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Wide metastatic spreading in infiltrating lobular carcinoma of the breast

S. Ferlicot[a,1], A. Vincent-Salomon[a,1], J. Médioni[b], P. Genin[a], C. Rosty[a], B. Sigal-Zafrani[a], P. Fréneaux[a], M. Jouve[c], J.-P. Thiery[d], X. Sastre-Garau[a,*]

[a]*Departments of Pathology, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex, France*
[b]*Biostatistics, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex, France*
[c]*Medical Oncology, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex, France*
[d]*CNRS UMR144, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex, France*

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Abstract

The aim of this study was to determine whether the metastatic potential of breast cancer could be related to phenotypic characteristics of the tumour. Therefore, we compared the metastatic patterns of invasive lobular (ILC) and ductal (IDC) carcinomas. In ILC, we also analysed this pattern according to the histological subtype of the primary and the E-cadherin (EC) expression level. Metastatic ILC cases ($n=96$) were retrospectively analysed and classified into classical, alveolar, solid, tubulo-lobular, signet ring cells or pleomorphic subtypes. Anatomical distribution of metastases was detailed for every patient and compared with that registered for IDC ($n=2749$). Immunostaining of EC (HECD1 antibody) was performed in 82 cases. Histologically, 78 of the 96 cases (81%) corresponded to classical ILC. The pleomorphic subtype was observed in 14 cases (15%), a rate that was higher than that expected. Others corresponded to alveolar (2 cases), signet ring cell (1 case) and solid (1 case) subtypes. EC was undetectable in 72/82 cases (88%). The rate of multiple metastases was higher in ILC (25.0%) than in IDC (15.8%) ($P=0.016$). Metastases were found more frequently in ILC than in IDC in the bone ($P=0.02$) and/or in various other sites (peritoneum, ovary, digestive tract, skin...) ($P<0.001$). In ILC, no significant link was found between the localisation(s) of metastases, the histological subtype and the EC status in the primary. In conclusion, in breast carcinomas, the frequency of multiple metastasis was found to be higher in ILC than IDC. This fact may be related to the phenotypic trait of discohesive small cells which characterises ILC. EC loss, observed in most cases of ILC, may result in alterations in cell–cell adhesion and a preferential growth at metastatic sites. A high rate of pleomorphic tumours was observed in the group of metastatic ILC, but the pattern of metastatic site(s) was not related to the histological subtype of the primary.
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1. Introduction

Metastatic spread represents a severe complication of breast cancer, but the biological factors related to epithelial cells ability to migrate and develop in distant organs remains unidentified. Our aim was to determine whether phenotypic traits could characterise the metastatic potential of breast cancers. Invasive ductal (IDC) and lobular (ILC) carcinomas represent 80 and 10% of breast carcinomas, respectively. IDC are composed of cells arranged in more or less well formed glandular structures [1,2], whereas ILC correspond to a proliferation of non-cohesive small cells irregularly dispersed in a fibrous stroma [3–9]. ILC are also defined by clinical [8,10] and radiological [11] characteristics, and by clinico-biological features such as a high rate of hormonal receptor expression [8,12], a low cell-proliferation rate [9,13] and a low frequency of ERBB2 overexpression [14,15].

Clinico-pathological analyses have shown that the overall outcome of ILC did not significantly differ from that of the common IDC type [16,17] and that these tumours could be treated similarly [8,18]. However, several studies have emphasised that ILC was characterised by a peculiar pattern of metastatic

* Corresponding author. Tel.: +33-1-4432-4254; fax: +33-1-4432-4072.
E-mail address: xavier.sastre@curie.net (X. Sastre-Garau).
[1] Equally contributing authors.

