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A study of immunohistochemical differential expression in pulmonary and mammary carcinomas

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The risk of developing a second primary cancer is increased in patients with breast cancer, and the lung is one of the major sites involved. Moreover, the lung is the major metastatic site for breast cancers. A distinction between metastatic breast cancer and primary lung cancer can be histologically difficult, and both show an overlapping CK7+/CK20− immunoprofile in a majority of cases. The degree of difficulty increases with poorly differentiated tumors. We investigated differential expressions of TTF-1, Napsin A, surfactant apoprotein A, estrogen receptor, GATA-3, mammaglobin, and GCDFP-15 immunostains in 197 pulmonary carcinomas (158 adenocarcinomas, 39 squamous) and 115 invasive mammary carcinomas (91 ductal, 24 lobular type). In mammary carcinomas, estrogen receptor, GATA-3, mammaglobin, and GCDFP-15 were expressed in 74, 72, 64, and 62%, respectively, whereas TTF-1, Napsin A, and surfactant apoprotein A were all negative. The expressions were diffuse in estrogen receptor and GATA-3, and variable in mammaglobin and GCDFP-15. For a combination of estrogen receptor/mammaglobin or GATA-3/mammaglobin, 83% of mammary carcinomas were positive, and the detection rate was not improved by using all three markers. All lung squamous cell carcinomas were negative for all markers studied. TTF-1, Napsin A, and surfactant apoprotein A were positive in 80, 77, and 45% of pulmonary adenocarcinomas. None of the TTF-1-negative tumors expressed surfactant apoprotein A. GCDFP-15 was focally expressed in 2.5% of pulmonary adenocarcinomas, and estrogen receptor was focally expressed in one case (1.2%) of pulmonary adenocarcinoma. When metastasis from breast cancer is suspected in the lung, a combination of either estrogen receptor/mammaglobin or GATA-3/mammaglobin as breast markers, and a combination of TTF-1 and Napsin A as lung markers may be helpful for differentiating between the two. Caution should be taken in the interpretation of GCDFP-15 due to its occasional expression in pulmonary adenocarcinomas.
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The risk of developing a second primary cancer is increased in patients with breast cancer, and the lung is one of the major sites involved. Moreover, the lung is the major metastatic site for breast cancers. A distinction between metastatic breast cancer and primary lung cancer can be histologically difficult, particularly when the tumor is poorly differentiated. Immunohistochemically both lung and breast tumors generally share a CK7+/CK20− immunoprofile.[1] We conducted an immunohistochemistry study using a panel of markers to investigate the differential expression in both cancers.

Materials and methods

A total of 197 pulmonary carcinomas composed of 158 adenocarcinomas and 39 squamous cell carcinomas, and 115 invasive mammary carcinomas were retrieved. Hematoxylin-and-eosin-stained slides of all the cases were reviewed, and the histologic diagnosis and grading were based on recent classifications.[2,3] The lung adenocarcinomas were subdivided to 20 cases of acinar type; 3 of papillary; 50 of solid; 30 of mixed type in any combination of acinar, papillary, micropapillary, and solid without bronchioloalveolar component (mixed acinar and

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solid in 21; mixed papillary and solid in 3; mixed acinar and papillary in 4; mixed acinar, papillary and solid in 2); 52 of mixed type with bronchioloalveolar component; and 3 mucinous carcinomas. The lung squamous cell carcinomas comprised 21 moderately differentiated and 17 poorly differentiated tumors. The invasive mammary carcinomas comprised 91 cases of ductal type (5 well differentiated, 23 moderately, 63 poorly) and 24 of lobular type (5 well differentiated, 19 moderately).

