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## Case Report

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# Two Cases of Invasive Micropapillary Carcinoma of the Breast without Lymph Node Metastasis and Apparent Lymphatic Vessel Invasion

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**Abstract:** Invasive micropapillary carcinoma (IMP) is a clinically aggressive variant of invasive ductal carcinoma with a high rate of axillary lymph node (LN) metastasis, lymphatic vessel invasion (LVI), and poor prognosis. We observed 2 rare cases of breast IMP without LN metastasis and apparent LVI. We report these cases and a review of the available literature. One case is that of a 74-year-old woman with clinical stage I breast carcinoma (T1NM0). The other case is that of a 65-year-old woman with clinical stage IIB breast carcinoma (T2N1M0). Both patients underwent modified radical mastectomy with axillary LN dissection. Microscopic examination revealed that most invasive parts of the tumours comprised the IMP component. LN metastasis or LVI was not detected. Both tumours tested positive for the oestrogen receptor but negative for the HercepTest. In case 1, postoperative letrozole was administered. In case 2, postoperative letrozole was sequentially administered after 4 cycles of adjuvant chemotherapy comprising docetaxel and cyclophosphamide. Both patients have an uneventful follow-up without signs of recurrence. Whether such rare IMP tumour types can be managed as effectively as other common forms of breast carcinoma is unknown. Further studies should evaluate the outcome of IMP treatment protocols and establish the therapeutic strategy.

**Key Words:** Breast cancer, Invasive Micropapillary Carcinoma, Lymph Node Metastasis, Lymphatic Vessel Invasion, Therapy.

## Introduction

Invasive micropapillary carcinoma (IMP) is a characteristic histological pattern of breast carcinoma. It is considered a clinically aggressive variant of invasive ductal carcinoma with a high rate of axillary lymph node (LN) metastasis, lymphatic vessel invasion (LVI), and poor prognosis<sup>1-8)</sup>. These

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characteristics are prevalent even when IMP is not a predominant component of the total neoplasm<sup>9-13</sup>. However, the 2 IMP cases described here did not demonstrate these pathological features. Here, we report 2 rare cases of IMP without associated LN involvement and apparent LVI. In addition, we review the relevant literature (Table 1).

### Case 1

A 74-year-old woman was admitted to our hospital with a mass in her left breast. Physical examination revealed a fixed firm mass (diameter, about 2 cm) in the lower inner quadrant, with no redness of skin and breast dimpling. The LNs were not palpable in the left axillary region.

Mammography revealed a microlobulated and serrated dense mass, on the left pectoralis major muscle (Fig. 1A). An irregular hypoechoic mass (area, 16×15 mm) with an indistinct boundary in the lower-inner quadrant of the left breast was revealed through ultrasonography (Fig. 1B). Enhanced computed tomography (CT) revealed an enhanced mass infiltrating the surrounding fat tissue (Fig. 1C). Swollen axillary LNs were not detected by ultrasonography or CT. Breast carcinoma without metastasis was diagnosed on the basis of our image analyses findings. A core-needle biopsy with a 14-gauge needle revealed small cancer nests floating within clear spaces. At the time of biopsy, the woman was diagnosed with mucinous carcinoma of the breast. Because the patient was reluctant to undergo breast-conserving therapy, we performed modified radical mastectomy with LN dissection. At the time of surgery, sentinel LN biopsy was not performed in our hospital.

Table 1. Clinicopathological features of invasive micropapillary carcinoma of the breast

