（様式Ⅱ）

診療等倫理審査結果通知書

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申請者　竹元 伸之　殿

社会医療法人ジャパンメディカルアライアンス
東埼玉総合病院
病院長　福田 良昭

診療等の名称　Pleomorphic carcinoma of the breast: A case report and review of the literature

主たる担当者名　竹元 伸之

従たる担当者名　安田 政実、島中 弘輔、山本 宏

2025 年 4 月 13 日に申請のあった上記診療等の実施計画については、
治験倫理・学会等承認委員会の審査に基づき、次の通り通知する。

①　**申請を承認する。**
2　申請は、条件付きをもって承認する。
3　申請は、不承認とする。
4　申請について内容の変更を勧告する。
5　申請は、要綱に該当しない。

条件 以　上

（様式Ⅰ）

診療等倫理審査申請書

令和 7 年　4 月　13 日

社会医療法人　ｼﾞｬﾊﾟﾝﾒﾃﾞｨｶﾙｱﾗｲｱﾝｽ
東埼玉総合病院　病院長　殿

申請名　竹元 伸之　印
所　属　乳腺・甲状腺外科
職　名　科長

※受付番号

1　診療等の名称　Pleomorphic carcinoma of the breast: A case report and review of the literature

2　主たる担当者名　竹元 伸之

3　従たる担当者名

1．安田 政実　所属　岐阜赤十字病院 病理部　職名　嘱託医師
2．島中 弘輔　所属　JMA 東埼玉総合病院 乳腺・甲状腺外科　職名　非常勤
3．山本　宏　所属　JMA 東埼玉総合病院 乳腺・甲状腺　職名　医員

4　診療等の必要性（意義）、対象、計画、期間及び実施場所

乳がん Pleomorphic carcinoma（以下 PC）は、日本では数件の症例報告のみであり、世界でも 10 例以上の症例をまとめて検討した論文は 3 本しかない非常に稀な乳がんである。それゆえ未知のことが非常に多いのだが、どの文献も PC の悪性度の高さ、成長速度の早さについては、その報告が共通している。本症例も患側全摘後 4 週間で対側乳腺への転移を認め、その 13 週間後には、左胸腔がほぼ腫瘤に占められるようになるという驚くべき進行スピードであった。PC について文献的考察を含めて報告する。投稿予定の Manuscript、そして appendix を資料として添付する。

5　診療等における医学倫理的配慮について（　1）～3）は、必ず記載とのこと）

1）　診療等の対象となる個人及びその家族の関係者に対する人権の擁護

今回の論文は症例報告であり、いわゆる study ではない。臨床を行っていく上で行った検査のみを材料に

検討を行っており、今回の論文作成のためだけに＝data 採取のためだけに、行った検査は一つもない。プライバシーの保持は慎重に行う必要があり、ID、氏名、生年月日、手術日等、個人の特定につながる可能性のあるデータは全て削除してある。

2）　診療等の対象となる個人及び家族等の関係者に対し理解を求め、同意を得る方法

乳腺・甲状腺外科では、患者さん、そのご家族に対し手術前、手術の内容、併発症等の説明の他に、画像検査をはじめとする臨床内容について、学会、論文等で発表する可能性があることについてもお話ししている。発表時には、ID、氏名、生年月日、手術日等は全て削除し、個人の特定につながるようなことが起こらないような処置をとることもお話しし、これらの内容は、口頭だけでなく文書で了承を頂いている。

3）診療等によって生ずる個人及びその家族等の関係者に対する不利益並びに医学上の貢献の度合いの予測

患者さん、ご家族に対する不利益はないと考える。
本症例の疾患は報告例が very rare なため、今後の症例の集積、解析が必須であるが、その結果次第では、今後の乳がんの治療方針に変更が生じる可能性も考えられ、そういう意味では、症例報告としての論文発表は意義のあることと考える。

