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Fine Needle Aspiration Cytology of Breast Pure Squamous Cell Carcinoma: Cytologic Differential Diagnosis from Mammary Lesions Associated with Aberrant Squamous Cells

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Abstract

Fine needle aspiration (FNA) cytology of two cases of breast pure squamous cell carcinoma (SCC) and one invasive carcinoma mixed with SCC is reported. Cytopathologic findings of breast cancer vary greatly because mammary carcinomas are composed of many subtypes. Squamous cells, both malignant and benign, are occasionally seen in the breast FNA smears. Many differential diagnoses including various neoplastic and non-neoplastic diseases should be raised when squamous cells are observed in the mammary FNA smears. Squamous cells endowed with severe grade atypia obviously indicate malignancy. However, apparently benign-looking squamous cells are seen in the FNA specimens of both malignant and benign breast disorders. Accurate interpretation of cytologic findings is essential for discriminating malignant diseases from benign conditions. As prognosis and therapeutic options depend on tumour subtypes, deducing tumour histologic subtypes from cytologic specimens is useful for the appropriate treatment planning. FNA samples of pure SCC and invasive carcinoma mixed with SCC were examined in detail in an attempt to clearly define the cytopathologic characteristics of pure breast SCC. Careful review of the FNA slides of these cases helped us to recognize cytomorphologic findings useful in the differential diagnoses and predicting of histologic pictures of mammary disorders containing squamous cells.

Keywords: Breast; Fine needle aspiration; Metaplastic carcinoma; Papanicolaou stain; Squamous cell carcinoma

Introduction

Breast cancer is a common neoplasm. Surgeons, and gynaecologists/obstetricians alike, are often encountered with mammary carcinoma in the daily practice. Breast cancer comprises many histologic subtypes, which affect prognosis. Squamous cell carcinoma (SCC) of the breast, a subtype of mammary cancer, is defined as the tumour in which >90% of tumour cells are composed of squamous carcinoma cells [1,2]. Breast pure SCC is rare, with an incidence from 0.05% to 0.4% of breast cancer [3-6]. As a result, its cytologic findings have been only sporadically described [5-14].

Squamous cells are occasionally seen in the cytologic specimens of various mammary disorders. These wide-ranging lists of differential diagnoses include pure SCC, metaplastic carcinoma with squamous differentiation, adenosquamous carcinoma, invasive ductal carcinoma mixed with SCC, phyllodes tumour, fibroadenoma (FA), duct ectasia, sub-areolar abscess, intra-ductal papilloma, and cyst [15]. Among these, malignancies should be correctly discriminated from benign disorders. Furthermore, once diagnosed as malignant, an accurate assessment of tumour subtypes is beneficial because the treatment options may need to be tailored accordingly. As fine needle aspiration (FNA) cytology is usually employed as the first examination for the breast mass of undetermined diagnosis, cytologic findings should be efficiently utilized to facilitate management of the patient. FNA cytologic findings of two cases of mammary breast pure SCC and one patient of invasive carcinoma mixed with SCC were compared with histologic findings in an effort to determine the cytologic findings useful for the differentiation of pure SCC from other malignant and benign mammary lesions. Prediction of histologic subtypes from cytologic specimens may be beneficial for the management of breast cancer.

Case Presentation

Case 1

A 49 year old woman with a painless lump in her right breast was referred to our hospital. Ultrasonography (US) demonstrated a 1.4 × 1.0 cm hypoechoic solid mass in the lateral region. FNA slides were very cellular with markedly atypical cells that appeared as clusters and as single cells in a necrotic/inflammatory background (Figure 1A).

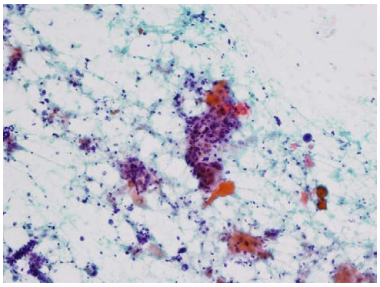

Figure 1a: The slides were very cellular. Highly atypical cells were plentifully observed both as single cells and clusters in a necrotic/inflammatory background. Numerous naked nuclei were also present. Many Orange G-philic cells were also seen (Papanicolaou stain, ×100).