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dissemination. Compared with IDC, a lower incidence of spreading to the lung and a higher incidence to the bone and to gastrointestinal tract were observed in ILC [8,19–21]. The molecular mechanisms underlying these differences have not been elucidated. Nonetheless, it has been suggested that the loss of the E-cadherin function, a cell–cell adhesion molecule frequently altered in ILC [22], could account for the state of non-cohesive epithelial tumour cells [23–26] and that this may play a part in local and metastatic tumour progression [27,28]. Successive histological studies have also documented the morphological heterogeneity of ILC. Besides the classical histological form corresponding to early descriptions, variants have been defined, recognised either by their characteristic architectural pattern, namely alveolar [5,29,30], solid [31,32] or tubulo-lobular [33], or by cytopathological features, signet ring cells [34] and pleomorphic [35–38]. Few data are available on the respective metastatic potential of these histological entities.

Our aim was to determine whether the metastatic potential of breast carcinomas could be related to the phenotypic characteristics of the tumour. We therefore compared the metastatic patterns of ILC and IDC and then we analysed this pattern in the group of ILC according to the histological characteristics of the primary.

2. Patients and methods

The cases, selected from the Breast Cancer database of the Institut Curie, corresponded with 109 patients with ILC treated at the Institute between January 1981 and March 1994, who developed, during the follow-up period, metastatic dissemination at any site apart from the axillary lymph node. Follow-up procedures included three annual clinical stagings during the first 2 years, two annual stagings between the third and fifth years, and one annual staging procedure in the sixth year. Paraclinical investigations consisted of one mammogram, one chest X-ray, and serological tests of tumour markers (CA15.3, carcinoembryonic antigen (CEA)) once every year. Metastases were clinically diagnosed by imaging analyses (magnetic resonance (MR) images, bone scans) and confirmed at biopsy or using a surgical specimen analysis when necessary.

For statistical analysis, we compared the clinicopathological data of patients with ILC with a group of patients with IDC ($n = 2749$) who were treated in the same period and who developed a metastatic disease at any site apart from the axillary lymph node during the same follow-up period. The time to metastatic progression and the site of metastasis were prospectively registered in the Institut Curie database. Metastatic localisations at the most frequently involved sites (bone, liver, lung, central nervous system (CNS), non-axillary lymph nodes) were prospectively registered. Other localisations were registered under the same heading of 'others'. These localisations were retrospectively specified for individual cases of ILC (96 cases), but not for the IDC (2749 cases).

2.1. Histological analysis

For each case, tissue sections of the primary tumour were retrospectively reviewed by two pathologists. This analysis confirmed the initial diagnosis of ILC in 96/109 cases (88%) and specified the histological subtype of the tumour. The histological grade (Nottingham Index), the proportion of *in situ* lobular carcinoma and the presence of vascular invasion were also registered. The classical form of ILC corresponded to a proliferation of non-cohesive cells individually dispersed through a fibrosis tissue or arranged in single file linear cords that invade the stroma [3–5]. Variants corresponded to tumours the characteristic architectural or cytological features of which represented more than 70% of the tumour surface analysed [32]. A solid pattern was defined by large sheets of uniform small cells of lobular morphology [31]. An alveolar pattern was defined by small clusters of at least 20 cells [29]. Pleomorphic lobular carcinoma retained the distinctive growth pattern of lobular carcinoma, but exhibited a greater degree of cellular atypia and pleomorphism than the classical form [36–38]. the tubulolobular variant was defined by the admixture of tubular glands and of small uniform cells arranged in a linear pattern [33]. Signet ring cells ILC was defined as a tumour composed of more than 90% of cells presenting a cytoplasmic vacuole. These vacuoles, filled with sialomucines differ from the intracytoplasmic lumen [2]. The percentage of signet ring cells was also assessed in common ILC.