Tissue microarrays were assembled using formalin-fixed, paraffin-embedded tissue. A representative area of each case was identified on the conventional sections, and at least one cylinder per tissue was arrayed using a punch biopsy (needle with a diameter of 2 mm). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissues using TTF-1 (mouse 8G7G3/1, 1:50, citrate buffer; Neomarkers, Fremont, CA, USA), Napsin A (mouse TMU-Ad02, 1:100, citrate buffer; IBL-America, Minneapolis, MN, USA), surfactant apoprotein A (SP-A) (mouse 6F10, 1:50; Santa Cruz Biotechnology, Santa Cruz, CA, USA), estrogen receptor (ER) (rabbit 6F11, 1:30, citrate buffer; Novocastra, Newcastle, UK), GATA-3 (mouse HG3-31, 1:50, citrate buffer; Santa Cruz Biotechnology), mammaglobin (mouse 304-1A5, rabbit 31A5, citrate buffer, 1:250; Zeta Corporation, Sierra Madre, CA, USA), and GCDFP-15 (mouse 19, 1:160, citrate buffer; Signet Lab, Dedham, MA, USA). The avidin–biotin peroxidase method was used in a Dako AutoStainer (Carpinteria, CA, USA). Appropriate positive and negative controls were included with the study sections. The extent of nuclear staining was graded as follows: 1+, 1–25%; 2+, 25–50%; 3+, 50–75%; 4+, ≥75%.

Results

The results of the immunohistochemistry study are listed in Table 1. TTF-1, Napsin A, and SP-A expressions were seen in 80, 77, and 45% of 158 pulmonary adenocarcinomas (Figures 1a–d). Apart from 3 mucinous carcinomas, 14 tumors (48%) were of solid type among the 29 TTF-1-negative adenocarcinomas whereas 21 (62%) were of solid type among the 34 Napsin A-negative adenocarcinomas. There were four adenocarcinomas of Napsin A(−)/TTF-1(+) pattern with TTF-1 being 1+ in all four tumors, which comprised three tumors of solid type and one tumor of mixed acinar and solid type. There were five adenocarcinomas of Napsin A (+)/TTF-1 (−) pattern with Napsin A expression being 1+ in two tumors, 2+ in one, 3+ in one, and 4+ in one. They constituted four tumors of acinar type and one tumor of mixed acinar and solid type. There were only two cases of SP-A (+)/Napsin A(−) pattern, with SP-A reaction being 1+ and 2+, respectively. There was no single case of SP-A (+)/TTF-1(−). Overall, 132 out of 158 lung adenocarcinomas (84%) expressed either TTF-1 or Napsin A, or both. Twenty-six tumors negative for the two markers comprised 14 tumors of solid type (54%), 7 of acinar, 2 of papillary, and 3 of mixed type without bronchioloalveolar component, whereas 132 tumor positive for either marker or both comprised 36 of solid (27%), 14 of acinar, 1 of papillary, 53 of mixed type with bronchioloalveolar component, and 27 of mixed type without bronchioloalveolar component.

ER was expressed only in one tumor with 2+ reaction. Mammaglobin was completely negative in all adenocarcinomas. Four pulmonary adenocarcinomas showed focal GCDFP-15 reaction (Figures 2a and b).

Table 1 Immunohistochemistry results

	Lung adenocarcinoma						*Lung squamous cell carcinoma*					
	0	*1*	*2*	*3*	*4*	*Total*	*0*	*1*	*2*	*3*	*4*	*Total*
TTF-1	31	9	12	14	92	127 (80%)	39	0	0	0	0	0 (0%)
Napsin A	36	8	14	22	78	122 (77%)	39	0	0	0	0	0 (0%)
SP-A	87	27	16	16	12	71 (45%)	39	0	0	0	0	0 (0%)
ER	157	1	0	0	0	1 (0.6%)	39	0	0	0	0	0 (0%)
GATA-3	158	0	0	0	0	0 (0%)	39	0	0	0	0	0 (0%)
Mammaglobin	158	0	0	0	0	0 (0%)	39	0	0	0	0	0 (0%)
GCDFP-15	154	4	0	0	0	4 (2.5%)	39	0	0	0	0	0 (0%)