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The nuclei were highly pleomorphic with respect to size and shape. The nuclear/cytoplasmic (N/C) ratio was elevated and the nuclear membrane was ragged and thickened. The nuclei contained coarsely granular chromatin and enlarged pleomorphic nucleoli (sometimes multiple). Naked atypical nuclei were also seen. The ample cytoplasm was dense, often Orange G-philic with distinct cell border (Figure 1B). These cytologic findings were compatible with SCC. Systemic surveys revealed no distant disease. In the resected breast, an 18 × 13 mm-sized solid tumour was confined within the mammary parenchyma (not shown). Histologically, both the main tumour and intra-ductal spreads had small central cystic spaces filled with necrosis (not shown). Anisonucleosis was marked, and many bizarre/giant nuclei associated with large nucleoli were present. Keratinization with intercellular bridge was clearly visible in the main tumour (Figure 1C) and also in the intra-ductal spread (not shown). These histologic findings confirmed the cytologic diagnosis of SCC. ER/PR/HER2 expressions were all negative. There was no metastasis in the sentinel lymph node. She has been followed for 86 months without any sign of recurrence.

Case 2

A 53 year old female presented with a mass in her left breast (upper medial region). Mammography and US demonstrated a 21 × 18 × 16 mm solid tumour, to which FNA was performed. The overall cytologic pictures in low power inspection were essentially the same as the Case 1. FNA yielded cellular slides enriched in numerous atypical cells, which appeared as both densely aggregated and dispersed cells. These cells had pleomorphic nuclei with high N/C ratio, hyperchromasia, rough and thickened nuclear border, and conspicuous nucleoli. Their cytoplasm was often Orange G-philic, broad, and solid. The background was necrotic and inflammatory (Figure 2A and 2B). These cytologic findings suggested SCC. Macroscopically, the tumour was solid but histologically centrally cystic both in the main tumour and ductal spread as in the Case 1 (not shown). Adipose tissue invasion was present. The cancer cells showed occasional keratinization and prominent intercellular bridges, with marked nuclear irregularity, anisonucleosis, hyperchromasia, coarsely granular chromatin, and irregularly/partially thickened nuclear membrane (Figure 2C). Mitoses, including aberrant ones, were sometimes seen (not shown). The histologic examination verified cytologic diagnosis of SCC. Molecular biomarkers status was triple negative. There was no lymph node involvement. The post-operation course has been uneventful for 83 months after the surgery.

Case 3

A 50 year old woman complained of an induration in her left breast and referred to our hospital from a local physician. A hard mass (7 × 6.5 cm) mass in the left lateral region and a ~∅2-cm axillary lymph node were palpable. The skin above the tumour was reddened

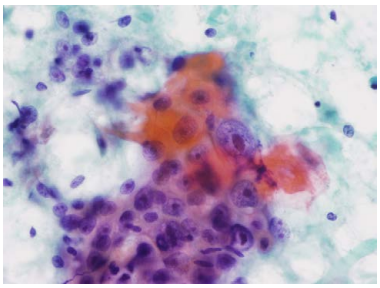

Figure 1b: High power view demonstrated severely atypical cells associated with giant nuclei with large nucleoli and coarsely granulated chromatin. Some cancer cells have thick, solid cytoplasm that is Orange G-philic suggesting keratinization (Papanicolaou stain, ×400).

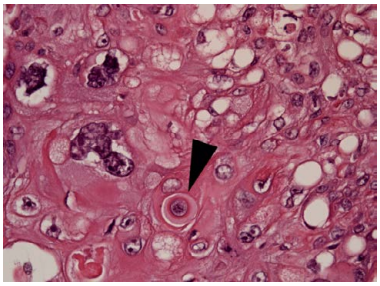

Figure 1c: Histology of the resected tumour. Atypical cells with bizarre, giant nuclei with hyperchromatic, coarsely granulated chromatin were seen. Keratinized cells with intercellular bridge formation were also noted (arrowhead) (gHematoxylin and eosin stain, ×200).

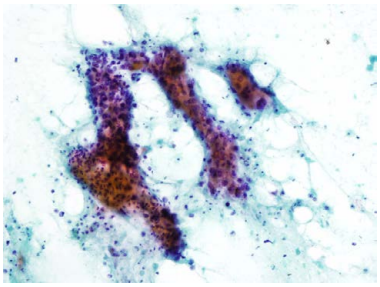

Figure 2a: The smears were cell-rich. Cells with marked atypia appeared as dispersed cells and aggregated clusters. The background showed tumour diathesis. (Papanicolaou stain, ×100).