Reference	Year	N	Mean age (years)	LNM (%)	Mean pos.LNs (%)	LVI (%)	ER (%)	PgR (%)	HER2 (%)	Follow-up	Prognosis
Siriaukgul[14]	1993	9	62	44	N/A	33	N/A	N/A	N/A	max 4.7Y	one case local rec. 2.8Y after mastectomy
Middleton[8]	1999	14	50	N/A	N/A	71	25	12.5	100	1-12Y	nine cases local rec. 50% dead of IMP, 50% alive with disease
Luna-More[7]	2000	68	54	91	9.5	58.8	74.5	46.3	36.4	mean 53M	37% dead, 7.4% alive with metastatic disease, 44.1% disease free
Tresserra[6]	1999	15	52	60	8.1	N/A	92 <sup>*)</sup>		N/A	2M-24M	27% local rec.
Paterakos[5]	1999	21	55	95	8.6	N/A	62	50	81	N/A	N/A
Nassar[10]	2001	83	61	77	6	N/A	N/A	N/A	N/A	mean 7Y	46% dead of IMP, 40% alive
Tsumagari[11]	2001	91	54	71	11	54	N/A	N/A	N/A	N/A	31.7% Sc rec., 6.7% local rec. 5-year survival 51%, 5-year relapse 63%
Walsh[12]	2001	80	59	72	N/A	63	91	70	59	N/A	N/A
Kuroda[4,18]	2004	27	53	67	12	89	70	56	26	max above 6Y	59% dead of IMP, 41% alive without disease
Pettinato[3]	2004	62	57	93	N/A	63	32	20	95	mean 8.9Y	71% local rec. 49% dead of IMP
Zekioglu[2]	2004	53	53	69	N/A	76	68	61	54	mean 57M	22.2% local rec., 25% distant meta. 28% dead of IMP
Chen[13]	2008	100	50	85	14	69	46	27	N/A	mean 60M	11% local rec., 39% distant meta. 37% dead of IMP
Yu[1]	2010	72	46 <sup>*)</sup>	N/A	N/A	68	75	72	36	median 45M	locoregional rec. 13.9% 5-year OS 86%, 5-year RFS 68%

LNM lymph node metastases, LVI lymphatic vessel invasion, pos. positive, LNs lymph nodes, N/A not available, Y years, M months, rec. recurrence, IMP invasive micropapillary carcinoma, Sc supraclavian lymph node, meta. metastasis, OS overall survival, RFS recurrence-free survival  
<sup>\*)</sup> ER and/or PgR positive  
<sup>\*\*)</sup> median age

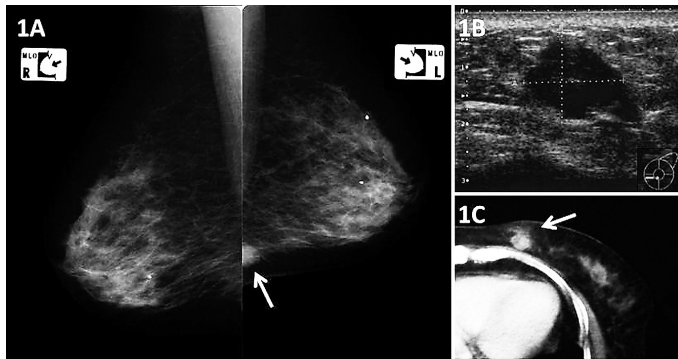


Fig. 1. Images of case 1

Mammography (1A): A microlobulated serrated dense mass is visible on the left psoas major muscle (arrow). Ultrasonography (1B): An irregular hypoechoic mass with an area of  $16 \times 15$  mm and an indistinct boundary is visible in the lower-inner quadrant of the left breast. Enhanced CT (1C): An enhanced mass infiltrating the surrounding fat tissue was observed in the left breast (arrow).

### Pathological findings

Macroscopic examination showed that the tumour was a firm mass, with an area of  $1.5 \times 1.5$  cm, was grayish-white in colour, and had an irregular margin. Microscopic findings demonstrated typical IMP structure within all the invasive parts of the tumour. Lymphovascular permeation was not detected by immunostaining with D2-40 or Victoria Blue (Fig. 2). Eleven LNs were resected, and no metastasis

