Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/5sppze07

ADENOSQUAMOUS CARCINOMA OF THE BREAST: A RARE METAPLASTIC NEOPLASM WITH DISTINCT HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

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Abstract

Background: Adenosquamous cell carcinoma of the breast is one of the rare and aggressive types of metaplastic breast carcinoma, which has a squamous differentiation and biphasic glandular. ASC is less than 1% of all breast malignancies, and it is problematic about its diagnosis because it is morphologically similar to other subtypes of breast carcinomas.

Case Presentation: A 37-year-old woman presented with a noticeable lump in her right breast. Radiological imaging revealed a metabolically active lesion with regional lymphadenopathy, and histopathological examination confirmed ASC with both glandular and squamous components. Immunohistochemistry showed a triple-negative immunophenotype, with p40 positivity and CK7 expression, indicative of squamous differentiation. The Ki-67 index was 70%, highlighting its high proliferative index.

Conclusion: ASC of the breast is a rare and aggressive neoplasm that presents great diagnostic and treatment problems. Its triple-negative nature requires chemotherapy because the targeted therapies are not effective. This case emphasises the importance of early diagnosis and multidisciplinary management.

Keywords: Adenosquamous carcinoma, metaplastic breast carcinoma, triple-negative, squamous differentiation, immunohistochemistry, Ki-67, breast cancer.

1. Introduction

"Metaplastic breast carcinoma" (MBC) is a rare and diverse group of invasive breast cancers characterized by the transformation of neoplastic epithelial cells into squamous and/or mesenchymal elements. MBC can be classified into various histological subtypes, which are squamous cell carcinoma, spindle cell carcinoma, carcinoma with heterologous differentiation, and "adenosquamous carcinoma" (ASC) according to the World Health Organisation (WHO).[1] These are considered to be

less than 1% of all invasive ductal carcinomas and are not the same as traditional invasive ductal carcinoma in terms of morphology, immunophenotype, or clinical behaviour.[2]

"Adenosquamous breast carcinoma" is a type of metaplastic carcinoma that is extremely rare, accounting for less than 1% of breast cancer. It is characterised histologically by an admixture of malignant glandular elements and squamous differentiation, often embedded within a desmoplastic or inflammatory stroma.[3] ASC presents a serious diagnostic problem, especially with small biopsy samples, because of its rarity and morphological similarity to other breast cancer types, e.g., invasive ductal carcinoma with squamous metaplasia and the primary squamous cell carcinoma.[4]

The majority of "adenosquamous carcinomas" are characterised by a triple-negative immunophenotype that is characterised by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression and can be associated with a high proliferative index. This molecular profile also causes their aggressive clinical behaviour and restricts the presence of specific therapeutic interventions. [5] Whereas several investigations indicate that low-grade adenosquamous carcinoma can have a rather positive outcome, high-grade variants are linked with greater incidences of local recurrence and unfavourable overall results.[6]

Since "adenosquamous carcinoma" is rare and few well-documented cases are found in the literature, it is important to report such cases in order to enhance the knowledge on its spectrum of clinicopathology, diagnostic criteria, and prognostic implications. This report is a rare instance of "adenosquamous carcinoma" of the breast, its histopathology, immunohistochemical findings, and its correlation with radiology, with a particular focus on the diagnostic issues.

2. Case Presentation

2.1 Clinical History

A 37-year-old woman reported a palpable lump in the right breast of short duration. The lump had been steadily growing and was unrelated to nipple discharge, skin fissures or systemic reaction like fever or loss of weight. There was no significant personal or family history of breast or ovarian malignancy. In the clinical examination, a hard and indistinct mass could be felt in the inferolateral quadrant of the right breast. The skin and nipple-areolar complex above was not remarkable, and there was no clinical fixation of the areas to underlying structures. A provisional diagnosis of a malignant lesion of the breast was made based on clinical findings, and further examination of the patient was done by means of radiological imaging and a subsequent surgical excision to establish a definite diagnosis.

2.2 Radiological Findings

The whole-body "fluorodeoxyglucose positron emission tomography-computed tomography" (FDG PET-CT) revealed a metabolically active, heterogeneously enhancing soft tissue mass with central necrosis located in the inferolateral quadrant of the right breast. In the axial dimension, the lesion had dimensions of approximately 4.3 × 3.1 cm, whereas in the craniocaudal direction, the lesion had a dimension of 4.6 cm; and the maximum standardised uptake value (SUVmax) was 32.6. The features in the imaging were very indicative of a malignant neoplasm that exhibited aggressive biological behaviour.

