exhibited a peau d'orange appearance. Axillary and supraclavicular lymph nodes were palpable and measured 4 and 2 cm in diameter, respectively. The axillary lymph node was fixed to the surrounding tissue. Ultrasonography (US) revealed a 7 cm breast mass with dermal thickening, edematous subcutaneous tissue, and enlarged lymph nodes (Fig 1a). These findings were also observed on computed tomography (CT) and magnetic resonance imaging (MRI).

Core needle biopsy led to a pathological diagnosis of invasive ductal carcinoma (grade 3, nuclear grade 3, and HER-2 negative) (Fig 2a). The tumor was negative for both estrogen and progesterone receptors. Chest X-ray, bone scintigraphy, abdominal US, and chest and abdominal CT revealed no distant metastases. Due to the presumed low incidence of brain metastases at this clinical stage, brain imaging was not done at

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Abbreviations:
pCR, Pathological complete response; NAC, neoadjuvant chemotherapy; US, ultrasonography; CT, Computed tomography; MRI, Magnetic resonance imaging

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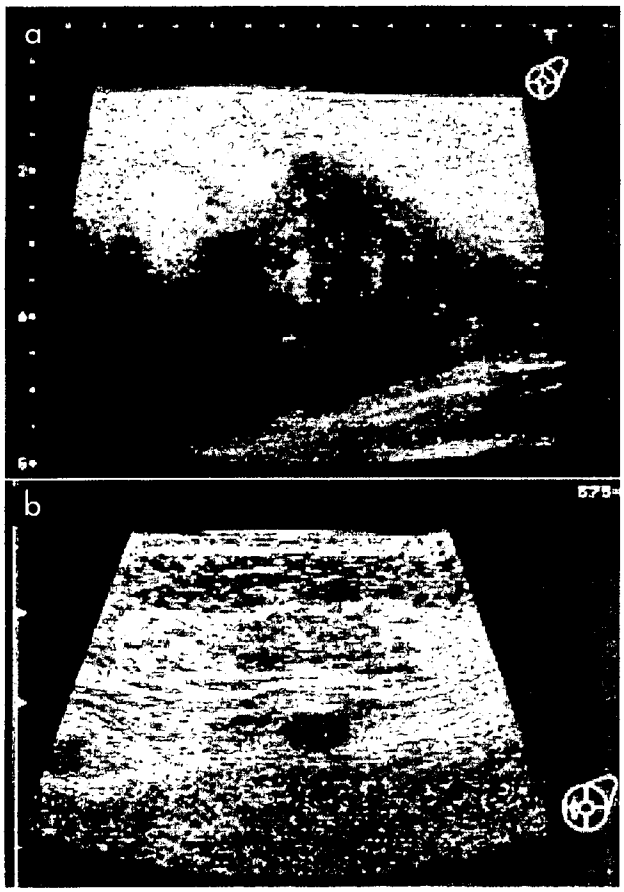

Fig 1. (a) US reveals a 7 cm breast mass with overlying skin thickening, edematous subcutaneous tissue. (b) US reveals no residual tumor following neoadjuvant chemotherapy.