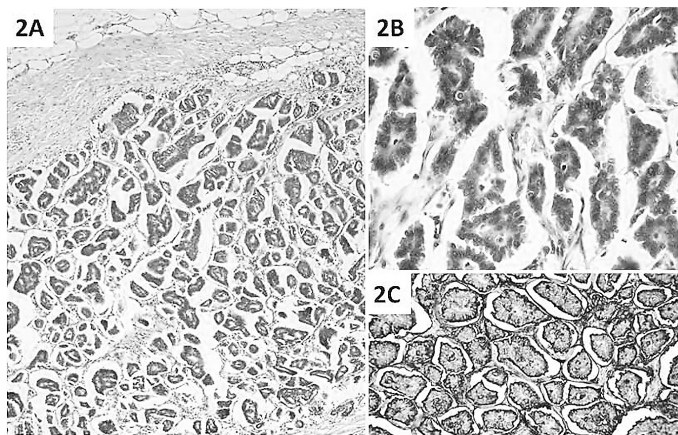


Fig. 2. Microscopic findings of case 1

Micropapillary cancer nests mimicking massive LVI were floating within clear spaces delimited by thin fibrocollagenous stroma (2A: H&E staining;  $\times 100$ ). Most of the papillae lacked true vascular cores. Lineal deposits of EMA rimmed the external clusters of cancer cells, and the polarity of each cancer nest was reversed (2B: H&E staining;  $\times 400$  and 2C: EMA staining;  $\times 200$ ).

was discovered. The tumour was determined to be of grade I by using the modified Scarff-Bloom-Richardson histological grading system (tubule formation, 2; nuclear atypia, 2; mitosis, 1). Immunohistologically, the tumours tested strongly positive for both oestrogen (ER) and progesterone (PgR) receptors but negative for the Her2/neu protein (HER2).

Postoperative letrozole was administered, and the patient continues to have an uneventful follow-up for 19 months after surgery without signs of recurrence.

## Case 2

A 65-year-old woman visited a clinic with a mass in her right breast. A core-needle biopsy was performed at the clinic with a 14-gauge needle, and the mass was diagnosed as IMP. She was introduced to our hospital for therapy 3 weeks after her first visit to the clinic. Physical examination revealed a fixed firm mass (diameter, 3 cm) located in the upper-outer quadrant, with no redness of skin or breast dimpling. LNs were not palpable in the right axillary region.

Mammography of the right breast revealed a lobulated dense mass with small, round, and grouped microcalcifications (Fig. 3A, 3B). Ultrasonography also showed a hypoechoic lobulated mass with an

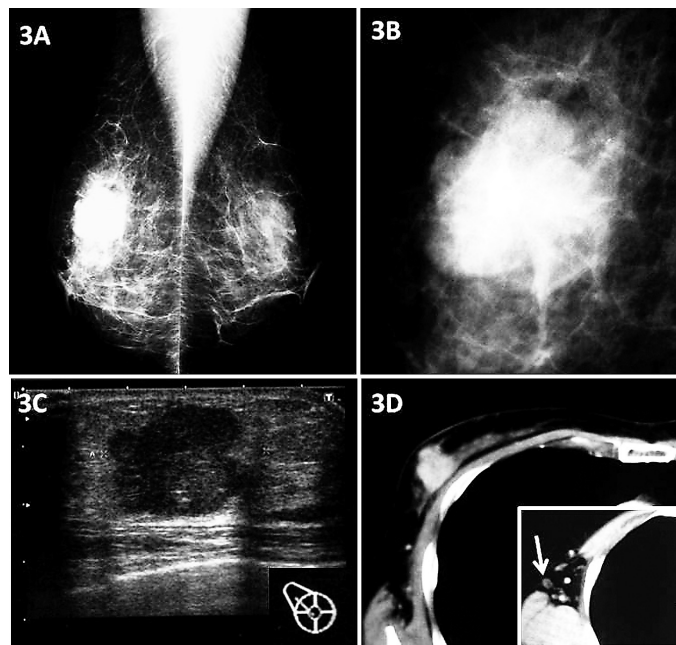


Fig. 3. Images of case 2

Mammography (3A, 3B): A lobulated dense mass is visible in the upper-middle area of the right breast (3A). The mass was accompanied by small, round, and grouped microcalcifications (3B). Ultrasonography (3C): A hypoechoic lobulated mass with an area of 28×24 mm is visible in the upper-outer quadrant of the right breast. Enhanced CT (3D): An enhanced mass with marked borders was detected in the right breast. In addition, few small, round axillary LNs considered as metastases were observed (arrow).

area of 28×24 mm possessing a posterior shadow (Fig. 3C). Enhanced CT revealed an enhanced mass with marked borders with 2 or 3 swollen right axillary LNs that were considered metastases (Fig. 3D).