Several FDG-positive axillary lymph nodes of the right axilla were detected, with the largest one (meaning 1.4 x 1.0 cm) exhibiting cortical thickening and augmented metabolic activity (SUVmax 2.8), which is indicative of nodal metastasis. No significant FDG uptake was observed in the contralateral breast or internal mammary lymph nodes. There was no definitive evidence of distant visceral metastasis. The chest X-ray showed no sign of radiographic pulmonary metastasis; bilateral lung fields were clear. The high-grade histological findings that were evident under pathological examination were well associated with the presence of central necrosis and high levels of metabolic activity.

2.3 Gross Pathology

The surgical specimen consisted of a skin-covered soft tissue mass measuring 12 × 6.5 × 5.5 cm, with an overlying skin ellipse measuring 7.5 × 3 cm. Serial sectioning revealed a cavitating lesion measuring 3.5 × 2.5 × 2.4 cm located within the breast parenchyma. The cut surface of the tumour was grayish-white to grayish-brown with areas of friability and focal necrosis. The lesion was said to be focal, invasive, with irregular edges, which is characteristic of a malignant process.

The tumour was positioned at different distances from the margins of the resection. The superior and inferior margins were at a distance of 2 cm and 6 cm, and the medial and the lateral margins were 6 cm and 1.5 cm, respectively. The skin and deep margins were one centimetre away. No significant involvement of the covering skin or skeletal muscle underneath was found. The histopathological examination of representative sections had been provided.

3. Histopathological Findings

Microscopic observation of the hematoxylin and eosin-stained sections showed an infiltrative high-grade epithelial neoplasm that involved the breast parenchyma. Under low-power observation, the tumour showed a mixed architectural type of irregular glandular formations mixed with solid nests, cords, and tissue sheets of tumour cells implanted into a highly desmoplastic stroma. The tumour margins were also infiltrative, and they extended into the surrounding fibrofatty tissue, which is a characteristic of an invasive carcinoma.

The examination was done with high-power that revealed significant cytological atypia in both glandular and squamous elements. The glandular compounds consisted of irregular, angulated tubules with atypical epithelial cells with enlarged, pleomorphic nuclei, coarse chromatin and large nucleoli. These were interproliferated with foci of squamous differentiation, which comprised sheets and nests of polygonal tumour cells with large eosinophilic cytoplasm and outlined cell borders. The focal findings indicated the presence of intercellular bridges that established the fact of true squamous differentiation and not metaplasia.

Keratin pearl foci and single cell keratinisation were observed, and it was once again indicative of the "adenosquamous carcinoma". Mitotic figures were visible, and numerous mitotic figures were observed in numerous high-power fields, including unusual mitoses which are indicative of high-grade neoplasm. The investigated sections did not show any areas of tumour necrosis.

The surrounding stroma exhibited a pronounced desmoplastic response, accompanied by a dense inflammatory infiltrate composed predominantly of lymphocytes and plasma cells. This stromal response is an epithelial trend that is common in metaplastic carcinoma and makes the tumour firm during gross examination. It is important to note that no element of "ductal carcinoma *in situ*" (DCIS) or other *in-situ* carcinoma was detected despite a lot of sampling, which also contributes to the diagnosis of a primary metaplastic carcinoma over and above the fact that it was an invasive carcinoma of a pre-existing in-situ lesion.[7]

Altogether, the histomorphological appearance, such as admixture of malignant glandular and squamous elements, keratinisation, high mitotic rate, and high stromal response, is characteristic of adenosquamous carcinoma of the breast.[8, 9]