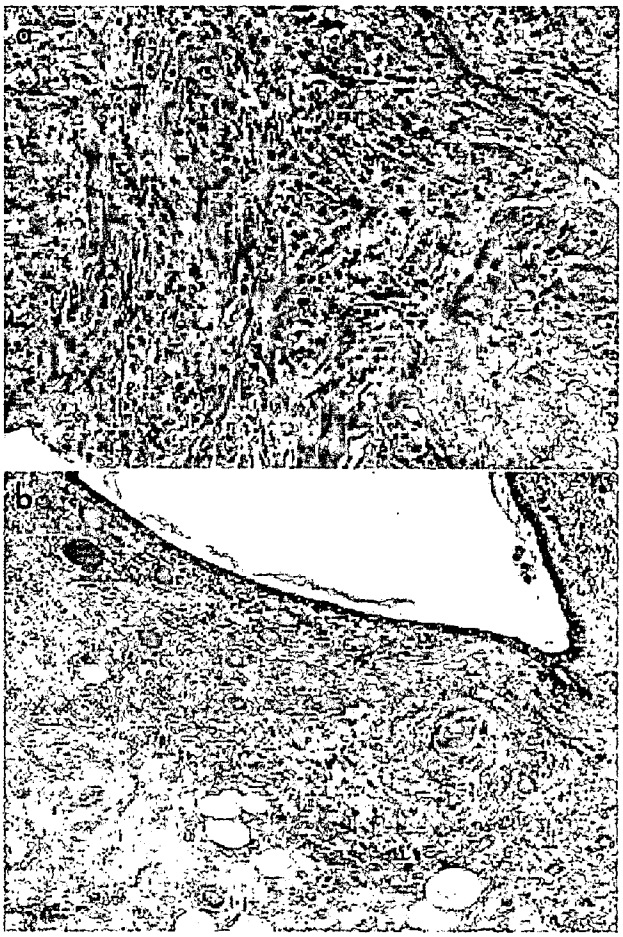

Fig 2. (a) Core needle biopsy reveals invasive ductal carcinoma, grade 3, nuclear grade 3. (b) No residual tumor is detected. The presence of inflammatory cells surrounding a duct with an increased number of enlarged capillary vessels, typical after tumor disappearance, is observed. (hematoxylin-eosin staining, ×100).

this point. Inflammatory breast cancer of the left breast was initially diagnosed, T4dN3M0, Stage IIIC, according to the general rules for clinical and pathological grading of breast cancers[4]. She received NAC from February to July consisting of doxorubicin and cyclophosphamide (60/600 mg/m^2) 4 times every 3 weeks, followed by paclitaxel (80 mg/m^2) weekly for 12 weeks. Following NAC, only induration of her left breast was apparent upon physical examination, and no breast masses or axillary lymph nodes were detected by US (Fig 1b) and CT. Additionally, serum levels of tumor markers (CEA, CA 15-3, ST 439) remained within normal limits before and after chemotherapy. We subsequently conducted a modified radical mastectomy in August, and no malignant cells were detected in the resected breast tissue and dissected axillary lymph nodes (Fig 2b). However, the patient presented with vertigo and severe headache prior to the initiation of radiotherapy to the left chest wall in September. Brain MRI revealed multiple metastatic lesions in her right frontal lobe, temporal lobe, and bilateral cerebellum (Fig 3). To control her symptoms, whole-brain radiotherapy with a total dose of 30 Gy/10 fractions was incorporated in October. However, her condition deteriorated, and she expired in December.

Case 2

A 44-year-old premenopausal woman was seen at a nearby hospital with a chief complaint of an erythematous enlarged right breast. Inflammatory breast cancer was suspected, so she was referred to our institution in December 2004.

On initial examination, the right breast was firm, erythematous, and edematous with a thickened dermis. Axillary and supraclavicular lymph nodes were palpable and measured 5 cm and 1 cm

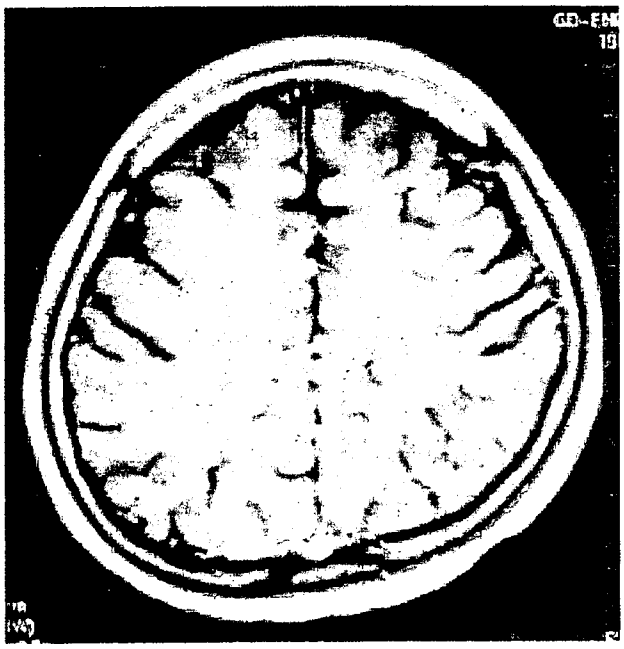

Fig 3. The metastatic lesions exhibited high signal intensity in the right temporal lobe by T1 weighted MRI.