4）倫理委員会、そして病院への要望

論文投稿規定は年々厳しくなっており、現在では投稿論文に「本 study は病院倫理委員会の承諾を得ている」ことを記載することは常識となった。しかしそれは Original Article の話しであり、自分の正直な意見を申し上げれば、Case Report で、倫理委員会への申請、承諾が必要とは思わない。それは「Defensive medicine」以外の何物でもなく、『やり過ぎ』だと思う。しかし症例報告であっても
「Manuscripts reporting studies involving human participants, human data or human tissue must:
・include a statement on ethics approval and consent (even where the need for approval was waived)
・include the name of the ethics committee that approved the study and the committee's reference number if appropriate」
と記載している雑誌もある。つまり Case Report であっても、倫理委員会を通すことが『常識』になりつつあるということである。
それが正しいことがどうかの議論は、ここで行うべきことではないので、これ以上は言及しないが、現実がそのように変わってきている以上、論文を投稿したいと考えるのならば、それに従うしかない。
今回の論文投稿に当たり、投稿先より「病院の倫理委員会が発行した Certification の添付」を要求された時には、病院、そして委員会の名で『英語』で Certification を発行して欲しい。現在の論文投稿はインターネット経由での投稿となっているため、Certification の書式は『Pdf』で頂けたら助かります。
よろしくお願いします。

注意事項　1　審査対象となる実施計画書又は診療成果の公表原稿があるときは、そのコピーを添付して下さい。

2　※欄は記入しないこと

Title: Pleomorphic carcinoma of the breast: A case report and review of the literature

Authors: Nobuyuki Takemoto[1)], Masanori Yasuda[2)], Kousuke Shimanaka[1)], and Hiroshi Yamamoto[1)]

Affiliations:

1) Department of Breast & thyroid Surgery, Japan Medical Alliance East Saitama General Hospital, 5-517, Yoshino, Satte-City, Saitama-Pref, Japan
2) Department of Pathology, Japanese Red Cross Gifu Hospital, 36-3, Iwakuramachi, Gifu-City, Gifu-Pref, Japan

Corresponding author

Nobuyuki Takemoto M.D. Ph.D.:

Department of Breast & Thyroid Surgery, Japan Medical Alliance East Saitama General Hospital, 5-517, Yoshino, Satte-City, Saitama-Pref, 0153-340, Japan

Tel: +81-480-40-1311 Fax: +81-480-40-1370

E-mail: monochrome-rainbow@iijmio.mail.jp

Abstract (250 words)

Introduction and importance: Pleomorphic carcinoma of the breast is extremely rare, accounting for less than 0.1 % of breast malignancies. It has

a poor prognosis, but its clinicopathologic features are not well characterized.
Case presentation: A 49-year-old woman was diagnosed with bilateral breast cancer (rt: cT2cN0M0 cstageIIA, lt: cT2cN1M0 cstageIIB) and its intrinsic type was non-luminal type (right breast) and lumina A-like (left breast). After neoadjuvant chemotherapy, the patient achieved pathologic partial response and underwent breast-conserving surgery with axillary lymph node dissection and radiotherapy. After 6 years and 7 months, local recurrence in the right breast was observed, and mastectomy was performed. However, after 4 weeks, metastasis to the contralateral breast was found, and a further 13 weeks later, 70% of the thoracic cavity was occupied by metastatic pleural tumors. Pathological findings suggested pleomorphic carcinoma. The patient passed away 181 days after the diagnosis of local recurrence.
Clinical discussion: Pleomorphic carcinoma could represent an extreme end of dedifferentiation of invasive breast carcinoma of no special type or part of the differentiation of metaplastic spindle cell carcinoma. It is also important to differentiate this from malignant tumors such as sarcomas with giant cells or spindle cells, and metastatic tumors. Diagnosis requires lack of heterologous non-epithelial components, and strong immunostaining with epithelial markers.
Conclusion: When a rapidly growing breast mass is encountered, pleomorphic carcinoma should be considered. More case accumulation and analyses are awaited to further characterize this carcinoma.

Key Words: pleomorphic carcinoma, breast, rapidly growing, differential

diagnosis

Case Report (1500 words)

1. Introduction

The term "invasive breast carcinoma (IBC) of no special type (NST)" refers to a large and heterogenous group of IBCs that cannot be classified morphologically as any of the special histological types [1]. Pleomorphic carcinoma (PC) belongs to this group, and is a rare pattern of high-grade IBC-NST characterized by proliferation of pleomorphic and bizarre tumor giant cells constituting > 50% of the tumor cells [1], with only three previous reports examining more than 10 cases [2-4]. The clinical course of PC is rapid and aggressive, with a poor prognosis [2-4]. However, because there are only a few reported cases, little research has been done, especially on imaging and treatment methods. We therefore report a case of breast cancer in which invasive ductal carcinoma transformed into highly malignant PC, resulting in rapid progression and poor prognosis. We report this case with a literature review.

