ORIGINAL ARTICLE

Fine-needle aspiration cytology of metaplastic carcinoma of the breast

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J Clin Pathol 2007;**60**:529–533. doi: 10.1136/jcp.2006.039412

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Accepted 8 May 2006
Published Online First
23 June 2006

Background: Metaplastic carcinoma of the breast encompasses a heterogeneous group of tumours with variable components of sarcomatoid, squamous or poorly differentiated carcinomas.

Aim: To review a series of 19 cytological preparations of metaplastic carcinomas to assess diagnostic cytological features.

Methods: 17 cases of fine-needle aspirates of histologically proven metaplastic carcinomas (4 monophasic spindle cell carcinomas, 4 squamous cell carcinomas and 11 biphasic tumours) were reviewed, with an emphasis on the presence of poorly differentiated carcinoma, squamous cell carcinoma, atypical spindle cells, benign stromal fragments and necrosis.

Results: All cases were diagnosed as malignant, with 68% of cases showing moderate to high cellularity, and 47% showing necrosis. If the tumours were analysed according to the constituting components histologically, 7, 15 and 8 cases, respectively, possess poorly differentiated carcinoma cells, sarcomatoid malignant cells and squamous carcinoma cells, whereas these components were cytologically identified in 11, 10 and 7 cases, respectively. Dual tumour populations were identified in only 5 of the 11 biphasic carcinomas in the cytological preparations; and the stromal material was cytologically identified in the only case with chondroid stroma.

Conclusions: Identification of metaplastic carcinoma in cytology remains problematic. There seems to be morphological overlap between various components. The identification of dual components, unequivocal squamous carcinoma cells and chondroid stroma is helpful for diagnosis, but it is uncommon. The presence of poorly differentiated carcinoma cells with a suggestion of focal spindle morphology is another clue to the suggestion of metaplastic carcinoma.

Metaplasia in mammary ductal epithelium and carcinoma is a well-known phenomenon. This includes squamous, neuroendocrine, apocrine, pseudosarcomatous and rarely pigmented melanocytic differentiation. Squamous metaplasia is the most common and occurs in 3.7% of a series of 1665 invasive carcinomas, whereas pigmented melanocytic differentiation is the rarest with only five cases reported in the literature.^{1–3} Breast tumours with these kinds of metaplasia or differentiation, excluding apocrine and neuroendocrine metaplasia, are dubbed as metaplastic carcinoma. It accounts for <1% of all invasive mammary carcinomas.⁴ Metaplastic carcinoma of the breast denotes tumours with malignant epithelial and malignant mesenchymal components, as well as primary or mixed adenocarcinoma and squamous carcinoma. Those cases with mixed epithelial and mesenchymal components can be classified into monophasic, composed of spindle cells only, or biphasic, showing distinct carcinomatous and sarcomatoid components.⁵ Wargotz *et al*^{6–10} have systematically grouped the tumours into various diagnostic labels, based on the presence of heterologous elements or osteoblastic giant cells, or whether the tumour cells are monophasic, biphasic or squamoid. These metaplastic components, together with typical invasive ductal carcinoma, may appear in the aspirated material, which gives clues for definitive diagnosis. With the current popularity of fine-needle aspiration cytology as a mode of preoperative diagnosis of breast tumours, a retrospective study was undertaken to identify any crucial cytological features of metaplastic carcinoma.

MATERIALS AND METHODS

The histopathological files of the six involved institutions were searched for metaplastic carcinoma of the breast, and those

cases with previous fine-needle aspirates that had sufficient material for interpretation were included in this review. The aspirates were obtained using a disposable 10 ml syringe and 22-gauge disposable needle, using single or multiple passes in the mass after penetrating the lesions under mild negative pressure. The aspirated material was immediately washed in a cytology container with 50% ethyl alcohol in physiological saline. The smears were stained with either Papanicolaou or Giemsa, or both with or without H&E stain. If there was residual tissue material, the cell block was prepared after centrifugation. All the smears were examined without knowledge of the excision by the pathologists from each respective institution. All the slides were assessed for the cellularity of the aspirate, the percentage and the degree of atypia of the following components:

- (1) Poorly differentiated carcinoma, characterised by cohesive sheets, clusters or single malignant cells with pleomorphic and hyperchromatic nuclei and increased nuclear cytoplasmic ratio. There was no obvious differentiation into either glandular or squamous morphology.
- (2) Squamous cell carcinoma, in which unequivocal evidence of squamous differentiation, notably intracytoplasmic keratinisation, was observed.
- (3) Spindle tumour cells, which include poorly cohesive clusters or mostly single malignant cells with plump to spindle nuclei.

In addition, the presence or absence of heterologous elements, stromal fragments and necrosis was also noted.