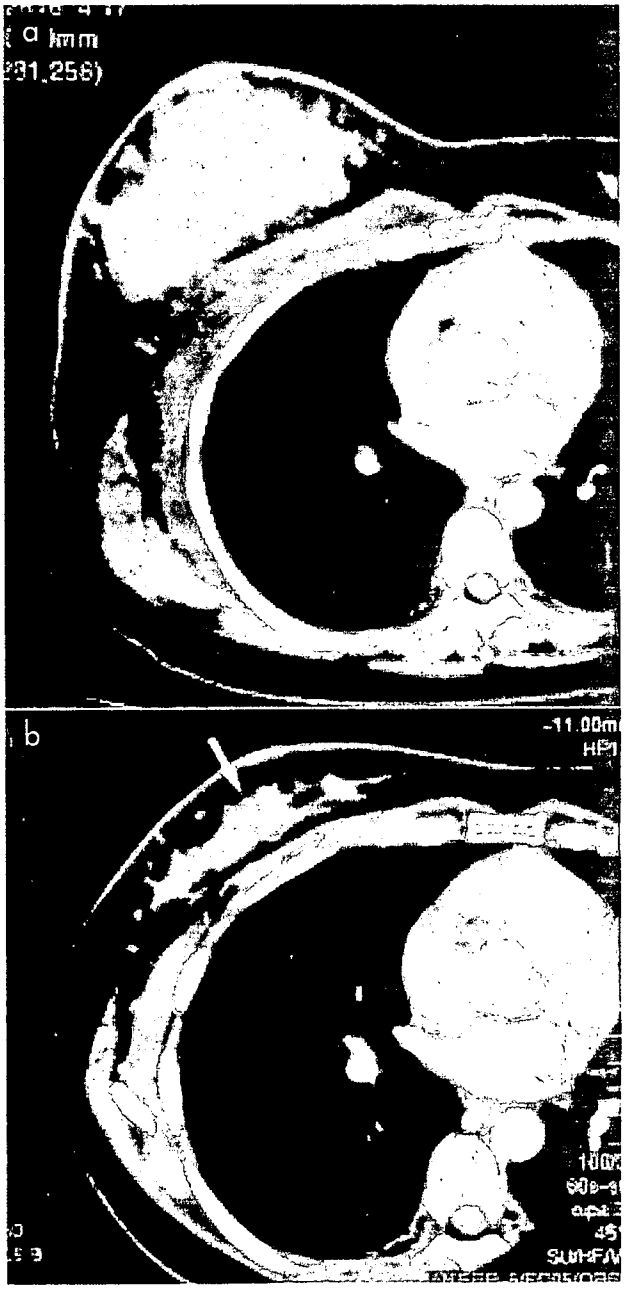

Fig 4. (a) CT shows a large right breast mass with overlying edematous subcutaneous tissue and thickened skin. This is not the early phase but late phase scan of breast CT, because only chest CT without an early phase scan was performed to detect distant metastasis instead of breast CT. (b) CT scan reveals a mass-like lesion measuring 3 cm, without enhancement, in the right breast.