	Breast invasive ductal carcinoma						*Breast invasive lobular carcinoma*					
	0	*1*	*2*	*3*	*4*	*Total*	*0*	*1*	*2*	*3*	*4*	*Total*
TTF-1	91	0	0	0	0	0 (0%)	24	0	0	0	0	0 (0%)
Napsin A	91	0	0	0	0	0 (0%)	24	0	0	0	0	0 (0%)
SP-A	91	0	0	0	0	0 (0%)	24	0	0	0	0	0 (0%)
ER	30	4	5	11	41	61 (67%)	0	0	0	2	22	24 (100%)
GATA-3	32	6	11	23	19	59 (65%)	0	0	0	7	17	24 (100%)
Mammaglobin	41	26	4	9	11	50 (55%)	3	5	4	7	5	21 (88%)
GCDFP-15	43	31	6	4	7	48 (53%)	10	6	3	2	3	14 (58%)

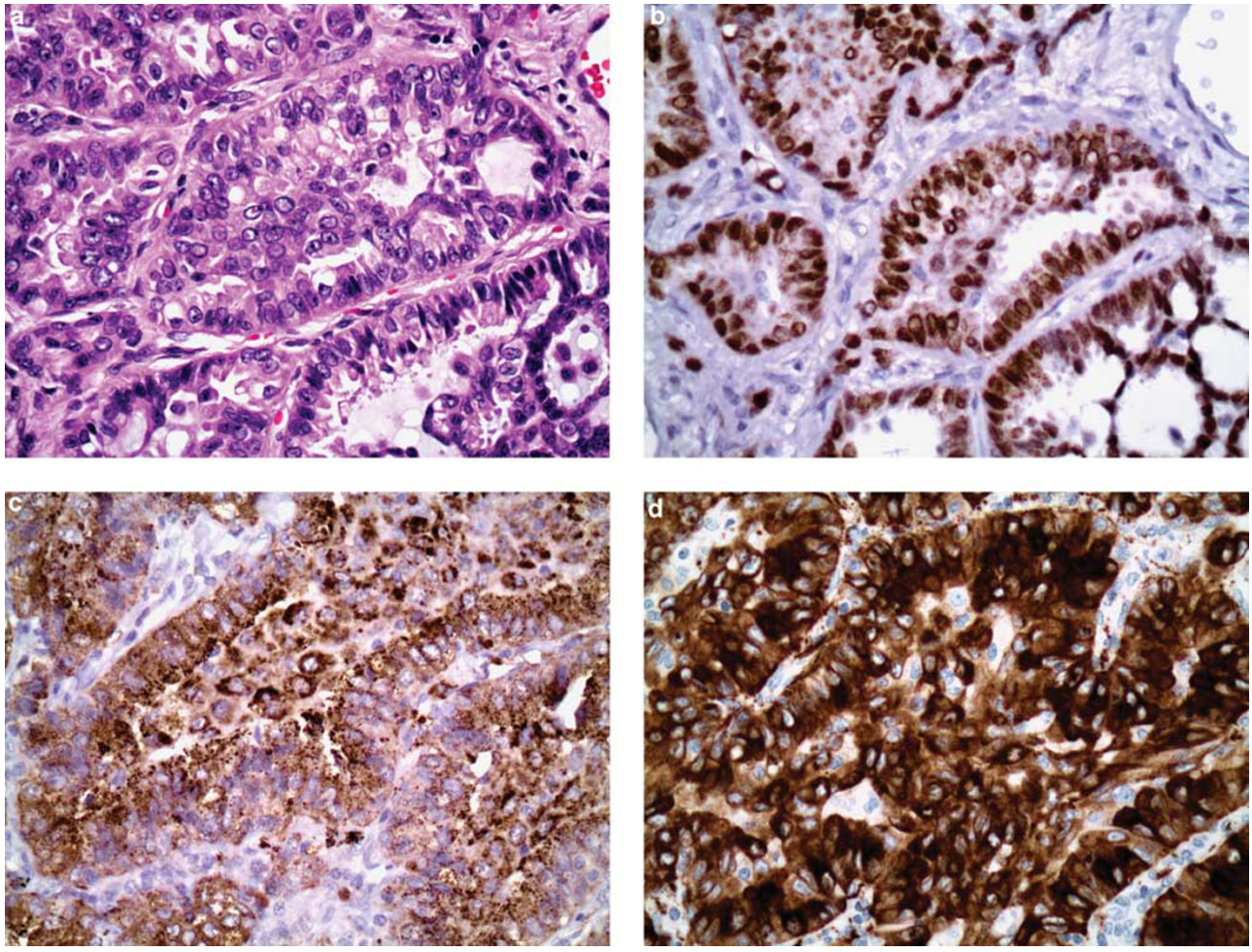

Figure 1 Pulmonary adenocarcinoma, acinar type: (**a**) hematoxylin and eosin (H&E) stain, (**b**) TTF-1 nuclear expression, (**c**) Napsin A cytoplasmic expression, (**d**) SP-A cytoplasmic expression.

TTF-1, Napsin A, and SP-A were expressed in two, two, and none, respectively, of the four tumors.

All lung squamous cell carcinomas were negative for all of the markers studied.

In 115 mammary carcinomas, ER, GATA-3, mammaglobin, and GCDFP-15 were expressed in 74, 72, 64, and 62%, respectively (Figures 3a–e), whereas TTF-1, Napsin A, and SP-A were completely negative. The expression was generally diffuse in ER and GATA-3, and variable in mammaglobin and GCDFP-15. 83.4% of the tumors were positive for ER, GATA-3, and/or mammaglobin whereas 82.6% were positive for ER and/or mammaglobin as well as for GATA-3 and/or mammaglobin.