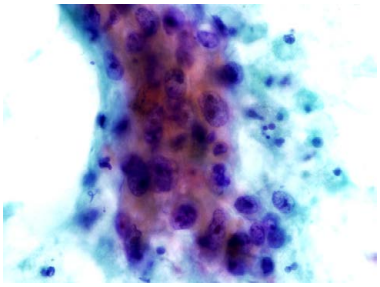

Figure 2b: Cancer cells had irregular and thickened nuclear membrane. The chromatin was remarkably hyperchromatic, and coarsely granular (Papanicolaou stain, ×400).

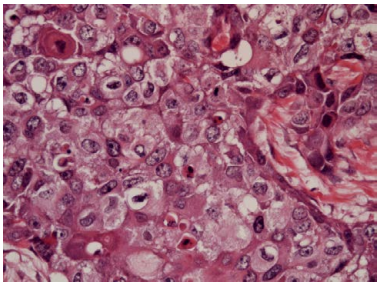

Figure 2c: Histologically, the cancer cells showed striking cellular/nuclear pleomorphism. Keratinized cell was present (left upper corner) (gHematoxylin and eosin stain, ×200).

indicating cutaneous infiltration. In low power field, the FNA smears were very cellular, in which highly atypical cells were abundantly seen in an inflammatory and necrotic background (Figure 3A). These cytologic findings were analogous to those of the Case 1 and 2. In close up view, atypical cells showed elevated N/C ratio, anisonucleosis, hyperchromasia, and coarse granular chromatin were observed. Some cancer cells had Orange G-philic broad cytoplasm. These cytologic pictures looked essentially same as previous two cases. However, careful observation of entire specimens in high power disclosed minor differences in some tumour cells. In these cells, nuclear atypia was less severe compared with Case 1 and 2. These nuclei, generally ovoid in shape, were less pleomorphic while those of the Case 1 and 2 were markedly so, occasionally associated with bizarre and giant nuclei. Chromatin granularity was finer. Scrupulous examination of the entire slides revealed remnant gland formation (Figure 3B). These findings indicated that the cancer cells had characteristics of adenocarcinoma besides SCC. Orange G-philic cell clusters (Figure 3C) and tadpole-like cells (Figure 3D) were also noted. In some Orange G-philic cells aggregates, the N/C ratio was lower, nuclear atypia was milder, and the chromatin was less hyperchromatic (Figure 3C). The tadpole-like cells lacked pyknotic, hyperchromatic nuclei. These findings suggested that these cells were squamous morule/metaplasia cells rather than true SCC cells. Core needle biopsy (CNB) specimens demonstrated solid growth of highly atypical cells (Figure 3E) and invasive growth of cancer cells with inconspicuous gland formation and squamous morules (Figure 3F). These histologic findings meant invasive carcinoma mixed with SCC. Hormonal receptor expression was ER (+), PR (-), and HER2 (3+). She was lost to follow up before the treatment.

All these cases had no skin tumours around the breast lesions or other SCC of oro-naso-pharingo-laryngeal, oesophageal, pulmonary, and gynaecologic origin.

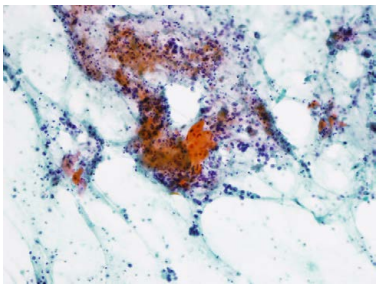

Figure 3a: In low power view, the slide looked similar as cases 1 and 2: atypical cells, some were Orange G-philic, were copiously procured in a necrotic/inflammatory background (Papanicolaou stain, ×100).

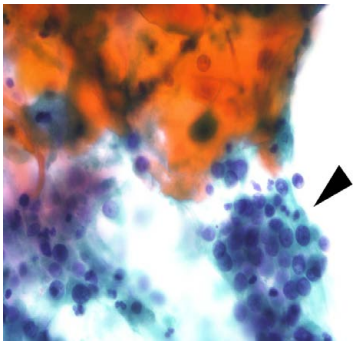

Figure 3b: Vestigial gland formation was discernible (arrowhead) (Papanicolaou stain, ×400).