The patient refused to undergo neo-adjuvant or breast-conserving therapy; therefore, we performed a modified radical mastectomy with LN dissection.

### Pathological findings

Macroscopic examination showed that the tumour was a grayish-white firm mass (area, 2.5×2.5 cm) with a well-defined margin. Microscopic findings demonstrated a typical IMP structure throughout most of the invasive part of the tumour. Lymphovascular permeation was not detected by immunostaining with D2-40 or Victoria Blue (Fig. 4). Twenty-nine LNs were resected, and no metastasis was found. The tumour was determined to be of grade II according to the modified Scarff-Bloom-Richardson histological grading system (tubule formation, 3; nuclear atypia, 2; mitosis, 2). Immunohistologically, 30-40% of the tumour cells tested positive for ER but negative for both PgR and HER2.

Postoperative letrozole was sequentially administered after 4 cycles of adjuvant chemotherapy. The chemotherapy involved administration of 75 mg/m<sup>2</sup> of docetaxel with 600 mg/m<sup>2</sup> of cyclophosphamide (TC therapy). The patient continues to have an uneventful follow-up for 14 months after surgery without signs of recurrence.

### Discussion

IMP was first described by Siriaunkgul and Tavassoli<sup>14</sup> as a distinct type of infiltrating papillary

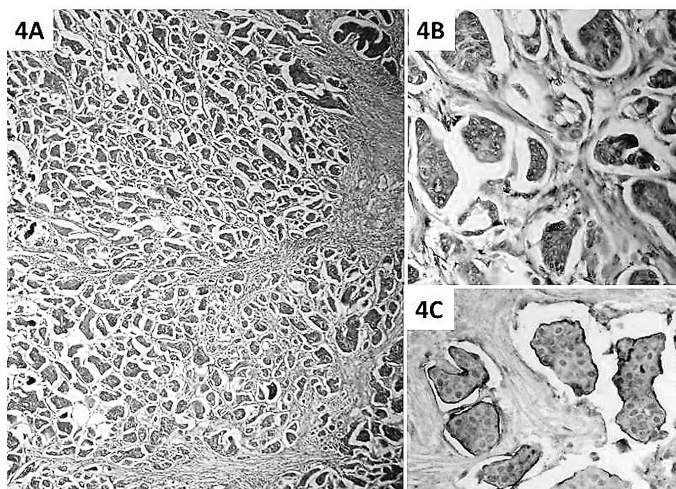


Fig. 4. Microscopic findings of case 2

The tumour consisted of micropapillary cancer nests mimicking massive LVI. They were floating within clear spaces lined by delicate strands of stroma (4A: H&E staining; ×100). Lineal deposits of EMA rimmed the external clusters of cancer cells, and the polarity of each cancer nest was reversed (4B: H&E staining; ×400 and 4C: EMA staining; ×400).

carcinoma characterized by small papillary structures within empty stromal spaces, mimicking massive LVI. Thereafter, IMP has received greater attention, because of its characteristic clinic-pathological features and prognosis (Table 1). IMP carcinoma cells form pseudo-papillary or micropapillary nests without vascular cores and float within the delicate strands of fibrocollagenous stroma. The polarity of each cancer nest is reversed, and the secretion border of each cell faces clear spaces that are formed by fixation change and are identified in HE sections<sup>6,14</sup>. The pathological findings from the above mentioned 2 cases met these criteria. Despite the fact that IMP only accounts for 2-7% of invasive breast carcinomas<sup>1-7,9-12</sup> it receives relatively great attention because of the high incidence of axillary LN metastasis, the large number of nodes involved, and increased incidence of LVI (Table 1). These cases represent a rare type of IMP because axillary LN metastasis and definite LVI were not detected.