Abbreviation: PT, phyllodes tumour

Figure 1 (A) Moderate to markedly atypical spindle cells. (B) Plump-looking spindle cells that are mistaken as atypical glandular cells.

Cellular atypia was graded as low, moderate and high. Low grade referred to the malignant cells having mild nuclear pleomorphism and hyperchromasia without nucleoli or bizarre nuclear features such as multinucleation. Moderate cellular atypia referred to the malignant cells having moderate nuclear irregularity, coarse chromatin and small nucleoli. No bizarre nuclear features were seen. Severe cellular atypia referred to the malignant cells possessing high nuclear cytoplasmic ratio, vesicular nuclei and prominent nucleoli.

RESULTS

A total of 19 cases were included in this review, derived from 19 patients, all were women. These included 4 cases with monophasic spindle cells, 4 cases of squamous cell carcinomas and 11 cases of biphasic tumours, including 7 cases with mixed poorly differentiated adenocarcinoma with sarcomatoid components and 4 cases with mixed squamous cell carcinoma with sarcomatoid components. Table 1 summarises the overall results. The mean age for the pure spindle cell group, the pure squamous cell group and the mixed component group were 61, 51 and 50.7 years, respectively.

When taken as a whole, all cases were diagnosed as either suspicious of carcinoma or frank carcinoma. Most cases were described as poorly differentiated, and one case each of metaplastic carcinoma and squamous cell carcinoma was diagnosed. The overall cellularity was moderate to high in most of the cases (11 of 17 cases, 65%). Necrosis was present in 8 of 17 cases.

For the four pure spindle cell carcinomas—that is, monophasic spindle cell subtype—the cytological diagnoses were carcinoma in three cases and suspicious carcinoma in one case. The cellularity ranged from low to moderate. Moderate to markedly atypical spindle cells were noted in all four cases (fig 1A). Squamous cells were consistently absent. In case 2, atypical carcinomatous fragments were noted. These may represent the more “plump”-looking spindle cells that are mistaken as atypical glandular cells or represent some reactive changes adjacent to the tumour (fig 1B). In one case, a few atypical squamous cells were noted in the smear, which were absent in the excision specimen, probably reflecting the detached spindle cells assuming a polygonal morphology.

For the pure squamous cell group, three cases were diagnosed as malignant and one as suspicious. The cellularity of the smears ranged from low to high. Two cases showed tumour necrosis. Three cases were correctly identified as malignant; malignant squamous cells were identified only in one case. In all other cases, malignant epithelial cells devoid of keratinisation were observed, leading to categorisation into poorly differentiated carcinoma rather than squamous cell carcinoma.

For the biphasic group, four cases were diagnosed as suspicious, six as carcinoma and one as metaplastic carcinoma. There were four cases with low, three with moderate and three with high cellularity. Poorly differentiated carcinomas were identified in all seven cases with adenocarcinomatous component, (fig 2A), and malignant spindle cell component was identified in five of these seven cases. In the remaining four squamous cell carcinoma containing biphasic tumours, three showed malignant squamous cells in the aspirate (fig 2B).

Alternatively, of all the seven cases containing poorly differentiated adenocarcinomas (all biphasic tumours), all seven cases (100%) showed poorly differentiated tumour fragments in the smears. For the 13 cases with the spindle cell component, including the 4 monophasic spindle cell tumours and the 9 biphasic cases, a total of 10 (76%) cases showed malignant spindle cells present in the aspirate. For the 12 cases with squamous cell carcinoma, including 4 pure squamous cell carcinomas and 8 biphasic tumours with squamous cells as the epithelial component, malignant squamous cells were correctly identified in 7 (58%) of these cases.

DISCUSSION

Metaplastic carcinoma of the breast is a rare malignant tumour, accounting for <1% of all invasive mammary carcinomas.⁴ The histogenesis of this tumour is not well known and a few theories have been proposed. Yang *et al*¹¹ proposed bidirectional differentiation of the small undifferentiated cells into carcinoma cells and rhabdomyosarcoma cells. This theory is supported by the demonstration of epithelial-to-mesenchymal plasticity under suitable conditions.¹² Padmore *et al*² suggested that the origin of the tumour is either from a “neoplastic derepression” of a single cell type or, less likely, from a “simultaneous differentiation of two separate cell types in a shared environment”. Hamperi¹³ suggested in 1970 that the histogenesis of the sarcomatous component is through the transformation of the myoepithelial cells. This observation is further substantiated by the expression of p63, a myoepithelial marker in the breast,^{14,15} in metaplastic carcinoma of the breast.^{14,16–19}

Several interesting observations can be made in the cytological assessment of this series of metaplastic carcinoma. From our review, it is apparent that most cases were correctly identified as malignant, with many cases showing the cytological features of a high-grade carcinoma, including a high degree of atypism as well as moderate to high cellularity. In addition, necrosis was present in 9 of the 19 (47%) cases, further attesting to the high-grade nature of the tumour being reflected in the aspirate.