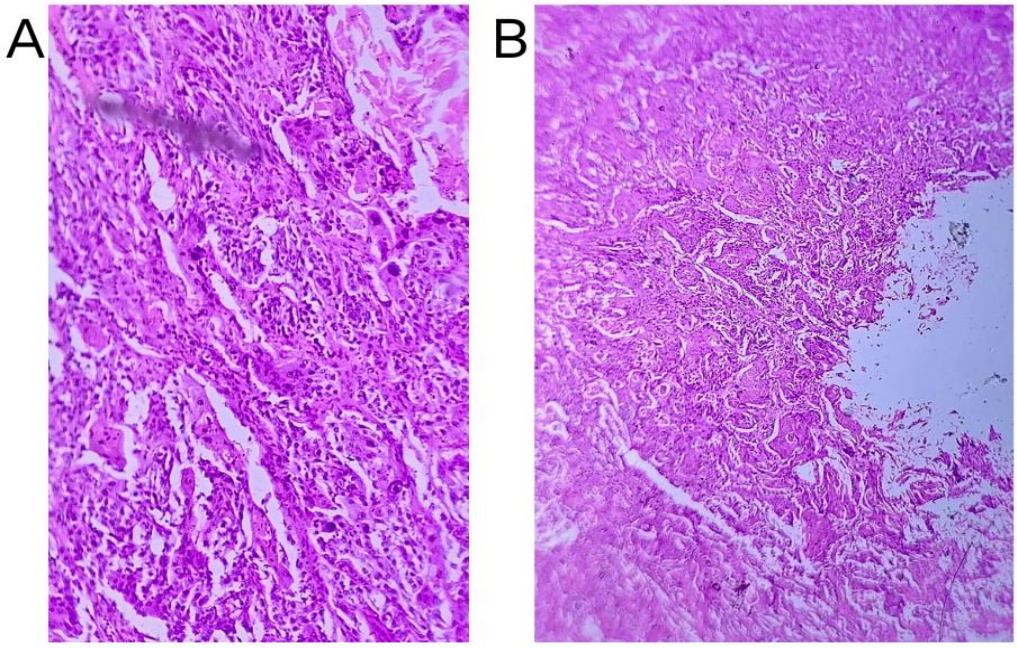


Figure 1. Hematoxylin and eosin (H&E) staining of adenosquamous carcinoma of the breast. The low-power view (A) shows an infiltrative tumour composed of both glandular and squamous components with dense stromal response. The high-power image (B) highlights the squamous differentiation with keratin pearl formation and individual cell keratinisation.

The "Hematoxylin and Eosin" (H&E) staining of the tumour is presented in Figure 1. The low power (A) shows how infiltrative the tumor is, and both glandular and squamous elements are found. The tumour is also encircled with a dense stromal background, which is a typical characteristic of metaplastic carcinomas. The structure is heterogeneous and exemplifies irregular glandular patterns between solid nests of squamous differentiation. This is characteristic of "adenosquamous carcinoma". The squamous differentiation of the tumour is manifested by the high-power view (B), where there are pearls of keratin and the cell keratinisation. These discoveries are diagnostic of squamous differentiation in the carcinoma. The presence of keratin pearls and intercellular bridges further reinforces the diagnosis of "adenosquamous carcinoma", a rare subtype of metaplastic breast carcinoma.

4. Immunohistochemistry

The immunohistochemical analysis was conducted to further describe the tumour and assess the biphasic character of the tumour described by histomorphology. Patchy nuclear positivity of the tumour cells with p40, one of the most specific differentiation markers of squamous, confirmed the existence of a genuine squamous component and not nonspecific metaplastic change. P40 expression is regarded to be better than p63 in detecting squamous lineage and is useful especially in the process of differentiating adenosquamous carcinoma among other metaplastic and poorly differentiated breast carcinomas.[10]

The neoplastic cells were focally cytoplasmically positive for "cytokeratin 7" (CK7), and this indicated the glandular epithelial constituent of the tumour. The CK7 expression facilitates the differentiation of epithelial cells and assists in the difference between adenosquamous carcinoma and primary squamous cell carcinoma of the breast, which do not normally express CK7.[11]

Analysis of hormone receptors demonstrated that the patient is negative for "estrogen receptor (ER)" and "progesterone receptor" (PR), and that she does not have HER2. This phenotype is typical of metaplastic breast carcinomas, and both therapeutic and prognostic implications are of significance since the tumours are resistant to hormonal or "HER2-based therapy".[3] The tumour cells were also

found to be negative for GATA3, which is usually positive in luminal-type breast carcinomas, and this further indicated that it was a metaplastic carcinoma with loss of luminal differentiation.
The Ki-67 proliferation index was found to be about 70%, implying that it is a very proliferative tumour and in line with the aggressive histological appearances. A high level of Ki-67 expression has been linked to poor prognoses in the metaplastic breast carcinomas and indicates their aggressiveness in biology.[12] Taken together, the results of the immunohistochemical tests confirmed the diagnosis of "adenosquamous carcinoma" of the breast and helped to rule out morphologic mimickers.

5. Final Diagnosis

Adenosquamous carcinoma of the breast, a rare form of metaplastic breast carcinoma, is characterised by malignant glandular and squamous differentiation, a triple-negative immunophenotype, high histological grade, and an increased proliferative index.