Among the 91 cases of invasive ductal carcinomas, ER, GATA-3, mammaglobin, and GCDFP-15 were expressed in 67, 65, 55, and 53%, respectively. There were only two cases of ER(−)/GATA-3(+) pattern with GATA-3 reaction being 2+ in both whereas there were four tumors of ER(+)/GATA-3(−) with ER reaction being 1+ in two tumors, 3+ in one, and 4+ in one. There were 12 cases of GATA3(−)/mammaglobin(+) and 10 cases of ER(−)/mammaglobin(+), in which mammaglobin expression was generally 1+. Nine cases were ER(−)/GATA-3(−)/mammaglobin(+). Overall 72 tumors (79%) expressed any of the markers ER, GATA-3 or mammaglobin. Nineteen mammary ductal carcinomas negative for all three markers constituted 3 moderately differentiated tumors and 16 poorly differentiated tumors.

All 24 lobular carcinomas expressed ER and GATA-3 in diffuse manner whereas mammaglobin and GCDFP-15 were variably expressed in 88 and 58% of the tumors.

Discussion

Women with breast cancer have a 30% higher risk of developing a second primary cancer than the general population.[4] Improved early detection of breast cancer, multiple-drug regimes, and adjuvant tamoxifen therapy has contributed to reducing breast cancer mortality[5] whereas the incidence of second primary cancers is reported to be increasing