Table 1 Overall results of this review

Subtype	Sex/age (years)	Cellularity of the FNA smears	Adenocarcinoma in histological sections (%)	SCC in histology section (%)	Spindle tumour cell in histology section (%)	Spindle tumour heterologous cell in histology (type) (%)	Poorly differentiated carcinoma fragments (type)	Pump spindle or spindle cellular fragments or single spindle cells	Atypia of the spindle cells	Squamous fragments or single squamous cells	Atypia of the squamous cells	Stromal fragments	Necrosis	FNA diagnosis
Pure spindle														
Case 1	F/69	Low	0	0	100	0	Absent	Present	Moderate	Absent	NA	Absent	Present	Suspicious cells present
Case 2	F/49	Moderate	0	0	100	0	Present	Present	Moderate	Absent	NA	Absent	Present	Poorly differentiated carcinoma
Case 3	F/76	Moderate	0	0	100	0	Absent	Present	Moderate	Present	Marked	Present	Present	Suggestive of SCC
Case 4	F/50	Moderate	0	0	100	0	Absent	Present	Marked	Absent	NA	Absent	Absent	Malignant cells compatible with carcinoma
Pure squamous														
Case 5	F/47	Moderate	0	100	0	0	Present (rare single glandular cells noted)	Absent	NA	Present	Moderate	Absent	Absent	Ductal carcinoma
Case 6	F/50	Low	0	100	0	0	Present	Absent	NA	Absent	NA	Absent	Absent	Carcinoma
Case 7	F/53	Moderate	0	100	0	0	Present	Absent	NA	Absent	NA	Absent	Present	Malignant cells compatible with carcinoma
Case 8	F/54	High	0	100	0	0	Present	Absent	NA	Present	Marked	Absent	Present	Suspicious cells seen
Mixed components														
Case 9	F/47	Moderate	90	10	0	0	Present	Present	Moderate	Absent	NA	Absent	Absent	Suspicious cells present
Case 10	F/42	Low	80	20	0	0	Present	Absent	NA	Absent	NA	Absent	Absent	Suspicious cells present
Case 11	F/41	High	0	70	30	0	Absent	Absent	NA	Present	Mild	Present	Absent	Carcinoma
Case 12	F/43	High	40	50	10	0	Present	Present	Mild	Present	Marked	Present	Present	Carcinoma
Case 13	F/49	High	0	10	90	0	Absent	Present	Mild	Absent	NA	Present	Present	Metaplastic carcinoma
Case 14	F/50	Low	40	10	50	0	Present	Present (in the chondroid stroma)	Mild	Absent	NA	Present	Present	Carcinoma
Case 15	F/54	Low	40	0	10	50 (chondroid)	Present	Present (in the chondroid stroma)	Mild	Absent	NA	Present (chondroid stroma with latic cords of glandular cells)	Absent	Suspicious of malignancy
Case 16	F/43	Low	5	0	95	0	Present	Absent	NA	Absent	NA	Absent	Absent	Malignant cells compatible with carcinoma
Case 17	F/74	Moderate	20	0	80	0	Present	Absent	NA	Absent	NA	Present	Absent	Suspicious of malignancy
Case 18	F/76	Moderate	0	50	50	0	Absent	Absent	NA	Present	Marked	Absent	Present	Malignant cells compatible with carcinoma
Case 19	F/39	Moderate	0	50	50	0	Present	Present	Marked	Present	Marked	Absent	Absent	Ductal carcinoma

F, female; FNA, fine needle aspiration; SCC, squamous cell carcinoma; NA, not applicable.

Figure 2 (A) Poorly differentiated carcinoma. (B) Malignant squamous cells.

To further differentiate the type of malignancy, one has to look at the individual cytological component. The poorly differentiated carcinoma component was present in 13 of 19 cases, including all 4 squamous cell carcinomas, and in all biphasic tumours with adenocarcinomatous components. In the two false-positive cases, such fragments were observed in a monophasic spindle cells only tumour and in a biphasic tumour with squamous and spindle cells. For malignant spindle cells, they were present in 10 of 19 cases including all 4 monophasic spindle cell tumours, 6 of 11 (54%) biphasic tumours and none of the pure squamous cell carcinomas. Squamous cell carcinoma cells were identified in 7 of 19 cases, including 5 cases with squamous cell components (2 pure squamous cell carcinomas, and 3 biphasic tumours with squamous cell components), only 1 spindle cell tumour and 1 biphasic tumour with adenocarcinoma.

