Adenosquamous Carcinoma of the Skin

A Case Series

Jennifer M. Fu, MD; Tim McCalmont, MD; Siegrid S. Yu, MD

Background: Adenosquamous carcinoma is an uncommon cutaneous malignant neoplasm with mixed glandular and squamous differentiation and a propensity for aggressive clinical behavior.

Observations: Of 27 patients diagnosed as having adenosquamous carcinoma, 19 were men and 5 were immunosuppressed. The mean age was 74 years. The majority of tumors were located on the face and scalp (19 of 27 [70%]) or upper extremity (4 of 27 [15%]). Squamous and glandular differentiation was characteristic. Thickness of the primary lesion ranged from 1.2 to 9.2 mm, with all tumors extensively invading the reticular dermis. Perineural invasion was seen in 4 of 27 primary cases (15%). Although 3 of 6 patients treated with Mohs micrographic surgery had subsequent locoregional recurrences, there was no evidence of distant metastasis after a mean of 2.3 years of patient follow-up.

Conclusions: Adenosquamous carcinoma is best considered as a locally aggressive high-risk subtype of cutaneous squamous cell carcinoma. Tumor thickness and perineural invasion are high-risk histopathological attributes, and immunosuppression is an important clinical risk factor. Although Mohs micrographic surgery may be the best initial treatment, locoregional recurrence is common.

Arch Dermatol. 2009;145(10):1152-1158

Adenosquamous carcinoma (ASC) is an uncommon cutaneous malignant neoplasm with mixed glandular and squamous differentiation, a propensity for local invasion and recurrence, and a rare association with distant metastasis. Adenosquamous carcinoma has typically been described as an indurated, erythematous keratotic papule or plaque, which occurs on the head or neck of an elderly patient who has a history of actinic damage. The classically observed histopathological characteristics of ASC consist of irregular anastomosing islands of squamous cells that often originate in the epidermis, with frequent formation of keratocysts or “keratin pearls.” Glandular differentiation occurs within well-differentiated squamous nests, with glands lined by a cuboidal or low columnar epithelium, and with ductular differentiation sometimes highlighted by an eosinophilic cuticle. Eosinophilic mucinous material is variably present within lumens.

When Weidner and Foucar1 first described ASC in 1985, they favored the view now held by several other authors,2,3 that ASC represents a high-grade variant of cutaneous squamous cell carcinoma (cSCC). Still, much confusion over classification remains. Adenosquamous carcinoma is generally thought to be more aggressive than conventional squamous cell carcinoma. However, given its rarity, data with regard to local recurrence and distant metastasis rates are sparse, and guidelines for the optimal method of excision and the role of adjuvant therapy are lacking.

Methods

Approval for this study was obtained from the University of California, San Francisco (UCSF), Committee on Human Research. A database maintained by the UCSF Dermatopathology Service was used to identify primary and referral patients diagnosed as having ASC by means of standardized microscopic criteria during the period of January 1, 1996, through December 31, 2006. Key epidemiologic information was extracted from pathology requisition slips. Cases were excluded if the pathological diagnosis of the biopsy specimen was equivocal or the specimen was unavailable for review. All cases were evaluated by a single board-certified dermatopathologist (T.M.) for histopathological features and immunohistochemical characteristics. Immunostaining was performed with antibodies against high-

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molecular-weight keratin 903 (clone E12; dilution, 1:50) (Enzo Life Sciences, Farmingdale, New York), carcinoembryonic antigen (polyclonal; dilution, 1:1000), cytokeratin 7 (clone OV-TL; dilution, 1:1000), epithelial membrane antigen (clone E212; dilution, 1:1000), cytokeratin 20 (clone K208; dilution, 1:50), thyroid transcription factor-1 (clone 8G7G3/1; dilution, 1:200), epidermal growth factor receptor, prostate-specific antigen (dilution, 1:1000), epithelial membrane antigen (clone E29; dilution, 1:200), and keratinizing cysts in a large subset (11 of 27 [41%]) characterized by cytoplasmic cornification in all 27 cases. As high as 80% of total tumor surface area. Recurrent tumors were more likely to have a higher degree of glandular differentiation than their primary counterparts. Ducts and glandular spaces were highlighted with carcinoembryonic antigen positivity in 16 of 18 cases (89%) (Figure 2B) and cytokeratin 7 positivity in 7 of 9 cases (78%).