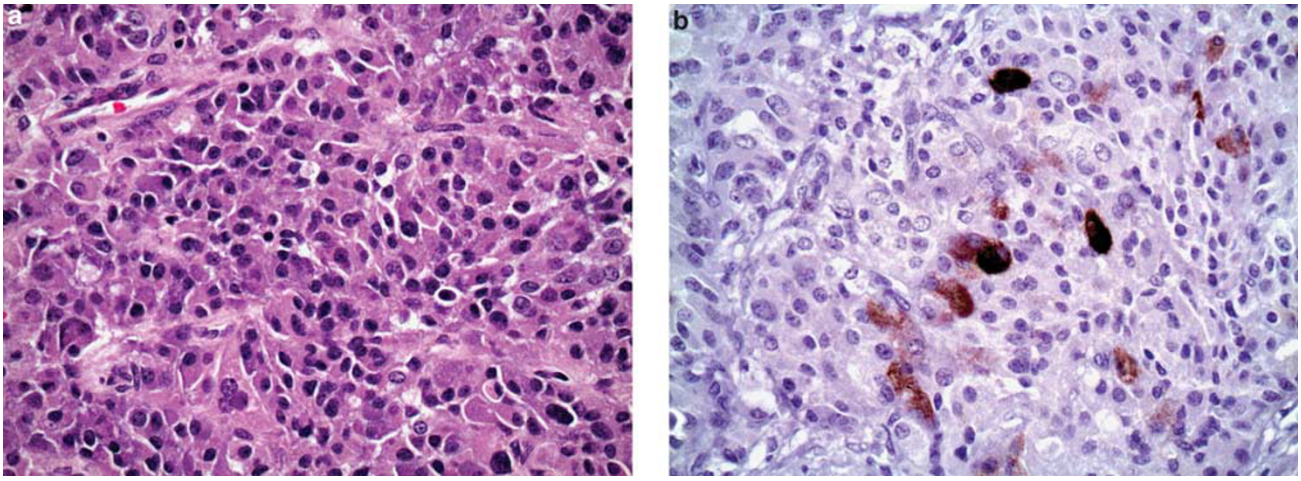

Figure 2 Pulmonary adenocarcinoma, solid type: (**a**) hematoxylin and eosin (H&E) stain, (**b**) GCDFP-15 expression seen in a few tumor cells.

in breast cancer survivors.[6] This second primary cancer often occurs in the lung,[7] and overall 4–9% of patients with breast cancers are expected to develop pulmonary cancers.[8,9] A statistically significant increased risk of lung cancer is seen more than 5 years after breast cancer diagnosis.[5] It has been reported that cigarette smoking and radiotherapy are significant risk factors.[10–13]

It should be also noted, however, that the lung is a major site of metastasis for breast cancer.[14,15] Various studies on surgically resected breast cancers reported an incidence of 8–10.2% of metastases to lung, pleura, or mediastinum.[16,17] Autopsy studies on breast cancers reported metastasis to the lung in 57–77% of cases.[14,15,18,19] A variety of thoracic metastasis patterns of breast cancers are recognized,[20] including pleural metastasis, mediastinal tumor, lymphangitic carcinoma, multiple pulmonary nodules, solitary pulmonary nodule, endobronchial metastasis, and pulmonary tumor emboli.[20] Among these metastatic patterns, a solitary lung metastatic nodule would likely mimic a primary lung cancer, and, therefore, may cause a significant diagnostic challenge. One study showed that a solitary pulmonary nodule in patients with breast cancers represented primary pulmonary malignancy in 52% of the cases, metastatic breast cancer in 43%, and benign lesions such as hamartoma and granuloma in 5%.[21] Such solitary nodules can present synchronously or metachronously in either the ipsilateral or contralateral lung. Lung metastasis commonly occurs within 5 years of the diagnosis of breast cancer, but the interval can vary considerably, and the metastasis can even appear more than 20 years after the initial diagnosis of breast cancer.[22,23] An endobronchial metastasis is another presentation that can simulate primary lung cancer. Although endobronchial metastasis is not a common pattern of metastasis, breast cancer is one of the most common causes of endobronchial metastasis.[24]

The distinction between a metastatic nodule and a new primary tumor can usually be made by comparing the histologic appearance of the lung lesion with that of the primary tumor or identifying the finding of histologic evidence of *in situ* change, but in some instances, this distinction may be difficult; for example, high-grade metastatic ductal carcinoma of the mammary gland may be indistinguishable microscopically from poorly differentiated pulmonary adenocarcinoma.[25,26]