2. Case

A 49-year-old woman was diagnosed with bilateral breast cancer (Rt: cT2cN0M0 cstageIIA , Lt: cT2cN1M0 cstageIIB) and its intrinsic type was non-luminal type (Estrogen & Progesterone receptor positive, HER2 3+, ki67 31%) in the right side and lumina A-like (Estrogen & Progesterone & HER2 negative, ki67 <5%) in the left side. As neoadjuvant chemotherapy,

four cycles of adriamycin and cyclophosphamide (60/600mg/m^2) every three weeks, followed by paclitaxel (80mg/m^2) and trastuzumab (loading 4mg/kg, maintenance 2mg/kg) given weekly for 12 weeks were administered, and the patient achieved clinical partial response on imaging. Bilateral breast-conserving surgery and axillary lymph node dissection were performed, and the pathological finding was pathologic partial response (Rt: ypT1bypN0M0 ypstageI, Lt: ypT1cypN0(i+)M0 ypstageI), and the therapeutic effect was Grade 1. After radiotherapy (50Gy/25Fr) of the residual mammary gland, trastuzumab (6mg/kg) was administered but the patient requested to discontinue treatment after 2 courses. Thereafter, the patient was subsequently followed with endocrine therapy (Tamoxifen). In February 2023 (6 years and 7 months after the initial operation), the patient visited the hospital complaining of swelling and erosion of the right nipple. CT scan showed a swollen right nipple **(Figure 1)**, and 3 stump cytology tests for the erosion were negative, but the nipple itself showed a tendency to grow, so a core needle biopsy (CNB) was performed. The pathological findings showed invasive carcinoma, and suggested that metaplastic carcinoma is suspected. As no metastases to other organs were found, a right mastectomy was performed and postoperative chemotherapy was planned, but 4 weeks after the operation, a round mass of approximately 1 cm was found in the B area of the left breast. CNB revealed a suspected malignant metaplastic carcinoma. It was determined that there was a high possibility of metastasis to the contralateral side, and since images did not reveal metastasis to other organs, a left mastectomy was performed. However, 12 weeks later, a left

pleural tumor and a right chest wall mass appeared, and after a further 13 weeks, the left thoracic cavity was occupied by almost 70% by a pleural mass, and the right chest wall mass grew to 10cm in size. **(Figure 2).** Furthermore, the WBC count rose rapidly to 98.8 x 103/μL (Ne 94.8, Lym 2.5, Mono 1.9). Bone marrow metastasis was suspected but bone marrow aspiration could not be performed due to the patient's poor general condition. The patient passed away 181 days after the diagnosis of local recurrence. Pathological examination showed PC transitioning from ductal carcinoma, and the subtype was triple negative breast cancer (TNBC). Based on immunostaining, AE1/3 (Anti-pan Cytokeratin), Beta-catenin, E-cadherin and Vimentin were positive, and CAM5.2 (cytokeratin), HBM45 (human melanin black45) and LCA (Leukocyte Common Antigen) were negative. It was a highly malignant transformation of ductal carcinoma, and it took the form of a so-called dedifferentiated carcinoma, consisting of differentiated and undifferentiated components. **(Figure 3)**.

3. Discussion

PC of the breast is extremely rare, accounting for less than 0.1 % of all breast malignancies. [4] It can occur at any age, but it apparently occurs most frequently during the perimenopausal period[4)]. It is highly malignant, and Silver et al. [2] point out that the most common characteristic is rapid growth, with palpable masses appearing in 65% of cases over a period of several weeks to two years. Invasion of the skin and pectoral muscles is not uncommon, and the disease progresses quickly to distant and lymph node

metastases. [4] In line with these previous reports, our case also had an astonishing rate of progression.