Usually, the IMP component of a tumour is observed in the more common forms of invasive carcinoma. Therefore, massive IMP tumours (the so-called pure-type IMP) like those diagnosed in the 2 patients of this study are rare. No consensus has been achieved on the IMP volume required for diagnosis. It remains controversial whether the malignancy potential depends on the proportion of IMP component within a tumour. Several articles investigate the correlation between the proportion of IMP component within a tumour and the aggressive clinicopathological features of the tumour<sup>9-13</sup>. Some articles have reported that there are no significant differences in the proportion of the IMP component in terms of massive axillary occupation or high LVI rate<sup>9,10,12,13</sup>. However, another study has reported that the cases with a high proportion of IMP component have poor prognoses and a high rate of LN metastasis<sup>11</sup>. The common thread of all of these articles is that tumours with an IMP component have malignant potential, even if the proportion of the IMP component is small. Hence, tumours with IMP should be recognized as a distinct entity.

Several studies have been conducted using univariate and multivariate analyses to investigate potential prognostic factors for IMP<sup>1,5,7,10,13</sup>. Peterakos et al.<sup>5</sup> and Nassar et al.<sup>10</sup> reported that the outcome of IMP patients did not differ significantly from that of patients with invasive ductal carcinomas of similar node status. However, Yu et al.<sup>1</sup> compared 72 IMP cases with 144 cases of invasive ductal carcinoma in which the stage and treatment methods were matched to those of IMP patients; they found that IMP history itself was a prognostic factor for poor locoregional recurrence and survival outcome. It remains controversial whether the histological form of IMP or its lymphotropic form — which is a strong prognostic factor in common forms of breast carcinoma — is a prognostic factor. Moreover, many cases of IMP with a high histological or nuclear grade have been reported<sup>2,6,8,12,13</sup>. Grade 3 cases are observed in 32-87% of the IMP cases<sup>2,6,8,12,13</sup>, and some authors have reported that no grade 1 case has been observed in IMP<sup>2,6,12</sup>. The correlation among histological or nuclear grade, lymphotropism, and prognosis of IMP has not been dealt with in studies published hitherto. However, the possibility of high grade itself contributing to the poor prognosis of IMP cannot be denied.

There is no special therapeutic strategy for IMP; therefore, determining primary therapy such as surgery or neo-adjuvant chemotherapy is difficult in cases wherein preoperative diagnosis of IMP has been made. In case 2, preoperative diagnosis of IMP was possible using core-needle biopsy because the tumour had a high proportion of the IMP component. However, in case 1, the patient was misdiagnosed as mucinous carcinoma at the time of preoperative needle biopsy. In case 2, the amount of material preoperatively derived from the core-needle biopsy was insufficient to accurately evaluate LVI. We did, however, inform the patient that in cases of IMP tumours, the resection margins may test positive for

massive LVI, and suggested that axillary LN resection be performed because CT images indicated LN metastases. In addition, the effects of neo-adjuvant chemotherapy were uncertain. The patient agreed to undergo mastectomy with axillary LN resection as the primary treatment for her breast cancer. Locoregional recurrence has been reported to occur frequently in IMP cases, the rates ranging between 11% and 71%<sup>1-3/6/8/11/13</sup>. Tresserra et al.<sup>6</sup> reported that of the IMP patients who received lumpectomy treatment, 27% showed local recurrence despite receiving adjuvant chemotherapy. In addition, 75% of the patients with local recurrence also received radiotherapy, leading the researchers to conclude that lumpectomy is insufficient, even when complemented with radiotherapy. With respect to surgical management of the axilla, some authors suggest that sentinel LN dissection may not be adequate for patients with IMP histology<sup>5/12</sup>. However, in addition to the 2 cases reported here, other cases of IMP without axillary LN metastasis and LVI have been previously reported<sup>15/16</sup>. Considering these cases, sentinel LN resection may be appropriate for IMP patients if preoperative diagnosis detects no axillary LN metastasis. Moreover, lumpectomy may be appropriate for IMP patients if massive LVI is not detected during the preoperative biopsy. Of course, patients need to be informed about potential changes in operative procedures or the need for subsequent operations, depending on their specific pathological diagnosis.