All primary tumors demonstrated neoplastic nests arranged in infiltrative pattern (Figure 1). Nuclear atypia was severe in 12 cases (44%), with an average mitotic rate of 3 per 10 high-power fields (Table 3). Additional findings, such as immunohistochemical evaluation of primary tumors undertaken to rule out the possibility of metastatic adenocarcinoma from an internal source, are summarized in Table 3 and Table 4.

Thickness of the primary lesion ranged from 1.2 to 9.2 mm, with all tumors extensively invading the reticular dermis; thickness of recurrent tumors ranged from 4.6 to 11.0 mm (Table 5). Ulceration was present in 8

Table 1. Clinical Characteristics of 27 Primary and 7 Recurrent Cases of Adenosquamous Carcinoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Tumors (n=27)</th>
<th>Recurrent Tumors (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age at diagnosis of primary tumor, mean (range), y</td>
<td>74 (50-97)</td>
<td>65 (51-75)</td>
</tr>
<tr>
<td>Patient sex, No. (%)</td>
<td>Male 19 (70)</td>
<td>3 (43)</td>
</tr>
<tr>
<td></td>
<td>Female 8 (30)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Tumor site, No. (%)</td>
<td>Face 15 (56)</td>
<td>3 (43)</td>
</tr>
<tr>
<td></td>
<td>Periorbital 2 (7)</td>
<td>0</td>
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<tr>
<td></td>
<td>Perioral 2 (7)</td>
<td>1 (14)</td>
</tr>
<tr>
<td></td>
<td>Forehead 4 (15)</td>
<td>1 (14)</td>
</tr>
<tr>
<td></td>
<td>Cheek 5 (19)</td>
<td>1 (14)</td>
</tr>
<tr>
<td></td>
<td>Nose 2 (7)</td>
<td>0</td>
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<td></td>
<td>Scalp 4 (15)</td>
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<tr>
<td></td>
<td>Trunk 1 (4)</td>
<td>0</td>
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<tr>
<td></td>
<td>Arm/shoulder 4 (15)</td>
<td>3 (43)</td>
</tr>
<tr>
<td></td>
<td>Leg 1 (4)</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

RESULTS

HISTOPATHOLOGICAL CHARACTERISTICS

The histopathological characteristics of 27 primary cases of ASC and 7 associated recurrences were evaluated. Of the 27 patients, 19 (70%) were men and 8 (30%) were women (Table 1). Recurrent tumors occurred in 7 patients. The mean age of the study population at diagnosis was 74 years overall (range, 50-97 years). Patients who would later have recurrent disease tended to be younger at the time of diagnosis (mean, 65 years; range, 51-75 years). Although favored sites for primary tumor location included the face (15 of 27 [56%]) and scalp (4 of 27 [15%]), a significant subset was located on the arm or shoulder (4 of 27 [15%]). Three of 7 tumors (43%) that subsequently recurred were located on the face, 3 (43%) were on the arm or shoulder, and 1 (14%) was on the leg (Table 1).

In no instance did the referring physician correctly make the clinical diagnosis of ASC. Listed entities on the pathology requisition slip were largely malignant (17 of 22 [77%]) and included, in order of frequency, basal cell carcinoma, cSCC, unspecified malignant neoplasm, metastasis, and keratoacanthoma (Table 2).

There was squamous differentiation in all 27 cases, characterized by cytoplasmic cornification in all 27 cases and keratinizing cysts in a large subset (11 of 27 [41%]) (Figure 1). In 6 of 6 cases (100%), there was positive immunoperoxidase staining for high-molecular-weight keratin 903 (Figure 2A). All primary tumors except 1 (96%) exhibited glandular differentiation (Figure 1); of note, the exceptional case was initially interpreted as desmoplastic cSCC, but on recurrence it showed attributes more consistent with ASC. An additional primary case was misclassified as cSCC but then later reinterpreted on identification of glandular differentiation. The degree of overall glandular differentiation—as typified by both ductular (24 of 26 [92%]) and glandular (15 of 26 [58%]) elements—was highly variable, with a range from 5% to as high as 80% of total tumor surface area. Recurrent tumors were more likely to have a higher degree of glandular differentiation than their primary counterparts. Ducts and glandular spaces were highlighted with carcinoembryonic antigen positivity in 16 of 18 cases (89%) (Figure 2B) and cytokeratin 7 positivity in 7 of 9 cases (78%).