Due to the small number of cases of PC, imaging tests have hardly been studied. PC often does not show typical cancer findings, and it has been reported that MMG and US are not useful. [2] However, it has also been reported that in cases of large tumors (average tumor diameter 7.8 cm), the tumors tend to show a cystic mass appearance due to cavitation caused by central necrosis. [5] In our case, the right nipple was enlarged compared to the opposite side, but there was no clear evidence of marginal irregularity, making it difficult to diagnose cancer through imaging tests.

PC is usually diagnosed by pathology, but the pathological findings via core needle biopsy in our case suggested that metaplastic carcinoma is suspected, and a diagnosis of PC could not be made. Silver et al. [2] reported that spindle cell infiltration was observed in 31% of PC cases, Nguyen et al. [3] reported 38%, and Jing et al. [4] reported 20%. In diagnosing PC, it is important to differentiate it from other malignant tumors such as giant cell or spindle cell sarcomas. Silver et al. [2] reported that 35% of PC cases were diagnosed as sarcomas or possible sarcomas. In particular, in cases where the tumor border is clearly fine, there have been reports of misdiagnosis as metastatic tumors. [4] In terms of histological diagnosis of PC, it is important to carefully search for areas where PC shows transition from invasive ductal carcinoma. It is also important to distinguish between PC and metaplastic carcinoma. For example, it is essential that there are no heterologous components including bone, cartilage, and striated muscle as non-epithelial tissues of the tumor for

a definite diagnosis of PC. When both epithelial and heterologous components look malignant, carcinosarcoma should be considered. Immunostaining can serve as a substantial tool for making a diagnosis of histological variants represented by PC. Specifically, immunohistochemical expression of epithelial markers such as a cytokeratin may be helpful for the diagnosis of PC. For example, PC can be differentiated from pleomorphic lobular carcinoma with positive reaction of e-cadherin. Jing et al. [4] reported that bizzare giant cells are also observed in sarcomas, but that immunostaining for epithelial and mesenchymal markers is useful for diagnosis because epithelial morphology of other tumor components is usually missing in sarcomas. In addition, it has been reported that the following points are helpful in distinguishing cancer from the osteoclastic giant cells: osteoclastic giant cells and fibroblasts are negative for epithelial markers [6], and osteoclastic giant cells are often regularly shaped, have round to ovoid nuclei, and are not hyperchromatic. [3] There are multiple reports showing that TNBC is the most common subtype of PC [2-4, 7], but one study showed that HER2 is overexpressed. [1]

Very little research has been conducted on postoperative treatment for PC, which may partly be explained by the fact that it is rare but this also could be related to the unique pathology of this disease, where the rate of progression is so rapid that treatment cannot keep up, as in our case. Treatment often consists of surgery [2,8,9], and the commonly chosen procedure is mastectomy, given that the tumor tends to be large at the time of diagnosis, and have high-grade characteristics, with increased likelihood

that lymph node metastasis exists [8]. Regarding chemotherapy, there are no reports of chemotherapy that is effective for PC and existing anticancer drugs has been ineffective [10]. Furthermore, there are reports of cases in which recurrent disease was resistant to chemotherapy and/or radiation therapy [11]. Based on previous studies, the prognosis of PC is known to be poor [2-4], Nguyen et al. [3] reported that a tumor size of 5 cm or more and the presence of spindle cell infiltration were independent poor prognostic factors, and that the 5-year survival rates differed significantly between those with and without spindle cell infiltration (38% and 89%), and between tumor size ≥5 cm and <5cm (39% and 87%). The recurrence rate is very high, and metastases occur in a wide variety of locations, including the liver, lungs, pleural surfaces, vertebral bone, and local recurrence. [2] According to Silver et. al [2], of 16 patients with follow-up, 6 (38%) were disease-free (mean, 74 months), 4 (25%) alive with disease (mean, 33 months) and 6 (38%) died at a mean of 22 months. In our case, local recurrence occurred despite negative surgical margins, suggesting that the cancer spread widely via blood vessels and lymphatic vessels. This is also thought to be a factor that contributes to the high recurrence rate.

4. Conclusion

When a rapidly growing breast mass is encountered, it is necessary to consider PC when making a differential diagnosis. Further case accumulation and analyses are awaited to gain more insight on the characteristics of PC.