Difficulties can also arise in tumors of squamous morphology with or without keratinization. Although metaplastic carcinoma including pure squamous carcinoma accounts for less than 1% of all invasive mammary carcinomas,[27] focal squamous differentiation (metaplasia) is not uncommon in invasive carcinoma, and it may be seen in 3.3% of invasive ductal carcinomas and up to 16% of medullary carcinomas.[28,29] However, the true frequency may be higher because inconspicuous foci of squamous metaplasia may be easily overlooked.[30] The squamous differentiation (metaplasia) can be accentuated in the metastatic site, which may lead to the erroneous diagnosis of primary bronchogenic squamous cell carcinoma.[31]

In addition, both mammary and pulmonary adenocarcinomas have a similar predilection for distant metastasis to the bone, liver, brain, and adrenal glands,[15,19,32,33] and metastasis of mammary carcinomas can clinically and radiographically present as a solitary lung mass with metastasis in any of the above-mentioned organs, a condition that can be interpreted as a lung cancer with distant metastasis.

There have been a handful of studies using different immunohistochemistry markers to distinguish between pulmonary and mammary carcinomas.[26,34–36] TTF-1, a well-characterized marker in lung and thyroid tumors, regulates SPs A, B, C, and Clara cell secretory protein.[37,38] TTF-1, by using clone 8G7G3/1, is expressed in 68–76% of lung