2.2. Immunohistochemical analysis

Formalin-fixed, paraffin-embedded archival tissue blocks were available for immunohistochemical analysis in 82 cases. E-cadherin (EC) immunostainings were performed on histological sections prepared from a biopsy sample or from the most representative sample of the resected tumour. Briefly, tissue sections 4 μm thick were cut, deparaffined, hydrated through graded alcohol, and incubated for one hour with the HECD1 monoclonal antibody (Zymed® Laboratories Inc. South San Francisco, CA 94080, USA) at a 1/50 dilution, after heat-induced antigenic retrieval in citrate buffer at pH 6.1. The revelation of the staining was performed using the Vectastain Elite ABC peroxyidase mouse IgG kit (Vector Burlingame, CA, USA) and using diamino-benzidine (Dako A/S, Glostrup, Denmark) as the chromogen. A positive control corresponding to a case of IDC

harbouring remnants of normal glands was included in each experiment. Positive samples were defined as cases showing a membranous staining in invasive malignant cells and scored on a three-tiered scale (0, +, ++), according to the intensity of staining. This intensity was compared with that of normal glands or of the positive control (scored ++). A negative control corresponding to a section of non-metastatic axillary lymph node was included in each experiment. All preparations were analysed by two pathologists who reached a consensus in unambiguous cases.

Oestrogen and progesterone receptor expression was assessed using the 6F11 (Novocastra, Newcastle, UK) and 1A6 (Novocastra, Newcastle, UK) antibodies, respectively. ERBB2 expression was assessed using the CB11 anti-p185$^{HER2\text{-}neu}$ monoclonal antibody (Novocastra, Newcastle, UK), according to the procedures previously described in Ref. [39].

2.3. Statistical analysis

The patterns of metastatic sites were analysed in the different groups of ILC ($n=96$) and compared with that of metastatic IDC ($n=2749$) using the Chi-square test. A P value lower than 0.05 was considered statistically significant. We also looked for a link between the nature of the different metastatic sites and/or the histological subtypes and the EC level of expression in the primary. The prognostic value of the proportion of signet ring cells was assessed separately.

3. Results

The series analysed was composed of 96 patients with ILC of the breast who presented with metastatic disease at anatomical sites apart from the axillary lymph nodes. The median age of patients at diagnosis of the primary tumour was 54.8 years old (SD = 10.8). The mean follow-up was 67 months (range 3–228 months). A retrospective histological analysis showed that 78 of the tumours (81%) corresponded to classical ILC and 14 (15%) to pleomorphic lobular carcinoma (PLC). Others exhibited morphological features of alveolar (2 cases), signet ring cells (1 case) or solid (1 case) variants. No case of tubulo-lobular carcinoma was found. Assessment of the histological grade showed that 48 of the tumours were grade I (50%), 42 grade II (44%) and 6 grade III (6%). PLC were scored as grade II (8 cases) or grade III (6 cases) according to the mitotic index, and all grade III tumours were PLC. Vascular invasion was noted in 3 cases (1 classical type, 1 alveolar and 1 signet ring cell variant). Features of lobular carcinoma *in situ*, observed in up to 80% of the surface of the tumour analysed, were identified in 41 cases (43%). In 14 cases, a prominent (>20%) component of vacuolated cells was found, but this feature was not associated with pathological or clinical characteristics (data not shown).

Analysis of metastatic sites in ILC, in comparison with those observed in IDC, showed a more varied anatomical pattern of tumour dissemination in ILC than in IDC (Table 1). In lobular carcinomas, metastatic spreading concerned the bone ($P=0.02$) and a large number of other organs (such as the peritoneum, ovaries, gastrointestinal tract, skin, the adrenal gland, gall bladder, pancreas, kidney, bladder, eyelid) more frequently than in ductal carcinomas ($P<0.001$). The frequency of metastasis to the liver, CNS or non-axillary lymph nodes was not significantly different in the two tumour types, whereas tumour spreading to the lung was more frequently observed in IDC than in ILC ($P<0.001$). Since the anatomical spectrum of tumour dissemination looked to be more varied in ILC, we have further analysed the data in order to determine whether multiple metastases were more commonly observed in ILC than in IDC. Only synchronous secondary visceral sites registered at the first diagnosis of metastases were taken into account. We found multiple synchronous metastases in 25.0% of the cases of ILC (2–7 sites per patient), whereas this rate was 15.8% in the IDC patients ($P=0.016$) (Table 2). In contrast, the mean time to metastatic progression was 37.5 months in ILC and 36 months in IDC patients ($P=0.07$).