Figure 1: Enhanced Thoracic Computed Tomography Scan (CT); The right nipple is swollen and has a mass-like appearance compared to the opposite side. A slightly high-density area is observed directly below the nipple, but the shape is flat, the internal density is homogenous, and there are no signs of invasiveness around it, making it difficult to diagnose a recurrence based on this image alone.

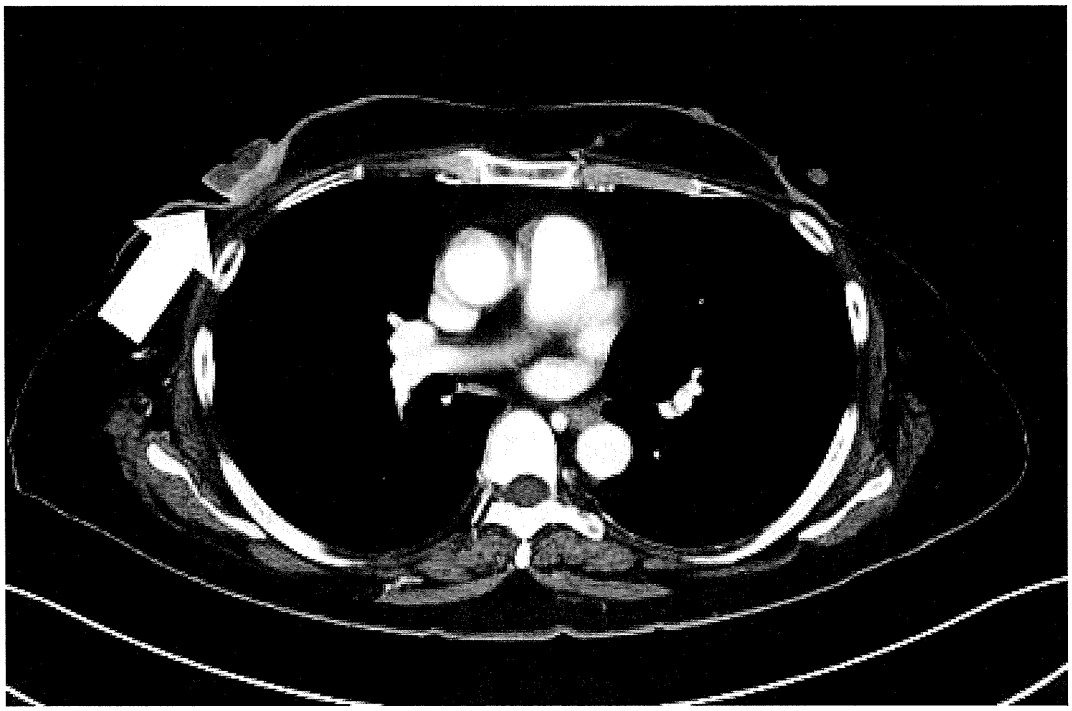


Figure 2: Simple Thoracic CT; (A) 4 weeks and (B) 17 weeks after operation of right local recurrence. The right chest wall mass and left pleural tumor grew rapidly, and after 17 weeks, the left thoracic cavity was almost 70% occupied by a pleural mass and the right chest wall mass grew to 10cm in size.