6. Discussion

6.1 Epidemiology and WHO Classification

"Adenosquamous cancer of the breast" (ASC) is a very rare type of cancer, and it constitutes less than 1% of all invasive breast carcinoma. The "World Health Organisation" (WHO) includes it in the group of the so-called "metaplastic breast carcinomas" (MBCs), which are defined by the presence of both glandular and squamous elements. MBCs are most commonly seen in middle-aged women and tend to be presented with a larger tumour than with conventional "invasive ductal carcinoma" (IDC). What makes ASC distinctly different to other metaplastic forms is the biphasic epithelial differentiation of the cells instead of mesenchymal transformation. Its rarity also means that the majority of existing data is obtained based on individual case reports and mini-series, which do not allow obtaining a comprehensive vision of its biological behaviour and the best way to manage it.[13, 14]

6.2 Histogenesis and Pathogenesis

The histogenesis of adenosquamous carcinoma remains incompletely understood. It is postulated to be a result of the pluripotent mammary epithelial stem cells being able to differentiate divergently to yield both glandular and squamous lineages. According to molecular investigations, metaplastic carcinomas, such as ASC, often show the basal-like genetic features, with the modifications of "TP53, PI3K/AKT, and Wnt-signalling pathways". It is believed that the squamous differentiation is actually the state of an aberrant epithelial transdifferentiation as opposed to actual metaplasia. The frequent absence of an associated in-situ carcinoma supports a de novo invasive origin. The histological aggressiveness in most of the cases could be explained by the presence of underlying genomic instability and high proliferation activity.[15, 16]

6.3 Differential Diagnosis

Primary squamous cell carcinoma (SCC) of the breast, invasive ductal carcinoma with squamous metaplasia, and other metaplastic types of breast carcinoma are the major differential diagnoses of "adenosquamous carcinoma". Primary SCC of the breast is made up of squamous cells without differentiation into glands, and is usually negative for CK7, as compared to the expression of CK7 in ASC. Invasive ductal carcinoma containing squamous metaplasia typically reveals a large ductal constituent and has a tendency to be related to ductal carcinoma in situ, which was not observed in the current case. Morphology and immunophenotype can be used to distinguish other metaplastic subtypes: spindle cell carcinoma and carcinoma with heterologous differentiation. True biphasic epithelial differentiation, which can be correctly diagnosed only with the help of relevant markers by immunohistochemistry, has a potential impact on the correct diagnosis due to the possible misclassification with serious prognostic and therapeutic consequences.[17, 18]

6.4 Immunohistochemical Profile

Immunohistochemistry plays a crucial role in confirming the diagnosis of adenosquamous carcinoma.

These tumors typically display a triple-negative phenotype, with the absence of ER, PR, and HER2 expression. Nuclear expression of high-specificity markers (p40) dictates the presence of squamous differentiation and glandular differentiation (CK7 positivity). The fact that GATA3 is lost also supports a metaplastic and not luminal origin. There is a high Ki-67 proliferation index that is often observed and is associated with the aggressive histological characteristics. This immunoprofile helps to discriminate between ASC and morphologic mimickers and promotes the position of this disease in the metaplastic spectrum.[19, 20]

6.5 Prognostic and Therapeutic Implications

Adenosquamous carcinoma of the breast is traditionally regarded as a severe neoplasm; its prognosis is unfavourable compared to other triple-negative breast cancers. Prognosis is influenced by tumour size, nodal involvement, histological grade, and proliferative index. Clear-marginal excision is the primary mode of treatment. With this triple-negative phenotype, hormonal and HER2-directed therapy is ineffective and systemic chemotherapy is usually used, though with fluctuating responses. According to recent researchers, it is possible that metaplastic carcinomas also show a relative chemoresistance to the traditional triple-negative breast cancers. The development of new molecular understanding can open the path to targeted therapy in the future.[21, 22]

7. Conclusion

Adenosquamous carcinoma of the breast is a rare and aggressive subtype of metaplastic breast carcinoma. Its diagnosis relies on careful histopathological examination, highlighting a biphasic pattern of glandular and squamous differentiation. Immunohistochemistry plays a crucial role in confirming the diagnosis, with p40 positivity and CK7 expression supporting squamous and epithelial differentiation, respectively. The triple-negative immunophenotype, high Ki-67 index, and absence of HER2/ER/PR expression underscore the tumour's aggressive behaviour and limited therapeutic options. Given its rarity, detailed case reports like this one are essential for improving the understanding of adenosquamous carcinoma’s clinicopathological features, prognosis, and management. Clinicians should remain aware of its aggressive nature and the importance of multidisciplinary management, including chemotherapy and surgical excision, while further investigations into targeted therapies for this rare subtype are warranted.

8. Patient Consent

The patient provided informed consent for the publication of this case report and the associated images. The patient understood the content and granted permission for the use of clinical, radiological, and pathological information in a public case report.

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