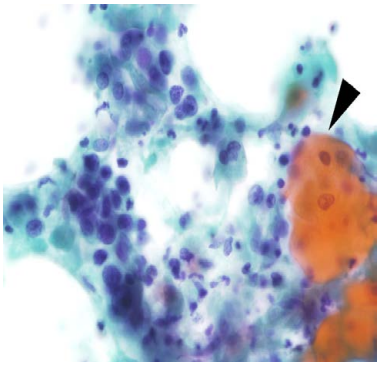

Figure 3c: The nuclei in the aggregated Orange G-philic cells (arrowhead) had lower nuclear/cytoplasmic ratio and less hyperchromasia compared with cancer cells in the Case 1/2 (Papanicolaou stain, ×400).

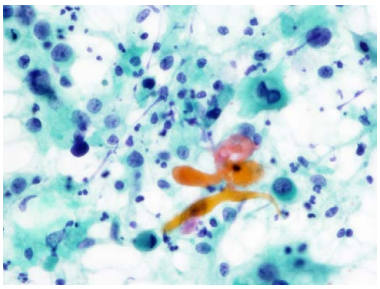

Figure 3d: Tadpole-like keratinized cells were seen. However, the nuclei were neither pyknotic nor hyperchromatic (Papanicolaou stain, × 400).

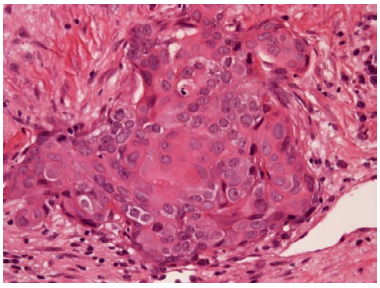

Figure 3e: In the excised tumour, foci of squamous cell carcinoma were observed (gHematoxylin and eosin stain, ×200).

Discussion

Squamous cells are rarely observed in the breast FNA smears. In one study, squamous cells, whether malignant or benign, are identified only in 0.34% of breast FNA samples, in which squamous cells are seen in the FNA smears of various kinds of mammary lesions such as metaplastic carcinoma with squamous differentiation, adenosquamous carcinoma, phyllodes tumour, fibroadenoma (FA), duct ectasia, sub-areolar abscess, intra-ductal papilloma, and cyst [15]. Usually, malignant squamous cells in metaplastic carcinoma, including pure SCC, are readily recognized by their marked cellular/nuclear atypia and pleomorphism, high mitotic activity, increased N/C

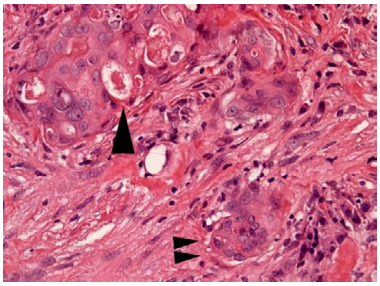

Figure 3f: In some part of the tumour, gland formation (single arrowhead) and squamous morule (double arrowheads) were also observed (gHematoxylin and eosin stain, ×200).

ratio, hyperchromatism associated with coarsely granular chromatin, thickened nuclear membrane [5,6,8,9,11,14,16].

Cytologic diagnosis of mammary SCC is readily made when atypical squamous cells with nuclear/cytoplasmic pleomorphism are abundantly obtained as dispersed cells and as clusters. Typically, the nuclei are associated with high N/C ratio, hyperchromasia, coarsely granular chromatin, and proliferated and ragged nuclear border. The cytoplasm is usually ample, thick, and often Orange G-philic suggesting keratinization [5,6,8,9,11,14,16]. Nonetheless, metastasis from more common SCCs to the breast should be ruled out because primary mammary SCC is rare. Though metastasis of SCC to the breast is also an unusual event, metastases from uterine cervix [5,7,17], oesophagus [18], and lung [5,19] have been reported. Since the cytologic findings of SCCs arising from extra-mammary organs are essentially the same as those of breast SCC [5], differential diagnosis with cytology alone is impossible. Systemic surveys for excluding extra-mammary SCCs are indispensable for the diagnosis of mammary SCC. Past history of SCC is helpful information. Multiple lesions, particularly when present within the breast [17], strongly suggest metastasis. Another differential diagnosis is SCC developed in skin and its appendage. SCC arising from the skin in the proximity of the breast should also be excluded.