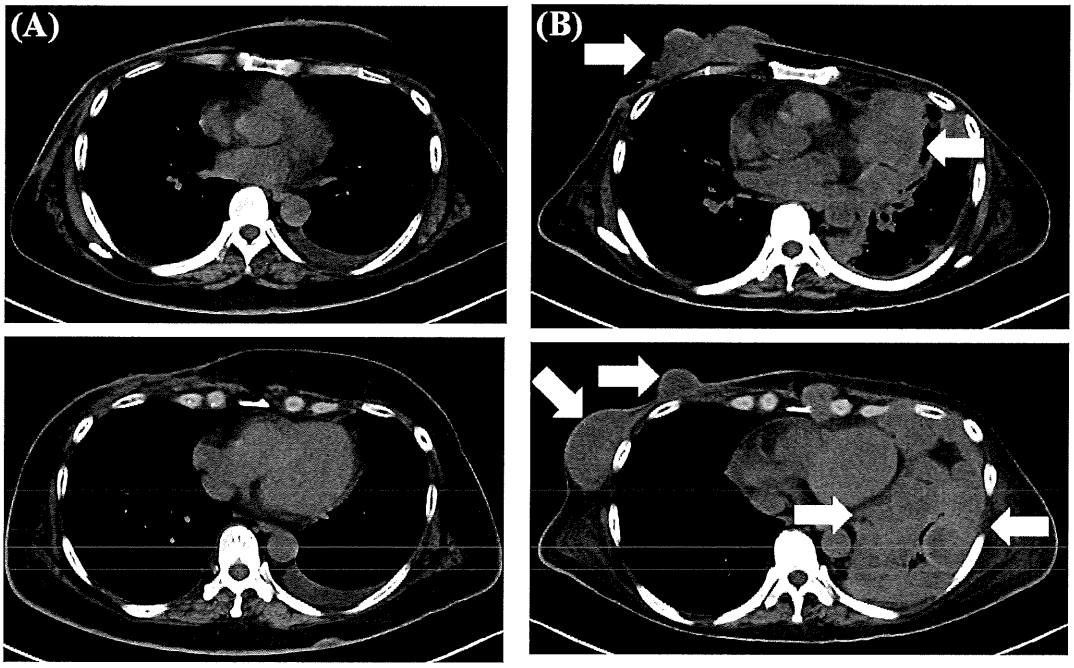
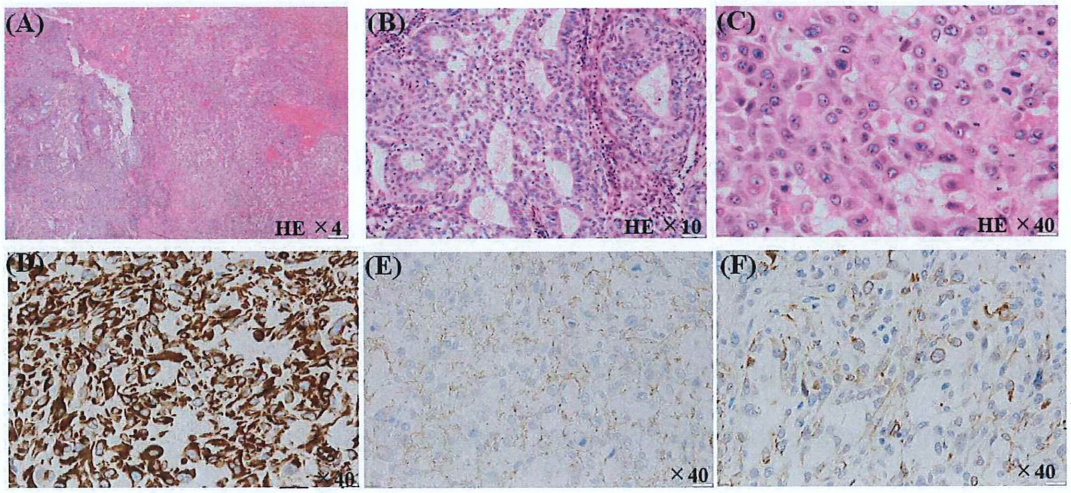


Figure 3: Pathological findings: (A) pleomorphic carcinoma of the left side transitioning from invasive ductal carcinoma of the right side (HE×4). (B) typical invasive ductal carcinoma. (HE×10) in the right side and (C) pleomorphic carcinoma in the left side. (HE×40). (D) is positive for Vimentin (×40), (E) is negative for E-cadherin (×40), and (F) is negative for AE1/3 (×40).



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Consent

Written informed consent was obtained from the patient and family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Guarantor

None.

CRediT authorship contribution statement

NT (Nobuyuki Takemoto) performed the operation, chemotherapy, and

outpatient follow up of the patient, conducted the literature review, and wrote the manuscript. MY (Masanori Yasuda) performed the histological examination. KS (Kousuke Shimanaka) and HY (Hiroshi Yamamoto) assisted in the operation. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://・・・

References

1) Breast Tumours WHO Classification of Tumours, 5th Edition, Volume 2 : WHO Classification of Tumours Editorial Board 2019, P102-110.
2) Silver SA, Tavassoli FA. Pleomorphic carcinoma of the breast: clinicopathological analysis of 26 cases of an unusual high-grade phenotype of ductal carcinoma. Histopathology. 2000 Jun;36(6):505-14.
3) Nguyen CV, Falcón-Escobedo R, Hunt KK, et al. Pleomorphic ductal carcinoma of the breast: predictors of decreased overall survival. Am J Surg Pathol. 2010 Apr;34(4):486-93.