Neo-adjuvant chemotherapy is used increasingly for operative breast cancer with the intention of down-staging large tumours, so that breast-conserving surgery can be considered. In addition, neo-adjuvant chemotherapy validates sensitivity to chemotherapy. We should use caution in adapting neo-adjuvant therapy for IMP tumours because it may not effectively treat them. Alvarado-Cabrero et al.<sup>17</sup> studied the pathological changes in 205 breast cancer patients who were treated with neo-adjuvant chemotherapy involving 4 cycles of anthracycline-based regimens and found that all 29 pure IMP tumours showed no pathological response, whereas tumours of other histological forms showed partial-to-complete response in more than 44% of each histological form of tumour.

In both the cases described in this report, the ER status was positive, and HER2 status was negative. The patients presented with the most common immunohistological subtype of breast carcinoma with respect to the ER/HER2 status. However, we cannot contend that the subtype pattern in our cases is the most common one in IMP. The difference in expression patterns of these markers between IMP and invasive ductal carcinoma remains controversial. ER positivity has been reported in 25-92% of IMP tumours, and over-expression of HER2 has been reported in 26-100% of IMP cases<sup>1-3/5-8/12/13/18</sup>. Zekioglu et al.<sup>2</sup> found that 53 IMP cases, in which the clinical course was worse than that of infiltrating ductal carcinoma, had higher ER and PR positivity than 60 control cases of infiltrating ductal carcinoma. However, ER positivity has generally been associated with highly differentiated tumours that have an improved outcome. Nevertheless, ER positivity may be a potential prognostic factor for IMP. Luna-More et al.<sup>7</sup> studied the progression of 54 IMP patients and found that ER positivity was the most powerful predictor of survival. Chen et al.<sup>13</sup> used the Cox model for multivariate survival analysis and determined that tamoxifen therapy improved the survival of 98 IMP patients. These reports indicate that hormone therapy may effectively treat ER-positive IMP as well as other forms of breast carcinoma.

We treated the IMP cases described above with the same adjuvant therapy used for other common forms of breast carcinoma. For case 2, adjuvant chemotherapy was administered because the diameter of the tumour was greater than 2 cm and the proportion of ER-positive cells was relatively low. Because

it has been reported that an anthracycline-based regimen may not improve the outcome of HER2-negative breast carcinomas<sup>19</sup>, we selected TC therapy, which is a taxane-based regimen recently reported to be more effective than doxorubicin and cyclophosphamide (the so-called AC therapy)<sup>20</sup>. However, the effect of taxane on IMP remains unknown.

### Conclusion

We described 2 cases of IMP that seemed to be of relatively low risk not considering their histological forms. It is not known whether such a rare type of IMP tumour can be managed as effectively as other common forms of breast carcinoma. Further studies are necessary to evaluate the outcome of IMP treatment protocols and to establish the therapeutic strategy.

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〈和文抄録〉

## リンパ節転移や明らかなリンパ管浸潤を伴わない 乳腺浸潤性微小乳頭癌の2例

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浸潤性微小乳頭癌 (IMP) は高頻度にリンパ節転移やリンパ管浸潤を伴い、臨床的に悪性度の高い浸潤性乳管癌の1亜形と考えられている。しかし今回、我々は、リンパ節転移や明らかなリンパ管浸潤を伴わない稀なIMP2例を経験したので、文献的考察を加えて報告する。症例1は74才女性、臨床診断 Stage I (T1N0M0) 乳癌、症例2は65才女性、臨床診断 Stage II B (T2N1M0) 乳癌である。両者に対して腋窩リンパ節郭清を伴う乳房切除術を施行した。組織検査では2例とも浸潤部のほとんどがIMP成分で占拠されていたが、リンパ節転移やリンパ管浸潤は認められず、エストロゲンレセプターは陽性、ハーセプチンは陰性であった。症例1には術後レトロゾールを投与、症例2には術後TC (docetaxel, cyclophosphamide) 療法4サイクル施行後レトロゾールを投与し、現在無再発状態で経過観察中である。このような稀なIMP症例が一般的な組織型の腫瘍と同様に治療されるべきかどうかは不明であり、今後さらなる症例の検討を行い、IMPに対して行った治療に対する結果を評価し治療戦略をたてる必要がある。

キーワード：乳癌，浸潤性微小乳頭癌，リンパ節転移，リンパ管浸潤，治療。