in diameter, respectively. CT showed a large right breast mass with an edematous dermis and subcutaneous tissue.Additionally, the axillary and supraclavicular lymph nodes were enlarged (Fig 4a). The specimen obtained by the core needle biopsy was consistent with an invasive ductal carcinoma (solid tubular type, grade 3, nuclear grade 3, HER-2 negative, estrogen and progesterone receptor negative) (Fig 5a). No metastatic lesions were detected by bone scintigraphy, chest X-ray, chest CT, or abdominal US, though diagnostic brain imaging was not performed at that time. Serum tumor markers were elevated, with a CEA of 52.4 ng/ml, CA 15-3 of 279 U/ml, and NCC-ST 439 of 910 U/ml. Inflammatory breast cancer, T4dN3M0, Stage IIIC[4] was diagnosed. She underwent NAC from December to May 2005, using the same treatment regimen as Patient 1. Following NAC, physical examination revealed only induration of the right breast with slight thickening of the overlying skin. CT revealed a slightly enhanced, 3-cm lesion in the breast (Fig 4b) without enlarged lymph nodes. All tumor markers were within normal limits after chemotherapy. We performed a modified radical mastectomy in July, and no tumor cells were pathologically detected in the breast tissue and axillary lymph nodes (Fig 5b). Following surgery, we performed local radiotherapy with a total dose of 60 Gy/30 fractions from August through October. However, the patient developed headache and ambulatory disturbance in early December. Brain CT and MRI scans performed in March 2006 detected a tumor measuring 5 cm in diameter in her right temporal lobe with surrounding edema (Fig 6). A right frontotemporal craniotomy followed by whole-brain radiotherapy of 37.5 Gy/15 fractions was carried out from

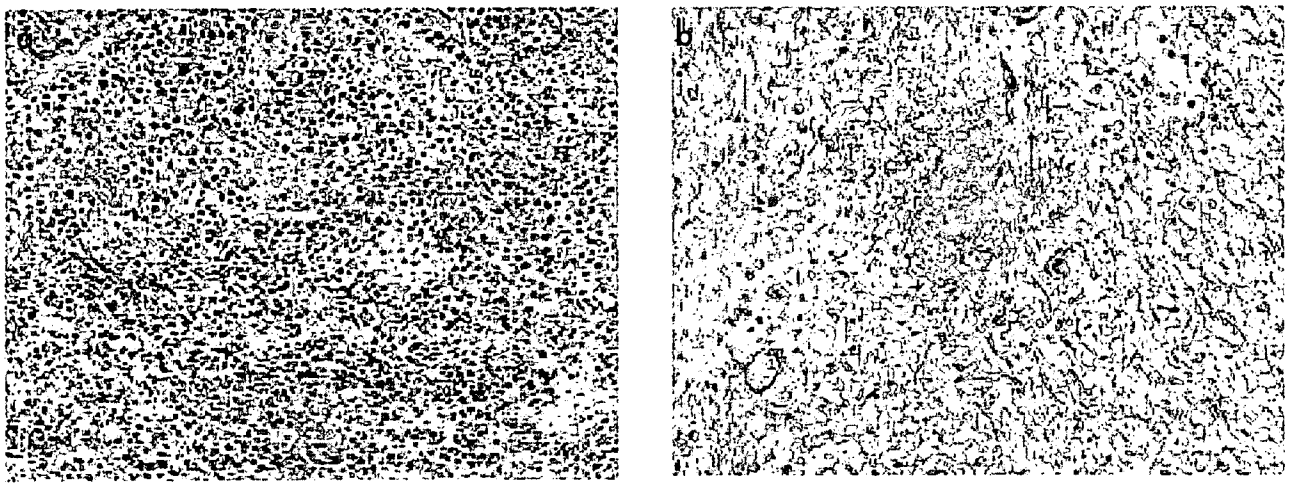

Fig 5. (a) Core needle biopsy reveals invasive ductal carcinoma, grade 3, nuclear grade 3. (b) No residual tumor is detected. Many foamy cells and a disturbance of the fiber rows after the disappearance of the tumor are observed (hematoxylin and eosin staining, × 100).