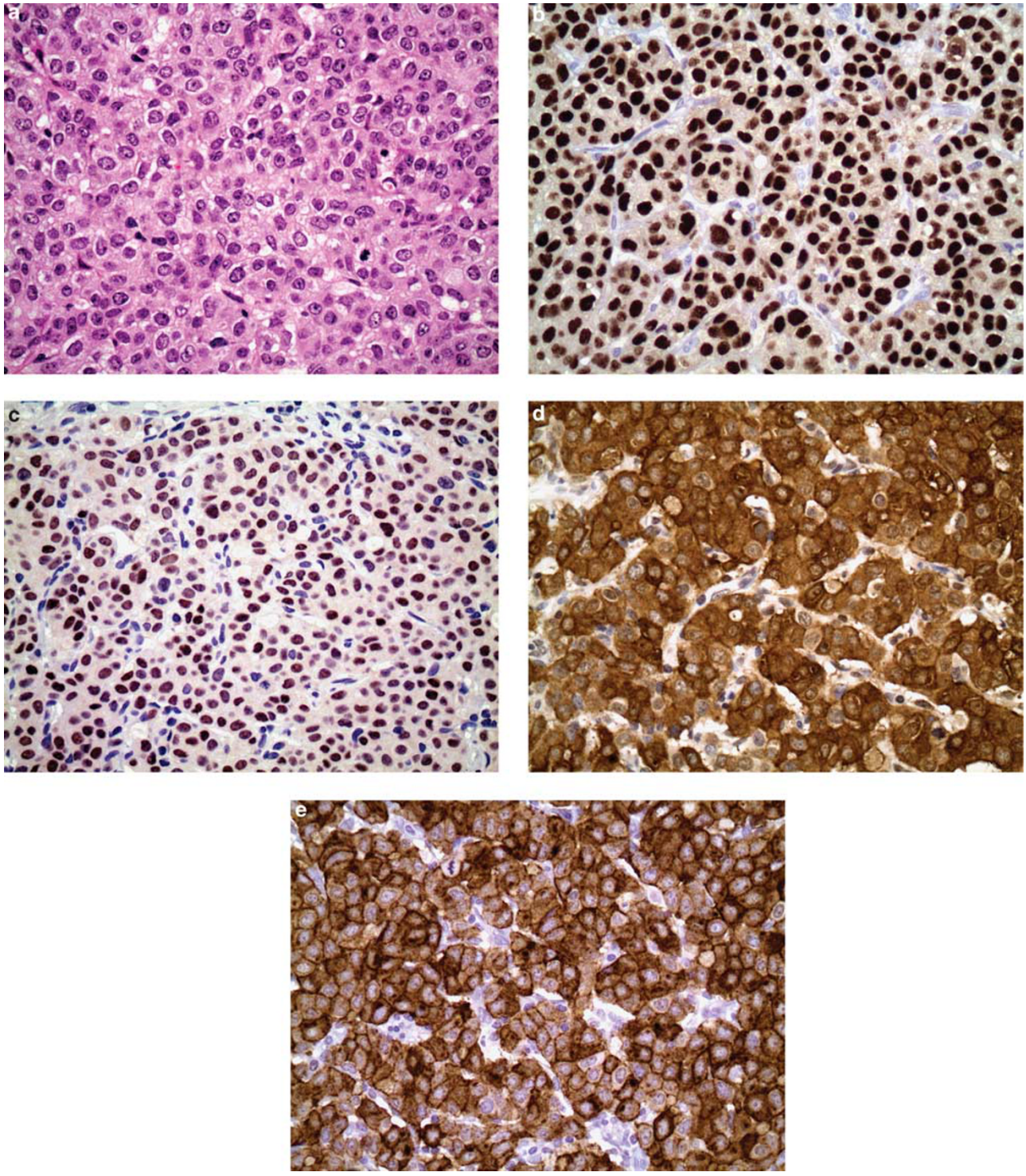

Figure 3 Mammary invasive ductal carcinoma, poorly differentiated: (**a**) hematoxylin and eosin (H&E) stain, (**b**) estrogen receptor (ER) nuclear expression, (**c**) GATA-3 nuclear expression, (**d**) mammaglobin cytoplasmic expression, (**e**) GCDFP-15 cytoplasmic expression.

adenocarcinomas[34,37–41] and the TTF-1-negative lung adenocarcinomas are often poorly differentiated.[38,41] In addition, TTF-1 tends to be usually negative in mucinous carcinoma,[39,42] and it is negative in bronchogenic squamous cell carcinomas.[34,37,39] TTF-1 is also negative in breast adenocarcinoma.[34,39] In our study, all the bronchioloalveolar carcinoma components were positive for TTF-1, indicating that there is no need for immunohistochemistry to confirm lung origin when the tumor contains a bronchioloalveolar carcinoma component, characterized by a lepidic pattern of growth and lining cells with morphologic features of Clara cells or type II pneumocytes.

SP-A is expressed in Clara cells and type II pneumocytes of the lung parenchyma,[43] and its gene expression is regulated by TTF-1.[44] It is, therefore, a marker for tumors differentiating into cells of such lineage, and as expected it is usually negative in poorly differentiated adenocarcinomas. It is expressed in approximately 45–64% of lung adenocarcinomas.[34,37–39] In our study, SP-A expression was seen in 61% of pulmonary adenocarcinomas but not seen in any of the mammary carcinomas, these findings are in keeping with those of the previous report. There was no single pulmonary adenocarcinoma showing TTF-1(−) and SP-A (+) pattern whereas there were 55 adenocarcinomas with TTF-1(+) and SP-A(−) pattern.

Napsin A is an asparatic protease expressed in type II pneumocytes, and is involved in the N- and C-terminal processing of prosurfactant protein B in type II pneumocytes.[45] The use of Napsin A has been sparsely described in diagnostic contexts. Two studies reported Napsin A expression in 84.3 and 90.7% of lung adenocarcinomas whereas squamous cell carcinoma was completely negative.[46,47] These two studies also examined a total of 14 mammary carcinomas and none of the cases expressed Napsin A.[46,47] None of the 115 mammary carcinomas in our study expressed this marker, either. Our results indicate that the sensitivity of Napsin A in pulmonary adenocarcinoma is comparable to that of TTF-1. There were 5 pulmonary adenocarcinomas with TTF-1(−)/Napsin A(+) whereas there were 4 pulmonary adenocarcinomas with TTF-1(+)/Napsin A(−).