All primary tumors demonstrated neoplastic nests arranged in infiltrative pattern (Figure 1). Nuclear atypia was severe in 12 cases (44%), with an average mitotic rate of 3 per 10 high-power fields (Table 3). Additional findings, such as immunohistochemical evaluation of primary tumors undertaken to rule out the possibility of metastatic adenocarcinoma from an internal source, are summarized in Table 3 and Table 4.

Thickness of the primary lesion ranged from 1.2 to 9.2 mm, with all tumors extensively invading the reticular dermis; thickness of recurrent tumors ranged from 4.6 to 11.0 mm (Table 5). Ulceration was present in 8
of 27 (30%) primary tumors and 1 of 6 (17%) recurrent tumors. Although there was no evidence of lymphovascular invasion in any of the cases, perineural invasion was seen in 4 of 27 (15%) primary and 3 of 7 (43%) recurrent cases. Intramuscular invasion was noted in 5 of 27 (19%) primary and 2 of 7 (29%) recurrent cases. Of the 7 primary tumors that subsequently recurred, 5 (71%) were more than 4 mm in depth, 2 (29%) were Clark level IV, 5 (71%) were Clark level V, 3 (43%) were ulcerated, 1 (14%) demonstrated perineural invasion, and 2 (29%) invaded muscle (data not shown).

**CLINICAL FEATURES**

The full medical records of 6 patients treated at our institution were evaluated. All patients were white with an age range of 51 to 75 years; 5 (83%) were men (Table 6). Of note, 5 of 6 patients (83%) were immunocompromised; immunosuppression was secondary to myelodysplastic syndrome, Waldenstrom macroglobulinemia, prednisone therapy for temporal arteritis, renal transplant–associated iatrogenic immunosuppression, and, in 2 instances, human immunodeficiency virus disease. Four
patients (67%) had a history of nonmelanoma skin cancer. Although 3 of 6 ASCs (50%) were located on the head or neck, as is described commonly in the literature, the other 3 (50%) in our series were on a proximal upper extremity. Three of 6 patients (50%) presented to our dermatologic surgery division for the management of primary ASC, whereas 3 (50%) were referred with recurrent disease.

A total of 8 MMS procedures were performed, with all 6 patients undergoing MMS at least once (Table 6). Three of 8 MMS procedures (38%; in patients 1, 4, and 6) were discontinued before clear margins were obtained, secondary to either the breadth or depth of tumor invasion; notably, all 3 of the tumors in these cases exhibited microscopic perineural invasion. Two patients (patients 4 and 6) underwent at least 1 additional surgical excision during their treatment course. The surface area of the postoperative MMS defect exceeded that of the clinically evident preoperative tumor by 2- to 148-fold (eTable; http://www.archdermatol.com). In all cases except one (patient 5), standard excision with 0.4-cm margins would have underestimated tumor size.

During a mean of 2.3 years of patient follow-up, there has been no evidence of distant metastatic disease (Table 6). Locoregional recurrences, on the other hand, have occurred in half (3 of 6) of the patients (patients 3, 4, and 6); 1 of these patients (patient 4; Figure 3) went on to develop in-transit metastasis as well as involvement of the primary nodal basin. Of the 3 patients (pa-
Adenosquamous carcinoma is an uncommon malignant neoplasm of the skin characterized by mixed squamous and glandular differentiation and aggressive clinical behavior, such as extensive local invasion, recurrence, and rare metastasis.1-3 To our knowledge, this is the largest case series to address the key epidemiologic and histopathological features of ASC. We were also able to characterize the clinical presentation, treatment, and course of a smaller subset of patients. Limitations included the bias inherent in referrals to a tertiary medical center, the retrospective nature of the study, and the small sample size, the latter owing to the rarity of ASC.