4) Jing Zhao, Ronggang Lang, Xiaojing Guo, et al. Clinicopathologic characteristics of pleomorphic carcinoma of the breast. Virchows Arch. 2010 Jan;456(1):31-7.

5) Kobayashi T, Okabayashi H, Takehara Y, et al. A case of pleomorphic carcinoma of the breast in a 102 years old woman. Surgery. 2018;80(7):738-743 (Japanese)

6) Eusebi V, Magalhaes F, Azzopardi JG. Pleomorphic lobular carcinoma of the breast: an aggressive tumor showing apocrine differentiation. Hum Pathol. 1992 Jun;23(6):655-62.

7) Tang H, Liu F, Li H, Huang X, et al. Pleomorphic carcinoma of breast: a case report and review of literature. Int J Clin Exp Pathol. 2014 Jul 15;7(8):5215-20.

8) Buchanan CL, Flynn LW, Murray MP, et al. Is pleomorphic lobular carcinoma really a distinct clinical entity?. J Surg Oncol. 2008 Oct 1;98(5):314-7.

9) Jacobs M, Fan F, Tawfik O. Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature. Ann Diagn Pathol. 2012 Jun;16(3):185-9. Lehmann

10) Lehmann BD, Bauer JA, Chen X, Sanders ME, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67.

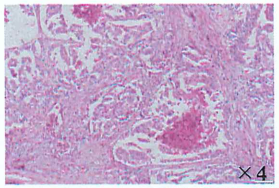
11) Kobayashi T, Kagawa T, Okabayashi H, et al. Pleomorphic carcinoma of the breast with multiple recurrence shortly after surgery th

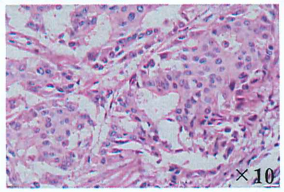
was resistant to chemo-radiation therapy. Jap J Breast Cancer 2014; 29: 375-384 (Japanese)

Appendix Images

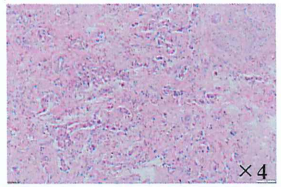
Figure A. Primary breast cancer pathological findings after NAC (HE)

(a) Right breast cancer





(b) Left breast cancer



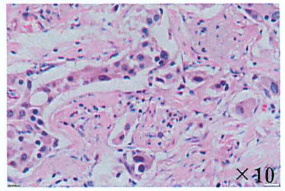
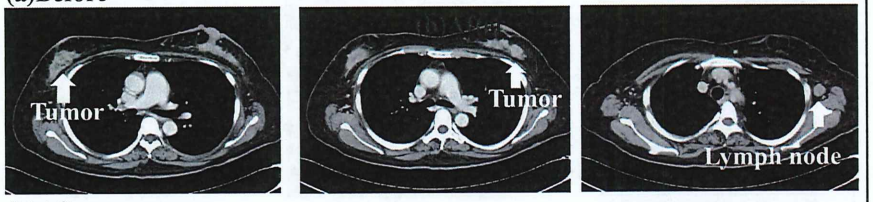