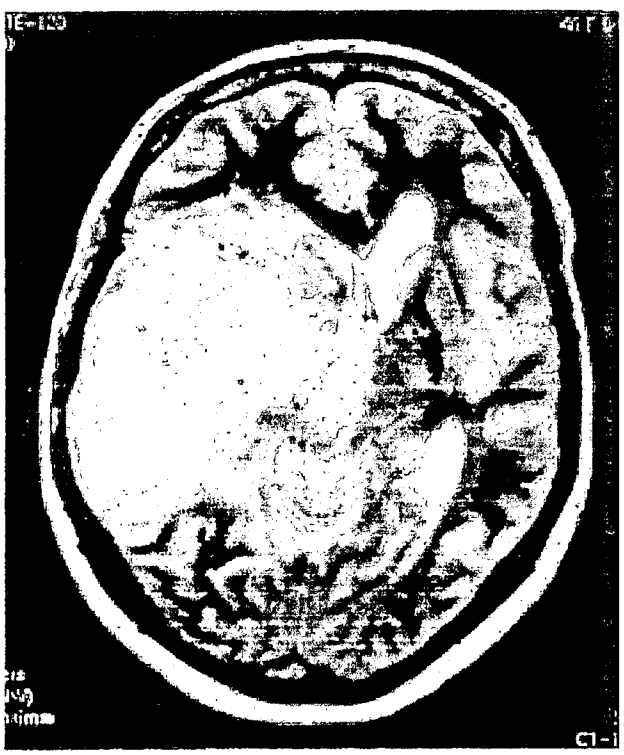

Fig 6. MRI demonstrates a tumor measuring 5 cm in diameter, with surrounding edema, in the right temporal lobe.

March through April. Intracranial recurrence is now controlled three months after radiotherapy.

Discussion

Several studies have indicated that breast cancer patients with pCR following NAC have better overall survival and disease-free survival rates[1-3]. Moreover, pCR of axillary lymph nodes is an excellent prognostic factor for locally advanced breast cancers[5-8]. The two cases presented were first diagnosed with inflammatory breast cancer with axillary and supraclavicular lymph node metastases. The patients achieved pCR for both the main tumors and the axillary lymph nodes following NAC, and favorable prognoses were expected from the published literature. However, both patients developed symptomatic brain metastases soon after mastectomy. The interval between surgery and the occurrence of neurological signs was only one month for Patient 1 and five months for Patient 2. This led us to the theory that the blood brain barrier restricted access of the chemotherapeutic agents to the central nervous system. Therefore despite locally effective NAC, occult brain metastases may continue to progress into clinical significance. This theory may help us understand the progression of brain metastases in these patients[9]. There have been no reports examining the rates of brain metastasis following NAC. Yet there are reports of patients receiving adjuvant chemotherapy having an increased incidence of brain metastases as the site of first recurrence compared to control[10, 11]. In the present cases, we suspect that subclinical metastases were present in the brain before initiating NAC. It is likely that, because of inadequate delivery of cytotoxic agents to the brain, these metastases continued to grow despite effective tumor control elsewhere the body.

Several studies have identified risk factors for brain metastases in patients with breast cancer. Young age[12, 13], unresponsiveness to the hormonal

therapies, and HER-2 over expression are reported risk factors[14-17]. Intracranial metastases are also related to the use of trastuzumab[18]. In the two patients presented here, relatively young age and the absences of both estrogen and progesterone receptor were concordant risk factors for developing brain metastases.

The combination of NAC and surgery can lead to favorable outcomes in many cases of breast cancer, but effective control over the primary lesions and the extracranial micrometastases by the cytotoxic agents may not predict future intracranial event. The blood brain barrier would likely prevent chemotherapeutic agents from reaching the central nervous system. As a consequence, brain metastases may continue to grow and become symptomatic despite pCR of primary sites and lymph node metastases. This can be a concerning factor, especially in patients at risk for developing brain metastases. Further investigations are warranted to identify the mechanisms leading to intracranial metastases, as well as pretherapeutic risk factors.