The FNA smears of our three cases looked similar in low power view. Many atypical cells with severe cellular/nuclear pleomorphism were seen in the tumour diathetic background. These cells were often Orange G-philic. These smears indicated high grade cancer, particularly SCC. However, close inspection in high power revealed some diagnostically meaningful differences in the Case 3. These included milder degree atypia (nuclear pleomorphism, nuclear membrane, hyperchromatism, and chromatin pattern), occurrence of metaplastic squamous cells, and vestigial gland formation.

Pure SCC cells showed marked nuclear pleomorphism, anisonucleosis and hyperchromasia. Their nuclei had thickened/ragged membrane, and contained roughly granular chromatin. Giant/bizarre nuclei were often present (Figures 1A, 1B, 2A and 2B). Their dense and solid cytoplasm was often Orange G-philic indicating keratinization (Figures 1B and 2B). These cytologic diagnoses as pure SCC were confirmed histologically in the resected tumours (Figures 1C and 2C). On the other hand, nuclear anisonucleosis and pleomorphism was less prominent in the Case 3. The nuclear contour was sometimes round to oval, and giant/bizarre nuclei were uncommon. The nuclear membrane was generally smooth and slim. The chromatin was paler and powdery granular (Figures 3B and 3C). Attentive observation of cytologic smears in high power magnification would disclose these differences of nuclear atypia.

Orange G-philic cell groups were also seen in the Case 3, but nuclear atypia, increased N/C ratio, and hyperchromasia was missing (Figure 3C) when compared with those of pure SCC cells (Figures 1B and 2B). These Orange G-philic cells were thought as metaplastic cells rather than SCC cells. Histologically, these clusters of Orange G-philic cells with bland nuclei (lower N/C ratio, smooth nuclear membrane, and fine chromatin pattern) corresponded to squamous morule (Figure 3F). Benign looking squamous cells are seen both in malignant and benign breast lesions including adenosquamous carcinoma, phyllodes tumour, FA, duct ectasia, sub-areolar abscess, intra-duct papilloma and cyst. Dyskeratosis (such as keratin pearl formation) is seen in SCC, adenosquamous carcinoma, sub-areolar abscess, and intra-ducat papilloma. Squamous eddies were present in SCC, adenosquamous carcinoma, FA and intra-duct papilloma [15]. Therefore, presence of bland squamous is inconclusive whether the lesion is benign or malignant. However, foamy macrophages, myxoid stroma (FA), and papillary epithelial clusters (intra-ductal papilloma) are suggestive of benign conditions [15]. In very well differentiated SCC, squamous cells with minimal cellular/nuclear atypia are observed along with numerous surface-type squamous cells with centrally located small nuclei and inflammatory cells. These cytologic findings are confusing with epidermal cyst. Nonetheless, cytologic differential diagnosis may be possible by paying rigorous attention to anuclear keratinized cells and granular cells, which are usually seen only in epidermal cyst [12].

Remnant gland formation was discernible in the FNA specimen of the Case 3 (Figure 3B), which was also recognized in the CNB specimens (Figure 3F). These findings suggested that pure SCC was an unlikely diagnosis. Even if a cytologic diagnosis of SCC becomes evident during the microscopic examination, rest of the whole specimens should be scrutinized in order not to overlook additional findings that may suggest other diagnostic possibilities. Whether the diagnosis is pure SCC or else would affect the treatment plan. Majority of breast SCC is usually ER/PR negative. For example in one case series, 84.8% and 87.9% of mammary SCCs were ER and PR negative, respectively [20]. In another study, 97.8% and 95.6% of breast SCC were ER and PR negative, respectively [21]. On the other hand, in adenosquamous carcinoma, ER was positive in 80% and PR was positive in 66.7%, respectively [4]. In fact in our cases, two pure SCC were both triple-negative while invasive carcinoma mixed with SCC was positive for ER and HER2.