Although clinically relevant and validated staging criteria for cSCC are currently lacking, several authors have detailed prognostic indicators likely to be incorporated into the new American Joint Committee on Cancer staging system for cSCC. These include size greater than 2 cm, site (lip and areas with parotid drainage), recurrence, thickness/depth of invasion (>4 mm in depth, Clark level >III), microscopic grade, histopathological variant, perineural invasion, lymphovascular invasion, recurrence, and immunosuppression.3-5,22 Because ASC, in our view, is best characterized as a high-risk subtype of cSCC, this diagnosis should be considered indicative of more aggressive tumor behavior. Although no distant metastases occurred in our series, we were able to identify lesion thickness/depth of invasion, microscopic perineural invasion, and immunosuppression as important predictors of extensive local disease and recurrence.

Adenosquamous carcinoma shares many of the features of desmoplastic cSCC, such as tumor cells enveloped in a desmoplastic stroma and the potential to be deeply invasive.
infiltrative, with the involvement of nerve, subcutis, muscle, and bone.\textsuperscript{1,2,23} Adenosquamous carcinoma differs from desmoplastic cSCC in that it has both squamous and glandular differentiation. Interestingly, the degree of glandular differentiation within our series varied from scant (5% of total tumor surface area) to striking (80%), with recurrent tumors displaying a greater degree of glandular differentiation than their primary counterparts. This may explain why a few of the cases in our series were initially designated cSCC only to be reclassified later as ASC, and it supports our assertion that ASC is a locally aggressive high-risk histologic subtype of cSCC, on a spectrum with desmoplastic cSCC. We consider ASC distinct from mucoepidermoid carcinoma, an entity with which ASC is often confused in the literature.\textsuperscript{24,25} In our view, mucoepidermoid carcinoma is a designation best reserved for tumors with both glandular and squamous features in extracutaneous sites, such as the salivary and other submucosal glands of the head and neck, for which the term has established significance.\textsuperscript{1,2} In the skin, it has been suggested that mucoepidermoid carcinoma is a low-grade counterpart of ASC, but this issue requires further study and substantiation.\textsuperscript{23,26,27}

Our cases were similar to those previously reported in the literature with respect to greater age, male sex, white race, and history of actinic damage.\textsuperscript{1,2,23-25,28} Of interest, patients in whom ASC recurred tended to be younger (mean, 65 years; range, 51-75 years) than the overall study population (mean, 74 years; range, 50-97 years). Immunosuppression, especially in patients with a history of organ transplantation or chronic lymphocytic leukemia, has been shown to be a high-risk feature in cSCC and has been reported in association with a few cases of ASC.\textsuperscript{1,3,20,23} In our series, immunosuppression was found to be a significant clinical risk factor for ASC.

In the largest series to date, Banks and Cooper\textsuperscript{2} observed that patients with ASC that infiltrates the subcutis appeared to be at higher risk for both tumor persistence and local recurrence. Our study confirms these findings; primary ASCs that subsequently recurred were more likely to be deeply invasive (71% \textgreater 4 mm in depth, 71% Clark level V). In addition, microscopic perineural invasion was found to be a high-risk feature, predictive of extensive and persistent primary tumor as well as multiply recurrent disease.

Although MMS may be the best initial treatment for ASC, patients must be monitored closely for locoregional recurrence. For the treatment of locally advanced cSCC, and in particular those cases with perineural involvement, adjuvant radiotherapy may be useful.\textsuperscript{20} The role of radiotherapy for ASC is less well characterized. The efficacy of cetuximab, a recombinant human and mouse chimeric antibody against the epidermal growth factor receptor, as treatment for locally advanced cSCC is still under exploration.\textsuperscript{30} To our knowledge, our series includes the first reported cases (in patients 4 and 6) of an epidermal growth factor receptor antagonist used as adjuvant therapy for the treatment of ASC.

Accepted for Publication: March 3, 2009.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fu, McCalmont, and Yu. Acquisition of data: Fu, McCalmont, and Yu. Analysis and interpretation of data: Fu, McCalmont, and Yu. Drafting of the manuscript: Fu, McCalmont, and Yu. Critical revision of the manuscript for important intellectual content: Fu, McCalmont, and Yu. Study supervision: McCalmont and Yu.
Financial Disclosure: None reported.
Additional Information: An eTable is available at http://www.archdermatol.com.
Additional Contributions: Mary McGrath, MD, contributed the clinical images shown in Figure 3. Diana Baughman, Mary Kate Fitzsimon, BA, Al Naklowycz, MBA, and Marilyn Hadden provided invaluable administrative assistance.

REFERENCES