The presence of more than one type of cytological feature may be helpful in assisting the cytological diagnosis of metaplastic carcinoma, but only in a subset of metaplastic carcinoma that is biphasic. In this review, 11 cases were biphasic on histological examination; only 5 cases showed more than one component in the aspirate. But of the 6 cases in which only one component was identified in the aspirate, the histology of 5 of these 6 (84%) cases showed predominance of one component constituting $\geq 80\%$ in the sampled tumour. It is apparent that relying on the presence of dual components in the aspirate is not a reliable criterion for diagnosing metaplastic carcinoma.

The presence of stromal fragments in the aspirate was identified in 7 (37%) of the cases, and there was no difference between the different groups of metaplastic carcinomas. In only one case was a heterologous element of chondroid material identified in the aspirate, allowing a diagnosis of metaplastic carcinoma to be made (fig 3).

The cytological differential diagnoses of atypical spindle cells in the smears include monophasic metaplastic carcinoma, leiomyosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberans and malignant peripheral nerve sheath tumour. In leiomyosarcoma, the tumour cells are histiocytic-like plump and spindly, with abundant vacuolated cytoplasm, as well as large, hyperchromatic and slightly pleomorphic nuclei with irregular nuclear contours and nucleoli.²⁰ For malignant fibrous histiocytoma, the spindle cells are pleomorphic. High-grade epithelioid tumour cells, multinucleated giant cells and bizarre malignant cells are commonly seen.²¹ The cytological features of dermatofibrosarcoma protuberans are characterised by compact clusters of spindle cells, with poorly defined cytoplasmic borders and uniform, spindle-shaped or oval nuclei.²² Malignant peripheral nerve sheath tumour is rare in the breast and shows pointed nuclei and bipolar slender cytoplasmic tails.²⁰

In the presence of atypical spindle cells, together with epithelial cells, the differential diagnosis will be with phyllodes tumours (PTs). The presence of bland-looking to mildly atypical epithelial cells, visible clefting and variable cellularity of the stromal fragments, the presence of single and bland columnar to spindle cells of stromal origin in the background is in favour of PT.^{23–25} However, in malignant PT, the stromal overgrowth may be so prominent that cytological smears may not show any epithelium at all, making it difficult, if not impossible, to distinguish these lesions from pure spindle cell mesenchymal tumours.²⁶ Another possibility for the differential diagnosis is the desmoplastic stroma of ductal carcinoma, but the cytological differentiation would not be possible.

The presence of squamous cells in the smear would make one consider epidermoid cyst, squamous metaplasia secondary to infarct of fibroadenoma or papilloma^{27–29} and abscess.^{30–31} Atypical squamous cells can be noted in the smears of seroma

Figure 3 Heterologous element of chondroid material identified in the aspirate.

Take-home messages

- Identification of dual components, unequivocal squamous carcinoma cells and chondroid stroma is helpful for diagnosis of metaplastic carcinoma.
- Presence of poorly differentiated carcinoma cells with features suggestive of spindle morphology gives rise to the suggestion of metaplastic carcinoma.

with post-irradiation atypia,³² PT with intracanalicular metaplastic epithelial lining cells^{33–34} and squamous cell carcinoma (metaplastic carcinoma). Therefore, the presence of atypical squamous cells in the aspirate may not necessarily indicate an underlying malignant lesion.

The cytological diagnosis of metaplastic carcinoma is fraught with pitfalls. Although the usually moderate to high cellularity, atypical epithelial fragments and necrosis that are almost always present allows a diagnosis of high-grade carcinoma to be made, the variable histomorphology with the carcinomatous (adenocarcinomatous and squamous) and sarcomatoid components makes the cytological picture highly variable. Irrespective of these various components, the fact that all components are clonal³⁵ probably contributes to the fact that in most cases, most of the tumour cells assume a rather poorly or undifferentiated appearance. The telltale signs of unequivocal malignant squamous cell with keratinisation or the presence of identifiable heterologous elements, most probably chondroid, are uncommon, but the presence of these in a background of poorly differentiated carcinoma cells in an aspirate will be diagnostic of metaplastic carcinoma. For the remaining cases, the presence of poorly or undifferentiated carcinoma, particularly when some fragments and single cells exhibit spindled appearance, should alert one to the possibility of metaplastic carcinoma. This is because metaplastic carcinoma behaves in a manner different from the conventional infiltrative ductal carcinoma as the metaplastic carcinoma is less likely to invade locally or metastasise at the presentation, despite its relatively large size, as well as its propensity for haematogenous rather than lymphatic metastasis.^{36–37}

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Competing interests: None declared.

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