Figure B. Enhanced CT images before and after NAC

(a)Before



(b)After

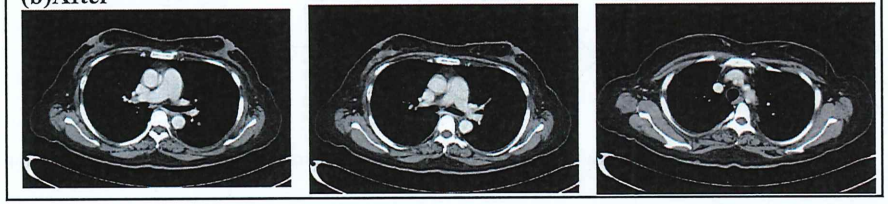
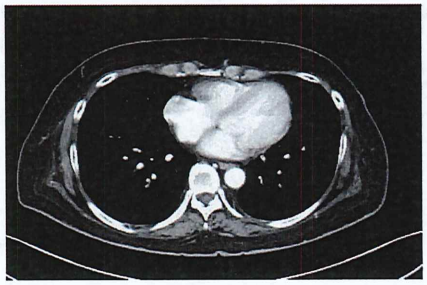
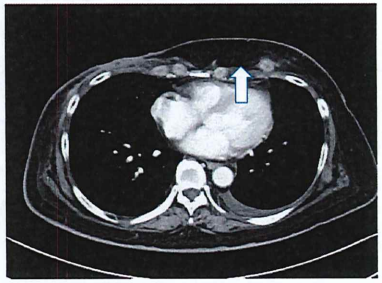


Figure C. Metastasis to left mammary gland

(a) Before operation of right breast local recurrence



(b) 4 weeks after right breast local recurrence operation



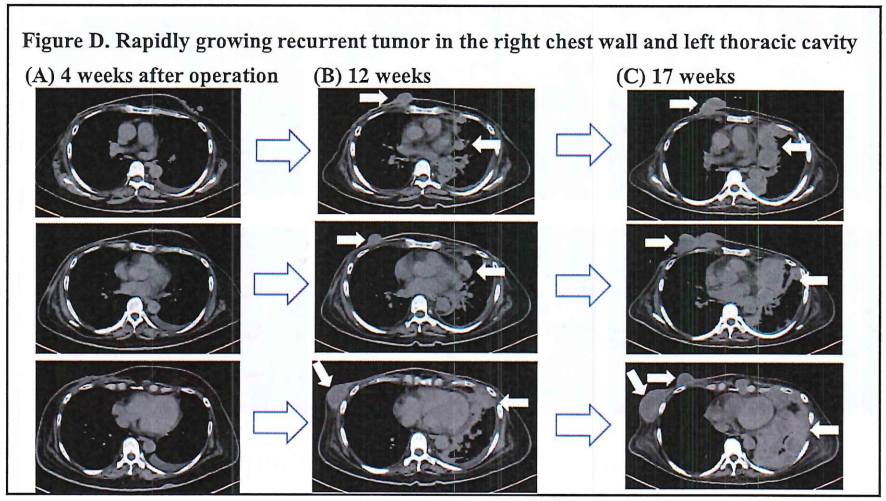


Figure D. Rapidly growing recurrent tumor in the right chest wall and left thoracic cavity
(A) 4 weeks after operation
(B) 12 weeks
(C) 17 weeks

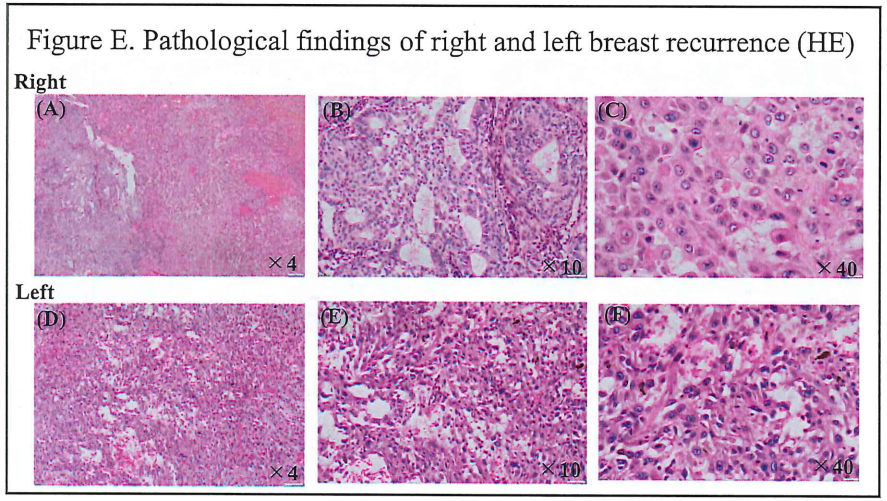


Figure E. Pathological findings of right and left breast recurrence (HE)
Right
(A)
×4
(B)
×10
(C)
×40
Left
(D)
×4
(E)
×10
(F)
×40