Meticulous analyses of cytologic findings would help to predict clinicopathologic characteristics of the specimens. Cytopathologic diagnoses should be maximally utilized for the guide of subsequent examinations for the definitive diagnosis and therapeutic planning. In addition to simply determining whether the sample is malignant or benign, cytopathologists should not miss additional findings that help to facilitate clinical processes.

References

1. Jones EL (1969) Primary squamous cell carcinoma of breast with pseudosarcomatous stroma. J Pathol 97: 383-385.
2. Wargotz ES, Norris HJ (1990) Metaplastic carcinomas of the breast. IV. Squamous cell carcinoma of ductal origin. Cancer 65: 272-276.
3. Toikkanen S (1981) Primary squamous cell carcinoma of the breast. Cancer 48: 1629-1632.
4. Eggers JW, Chesney TM (1984) Squamous cell carcinoma of the breast: a clinicopathologic analysis of eight cases and review of the literature. Hum Pathol 15: 526-531.
5. Gupta RK (1997) Fine needle aspiration cytodiagnosis of primary and metastatic squamous cell carcinoma of the breast. Acta Cytol 41: 692-696.

6. Gupta RK, Dowle CS (1997) Cytodiagnosis of pure primary squamous-cell carcinoma of the breast by fine-needle aspiration cytology. Diagn Cytopathol 17: 197-199.
7. Leiman G (1982) Squamous carcinoma of the breast: diagnosis by aspiration cytology. Acta Cytol 26: 201-209.
8. Hsiu JG, Hawkins AG, D'Amato NA, Mullen JT (1985) A case of pure primary squamous-cell carcinoma of the breast diagnosed by fine needle aspiration biopsy. Acta Cytol 29: 650-651.
9. Macia M, Ces JA, Becerra E, Novo A (1989) Pure squamous carcinoma of the breast. Report of a case diagnosed by aspiration cytology. Acta Cytol 33: 201-204.
10. Chen KT (1990) Fine needle aspiration cytology of squamous cell carcinoma of the breast. Acta Cytol 34: 664-668.
11. Nakayama K, Abe R, Tsuchiya A, Watanabe T, Furukawa Y, et al.(1993) Squamous cell carcinoma of the breast. Report of a case diagnosed by fine needle aspiration cytology. Acta Cytol 37: 961-965.
12. Motoyama T, Watanabe H (1996) Extremely well differentiated squamous cell carcinoma of the breast. Report of a case with a comparative study of an epidermal cyst. Acta Cytol 40: 729-733.
13. Vera-Alvarez J, García-Prats MD, Marigil-Gómez M, Abascal-Agorreta M, López-López JI, et al.(2007) Primary pure squamous cell carcinoma of the breast diagnosed by fine-needle aspiration cytology: a case study using liquid-based cytology. Diagn Cytopathol 35: 429-432.
14. Annam V, Giriyan SS, Kulkarni MH (2009) Diagnosis of pure squamous cell carcinoma of the breast by fine needle aspiration cytology. Acta Cytol 53: 722-723.
15. Ng WK, Kong JH (2003) Significance of squamous cells in fine needle aspiration cytology of the breast. A review of cases in a seven-year period. Acta Cytol 47: 27-35.
16. Lazarevic B, Katatikarn V, Marks RA (1984) Primary squamous-cell carcinoma of the breast. Diagnosis by fine needle aspiration cytology. Acta Cytol 28: 321-324.
17. Gupta S, Gupta MK, Gupta, Mishra RS (1998) Breast metastasis of cervical carcinoma diagnosed by fine needle aspiration cytology. A case report. Acta Cytol 42: 959-962.
18. Miyoshi K, Fuchimoto S, Ohsaki T, Sakata T, Takeda II, et al.(1999) A case of esophageal squamous cell carcinoma metastatic to the breast. Breast Cancer 6: 59-61.
19. Hsu W, Sheen-Chen SM, Wang JL, Huang CC, Ko SF (2008) Squamous cell lung carcinoma metastatic to the breast. Anticancer Res 28: 1299-1301.
20. Hennessy BT, Krishnamurthy S, Giordano S, Buchholz TA, Kau SW, (2005) Squamous cell carcinoma of the breast. J Clin Oncol 23: 7827-7835.
21. Menes T, Schachter J, Morgenstern S, Fenig E, Lurie H, et al. (2003) Primary squamous cell carcinoma (SqCC) of the breast. Am J Clin Oncol 26: 571-573.