Table 1
Anatomical pattern of the first metastatic site(s) in ILC and IDC

Sites	Histological type		P value[b]
	ILC ($n=96$) n (%)	IDC ($n=2749$) n (%)	
Bone	48 (50)	1058 (38.5)	0.02
Liver	17 (17.7)	483 (17.6)	0.97
Lung	9 (9.4)	821 (29.9)	<0.001
NALN	6 (6.3)	324 (11.8)	0.1
CNS	5 (5.2)	224 (8.2)	0.3
Others[a]	33 (34.4)	272 (9.9)	<0.001

NALN, non axillary lymph node; CNS, central nervous system; ILC, invasive lobular carcinomas; IDC, invasive ductal carcinomas.

[a] Peritoneum, skin, pleura, ovaries, meninges, stomach, uncommon sites...

[b] Comparing presence versus absence of metastases at every anatomical site.

Table 2
Number of metastatic sites[a] in ILC and IDC

Number of sites	ILC ($n=96$) n (%)	IDC ($n=2749$) n (%)	P value
1	72 (75.0)	2314 (84.2)	
2	18 (18.8)	366 (13.3)	0.016[b]
>2	6 (6.3)	69 (2.5)	

ILC, invasive lobular carcinomas; IDC, invasive ductal carcinomas.

[a] Prospectively registered at the time of the first diagnosis of metastasis.

[b] Chi^2 test for heterogeneity comparing one site versus two sites.

In order to specify the global metastatic pattern of ILC, we have further analysed the patient's files and recorded all of the metastatic sites observed during the whole course of the disease. We have also looked for a link between this pattern and the phenotype of the primary. The details of this analysis are provided in Table 3. No metastatic site(s) were found to be preferentially associated with any of the histological subtypes of the primary tumours. Using immunohistochemistry, EC expression was evaluated in 82 cases. A complete loss of expression was observed in 72 of these cases (88%) (Table 4). In 10 cases, a significant membrane immunostaining was maintained, the intensity of which was scored as moderate (7 cases) or strong (3 cases). A complete loss of expression was observed in 9/10 cases of PLC. The comparison between the EC status and the number of metastatic sites showed that the rate of tumours with synchronous metastases was 33% (18/54), in the group of EC-negative carcinomas, whereas this rate was only 11% (1/9) in the group of EC-positive tumours. This difference was not statistically significant ($P = 0.30$) (Table 4).

Table 3
Metastatic sites involved during the course of ILC ($n = 96$)

Metastases ($n = 247$)		Subtype of ILC		
Sites	N (%)	Classical	Pleomorphic	Others
Bone	70 (28.3)	62	5	3
Liver	38 (15.4)	33	4	1
Lung	8 (3.2)	8	–	–
NALN	12 (4.9)	11 1	–	
CNS	9 (3.6)	8	1	–
Others	110 (44.5)	101	8	1
Peritoneum	36 (14.6)	35	1	–
Skin	22 (8.9)	19	2	1
Pleura	18 (7.3)	14	4	–
Ovary	11 (4.5)	10	1	–
Meninges	10 (4.0)	10	–	–
Stomach	7 (2.8)	7	–	–
Uncommon[a]	6 (2.4)	6	–	–

ILC, invasive lobular carcinomas; NALN: non-axillary lymph nodes including cervical ($n = 8$), abdominal ($n = 3$) and inguinal ($n = 1$); NS, not specified; CNS, central nervous system.

[a] Adrenal gland ($n = 1$), gall bladder ($n = 1$), pancreas ($n = 1$), kidney ($n = 1$), bladder ($n = 1$), eyelid ($n = 1$).

Since PLC is likely to represent a subgroup of ILC that is associated with a poor outcome, the immunophenotype of these tumours was further specified. In 10 of 14 cases, oestrogen receptor (ER), progesterone (PR) receptor and ERBB2 expression could be analysed. PLC were found to express ER (8/10) and PR (9/10). In contrast, in none of the cases was there a significant membrane immunostaining for ERBB2.