Reported ER expression in lung cancer is significantly variable with the frequency ranging from 0 to 96.8%.[48–50] The variability in the detection rates may be attributed to different clones, dilutions of primary antibodies, and antigen retrieval techniques among the studies. ER expression in the lung adenocarcinoma by using the monoclonal antibodies 1D5 and 6F11 and recent antigen retrieval techniques is much less variable with the rate ranging between 0 and 18%[51–54] although an exception exists where its expression by using 6F11 was reported in 56% of bronchioloalveolar carcinoma and 80% of invasive adenocarcinoma.[55] In our study, only one case showed focal ER expression, and none of the lung adenocarcinomas showed more than focal ER expression. Our results indicate the validity of ER as a diagnostic marker for mammary carcinoma.

GCDFP-15 (BRST-2) is 15 kDa glycoprotein originally isolated from human breast gross cystic disease fluid, and its reaction in mammary carcinomas ranges from 41 to 73%.[56–58] Its expression is seen in sweat gland and salivary gland carcinomas as well. GCDFP-15 has been regarded as a specific marker for mammary adenocarcinomas in the context of differentiating between pulmonary and mammary adenocarcinoma.[26] However, it has been recently reported that a subset of primary lung adenocarcinomas express this marker, with the reported expression rate ranging from 5.2 to 15%.[16,59–61] These figures as well as our results indicate that caution must be taken in the interpretation of this marker in this diagnostic context.

Mammaglobin is 10.5 kDa secretory protein, and it belongs to the secretoglobin family that encompasses nine members. It shares a high degree of homology with lipophilins A, B, C, and uteroglobin (Clara cell 10 kDa protein CC10). Its expression has been reported in 48–72.1% of mammary adenocarcinomas, 11–39% of endometrial adenocarcinomas, 40% of sweat gland carcinomas, and 20% of tumors of salivary gland origin,[57,58,62] but it is negative in pulmonary adenocarcinomas and squamous cell carcinomas.[57,61,62] Although mammaglobin A is often associated with ER-positive tumors, its expression does not appear to be directly regulated by the ER signaling pathway.[63] There were 10 cases of ER(−)/mammaglobin (+) in breast ductal carcinomas.

GATA-3 belongs to the GATA family of transcription factors comprising six members (GATA-1 to GATA-6), and it is expressed exclusively in the luminal epithelial cell population of the mammary gland but absent in myoepithelial cells.[64] GATA-3 is necessary for the specification and maintenance of the luminal cell fate. It has been found that positive GATA-3 expression is among the best predictors of ER-positive status, and that low GATA-3 protein expression is an independent predictor of tumor recurrence after treatment.[65,66] GATA-3 expression was also strongly correlated with the luminal A subtype of mammary carcinomas.[65] However, it appears that GATA-3 may not be a downstream target of ER, and the GATA-3 and ER pathways may have nonoverlapping functions in mammary luminal cells.[64] GATA-3 has not been investigated in the diagnostic context previously. In our study there were two cases of ER(−)/GATA-3(+) pattern whereas there were four tumors of ER(+)/GATA-3(−). It seems that they can be complementary diagnostic markers for mammary carcinomas. However, a combination of three markers, ER/GATA-3/mammglobin, detect 83.4% of mammary carcinomas while a combination of two markers, either ER/mammaglobin or GATA-3/mammaglogin, detects 82.6% of mammary carcinomas. There was no significant improvement over a combination of the three markers. Therefore, an addition of GATA-3 adds little diagnostic yield to more commonly used markers, ER and mammaglobin.

In conclusion, mammary carcinomas were detected by a combination of ER/mammaglobin or GATA-3/mammglobin at 83%, and the detection rate was not improved by using a combination of the three markers. 84% of pulmonary adenocarcinomas were positive for TTF-1 and/or Napsin A. Consequently, when metastasis from breast cancer is suspected in the lung, we recommend ER/mammaglobin or GATA-3/mammglobin as breast markers,

and TTF-1/Napsin A as lung markers. Caution should be taken in the interpretation of GCDFP-15 due to its occasional expression in pulmonary adenocarcinomas.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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