References

1) Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher R, Wickerham L, Begovic M, DeCillis A, Robidoux A, Margolese G, Cruz B, Hoehn L, Lees W, Dimitrov V, Bear D: Effect of preoperative chemotherapy on the outcome of woman with operable breast cancer. *J Clin Oncol* 16: 2672-2685, 1998.
2) Norman W, Jiping W, Eleftherios M, John B, Bernard F: Preoperative chemotherapy in patients with operable breast cancer: nine-year results from national surgical adjuvant breast and bowel project B-18. *J Natl Cancer Inst Monogr* 30: 96-102, 2001.
3) Sataloff D, Mason B, Prestipino A, Seinige U, Lieber C, Baloch Z: Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. *J Am Coll Surg* 180: 297-306, 1995.
4) Sakamoto G, Inaji H, Akiyama F, Haga S, Hiraoka M, Inai K, Iwase T, Kobayashi S, Sakamoto G, Sano M, Sato T, Sonoo H, Tsuchiya S, Watanabe T; The Japanese Breast Cancer Society: General rules for clinical and pathological recording of breast cancer 2005. *Breast cancer* 12 (Suppl): S1-27, 2005.
5) Hennessy T, Hortobagyi N, Rouzier R, Kuerer H, Sneige N, Buzdar U, Kau W, Fornage B, Sahin A, Broglio K, Singletary E, Valero V: Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metasteses following primary chemotherapy. *J Clin Oncol* 23: 9304-9311, 2005.
6) Rouzier R, Extra M, Klijanienko J, Falcou C, Asselain B, Salomon V, Vielh P, Bourstyn E: Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastic lymph nodes. *J Clin Oncol* 20: 1304-1310, 2002.
7) Hennessy T, Gonzalez-Angulo M, Hortobagyi N, Cristofanilli M, Kau W, Broglio K, Fornage B, Singletary E, Sahin A, Buzdar A, Valero V: Disease-free and overall survival after pathologic complete disease remission of cytologically proven inflammatory breast carcinoma axillary lymph node metastases after primary systemic chemotherapy. *Cancer* 106: 1000-1006, 2006.
8) Kuerer M, Newman A, Smith L, Ames C, Hunt K, Dhingra K, Theriault L, Singh G, Binkley M, Sneige N, Buchholz A, Ross I, McNeese D, Buzdar U, Hortobagyi N, Singletary E: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 17: 460-469, 1999.
9) Freilich J, Seidman D, DeAngelis M: Central nervous system progression of metastatic breast cancer in patients treated with paclitaxel. *Cancer* 76: 232-236, 1995.
10) Paterson G, Agarwal M, Lees A, Hanson J, Szafran O: Brain metastases in breast cancer patients receiving adjuvant chemotherapy. *Cancer* 49: 651-654, 1982.
11) Crivellari D, Pagani O, Veronesi A, Lombardi D, Nole F, Thurlimann B, Hess D, Borner M, Bauer J, Martinelli G, Graffeo R, Sessa C, Goldhirsch A: High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel. *Ann Oncol* 12: 353-356, 2001.
12) DiStefano A, Yap Y, Hortobagyi N, Blumenschein R: The natural history of breast cancer patients with brain metastases. *Cancer* 44: 1913-1918, 1979.
13) Tsukada Y, Fouad A, Pickren W, Lane W: Central nervous system metastasis from breast carcinoma: autopsy study. *Cancer* 52: 2349-2354, 1983.
14) Slimane K, Andre F, Delaloge S, Dunant A, Perez A, Grenier J, Massard C, Spielmann M: Risk factors for brain relapse in patients with metastatic breast cancer. *Ann Oncol* 15: 1640-1644, 2004.
15) Clark M, Sledge W, Osborne K, McGuire L. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 5: 55-61, 1987.
16) Miller D, Weathers T, Haney G, Timmerman R, Dickler M, Shen J, Sledge W: Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. *Ann Oncol* 14: 1072-1077, 2003.
17) Bendell C, Domchek M, Burstein J, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R, Winer E: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 97: 2972-2977, 2003.
18) Matsumoto K, Shimizu C, Fujiwara Y: The next step to approaching central nervous system metastasis in HER-2-positive metastatic breast cancer patients. *Asia-Pac J Clin Oncol* 2: 6-8, 2006.