4. Discussion

In order to determine whether the metastatic potential of breast carcinomas could be related to the phenotypic characteristics of the tumour, we compared the metastatic patterns in ILC and IDC patients. This analysis showed that synchronous tumour dissemination at several sites was more frequently observed in ILC than in IDC. Furthermore, the pattern of tumour spread was different in the two types of tumours: tumour extension to the bone and peritoneum was more frequently observed in ILC than in IDC, and lobular carcinomas were found to result in metastasis in organs that were infrequently involved in IDC patients. Altogether, these data suggest that the metastatic spread in ILC is more varied than in IDC. Several studies reported a peculiar pattern of metastatic extension of ILC [8,19–21,40,41], but an increased frequency of metastatic sites in ILC has rarely been mentioned [16]. It is noteworthy that the overall survival rate has not been found to be different in IDC and ILC [8,16,18]. This fact may be related to the low rate of cell proliferation [9,13] and to the high frequency of hormone receptor expression [12,16] that characterise most ILC and thereby balance the negative effect of a wide dissemination on disease outcome.

EC was found to be altered in most cases of ILC [22,23]. In our series of metastatic ILC, a complete loss of EC expression in the primary was observed in 88% of the cases and a significant reduction in 3%. This high rate, also observed in other studies [23,25,26,42,43], contrasts with the mere decrease in staining intensity found in a minority of IDC [44]. Downregulation of EC may play a role in tumour growth and dissemination [27,45]. In an experimental model, decreased cellular

Table 4
E-cadherin expression in ILC according to histological types and number of metastatic sites

E-cadherin expression		Histological types			P value	No. of metastatic sites		P value
staining	N (%)	Classical	Pleomorphic	Others		1	>1	
–	72 (88%)	61	9	2		54	18	
+	7 (9%)	6	1	–	0.66	6	1	0.30
++	3 (4%)	3	–	–		3	–	
	82	70	10	2		63	19	

ILC, invasive lobular carcinomas.

adhesion and increased cellular motility were found to be induced by tumour-associated EC mutations [46]. We have looked for a link between the plurality of the metastatic sites in ILC and the loss of EC. EC expression was maintained at a detectable level in only 10 cases and no significant conclusions could be drawn from this small series, although only one of these cases developed synchronous metastasis. Like EC-negative carcinomas, EC-positive ILC exhibited a pattern of non-cohesive malignant epithelial cells. It has been reported that the alteration of membrane-associated molecules such as α-catenin [47], β-catenin [48] or plakoglobin, closely linked to EC in a multimolecular complex, could also account for some of the cases of ILC with normal EC expression.

Another aim of our study was to determine whether the metastatic pattern of ILC could be related to the histological subtype of the primary. More than 80% of the tumours corresponded to the classical type of ILC, but PLC represented 15% of the cases. This rate was higher than that expected, considering that only 10.5% of the cases of ILC registered in our database corresponded to histological grade 2-high or grade 3 tumours [8], a group in which all of the PLC should be included. The poor outcome of PLC observed in several studies [36,38,49] might be related to an abnormal tumour expression of ERBB2 and p53 [37]. The high rate of PLC observed in the present series of metastatic ILC argues for an unfavourable course of PLC, but no case with ERBB2 overexpression was found. It is also worth mentioning that only one case of signet ring cell carcinoma was found and that the presence of a large component of vacuolated cells, when present in classical ILC, was not associated with an unfavourable outcome. These data contrast with the poor prognosis of signet ring cell tumours reported in other studies [34,50].

On the whole, our study indicates that the metastatic spread in ILC is significantly wider than that observed for IDC. Clinicians should be aware when facing the metastatic relapse of ILC that multiple metastatic sites are likely to be observed in at least 25% of cases. This clinical characteristic might be related to the loss of EC which may facilitate cell spreading and/or cell growth, but further basic and clinical analyses are necessary to validate this hypothesis.

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