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CASE REPORT PEER REVIEWED | OPEN ACCESS

Mixed neuroendocrine and squamous rectal carcinoma: A poor prognosis

Radha Senaratne, Stephanie Curran, William Joyce

ABSTRACT

Introduction: Colorectal cancer is one of the most common cancers diagnosed globally with the majority being adenocarcinomas. Mixed tumors can occur, however, it is very rare for no adenocarcinoma component to be present.

Case Report: We describe a patient who presented with a recto-sigmoid tumor and subsequently underwent a low anterior resection. She unfortunately developed metastatic disease and died three months after surgery. Histological analysis of the resected specimen showed a mixed neuroendocrine and squamous carcinoma with no features of adenocarcinoma.

Conclusion: Mixed neuroendocrine carcinoma with a squamous component is a very unusual histopathological subtype of colorectal cancer. It can metastasize rapidly and carries a poor prognosis.

Keywords: Carcinoma, Neuroendocrine, Rectal cancer, Squamous

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INTRODUCTION

Colorectal cancer accounts for 11% of all cancer diagnoses globally [1]. Approximately 96% of colorectal cancers are adenocarcinomas which arise from the columnar cells of the mucosa [2]. Mixed colorectal tumors are described however those with neuroendocrine and squamous features are exceptionally rare. It is especially unusual for mixed colorectal tumors to lack any adenocarcinoma component. Here we describe a case of a patient who underwent low anterior resection for a recto sigmoid tumor with subsequent histology showing a mixed neuroendocrine and squamous carcinoma.

CASE REPORT

An 88-year-old female was referred from her general practitioner with tenesmus to our colorectal service. She underwent an urgent colonoscopy demonstrating a semi-obstructing recto-sigmoid carcinoma. Staging computed tomography (CT) of her chest, abdomen, and pelvis showed no evidence of metastatic disease (Figure 1A).

Despite her age, she had no other significant underlying conditions and was deemed a candidate for surgical intervention. The patient underwent an open low anterior resection and total mesorectal excision with a defunctioning right upper quadrant loop colostomy. She had a slow postoperative recovery which was complicated by a wound infection. Computed tomography imaging on postoperative day 12 showed multiple peripherally enhancing areas of hypoattenuation in the liver which were not present on her staging imaging only four weeks prior. These were indicative of metastatic disease (Figure 1B).

She was discharged on postoperative day 17. Computed tomography imaging at six week follow-up showed severe progression of her disease with her liver

being almost completely replaced with innumerable metastases (Figure 1C).

The patient was considered unsuitable for further treatment due to her age and decline in performance status. She was treated palliatively and died three months after surgery.

The resected specimen revealed a 43 × 40 mm sessile tumor with a necrotic ulcerated center. Microscopy revealed features of invasive carcinoma, associated with tubulovillous adenoma. The invasive tumor was widely sampled and did not demonstrate any areas of conventional gland forming morphology typical of adenocarcinoma. The tumor was composed of two cell types: the majority of the tumor was composed of sheets of poorly differentiated malignant cells, with hyperchromatic grainy chromatin, and scant cytoplasm, resembling neuroendocrine carcinoma. A second malignant cell population, which was intimately admixed and found in all sections of tumor, displayed squamoid morphology (Figure 2).

Immunohistochemistry supported the morphological diagnosis; synaptophysin, chromogranin, and CD56 were positive in the neuroendocrine cell population (Figure 3), together with nuclear staining for CDX2. The mitotic count in this cell population was >20 per 10 high power fields with Ki67 index of >50% (Figure 4). The squamoid cells were positive for cytokeratin 5/6 (Figure 5) but negative for p63, p40, cytokeratin 20, and cytokeratin 7. Of interest, thyroid transcription factor 1 (TTF-1) showed focal nuclear staining of moderate intensity within the neuroendocrine cell population.

The histological features of the resected tumor were of a grade three neuroendocrine carcinoma of the rectosigmoid junction with extensive squamoid differentiation.

Eight of the twenty-four lymph nodes resected were positive for metastatic carcinoma. The nodal metastases contained both the neuroendocrine and squamoid cell populations. The final staging based on combined pathological and radiological findings was a T4a N2b R0 M1 carcinoma.

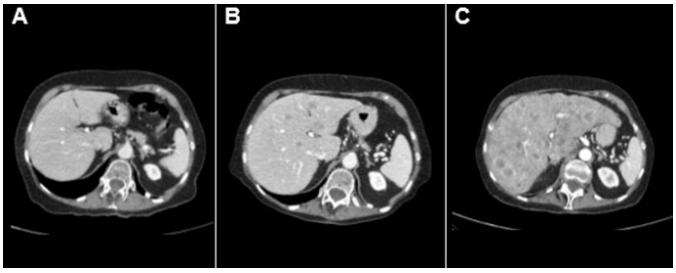

Figure 1: Computed tomography (CT) imaging showing progression of liver metastases with intravenous contrast. (A) CT imaging of liver four weeks preoperatively—no evidence of metastases. (B) CT imaging of liver day 12 postoperatively—multiple liver metastases present. (C) CT imaging of liver at six week follow-up—innumerable liver metastases, liver largely replaced by metastatic disease.

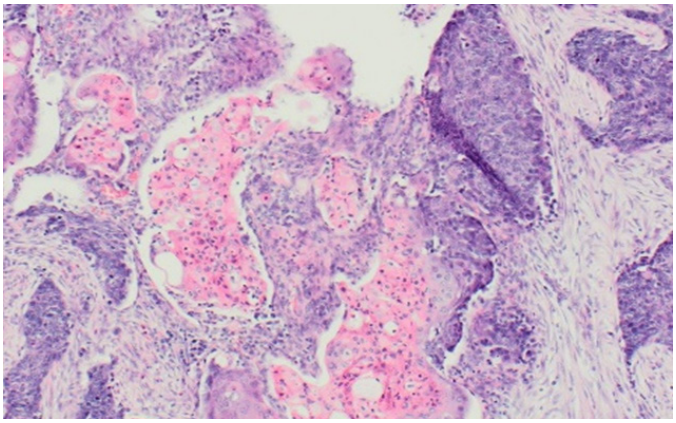

Figure 2: H&E staining of the invasive tumor showing both neuroendocrine and squamoid components (×10).

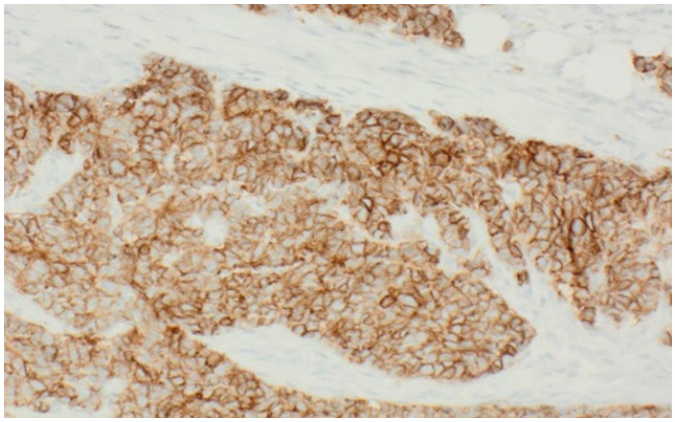

Figure 3: CD56 staining of neuroendocrine element (×40).

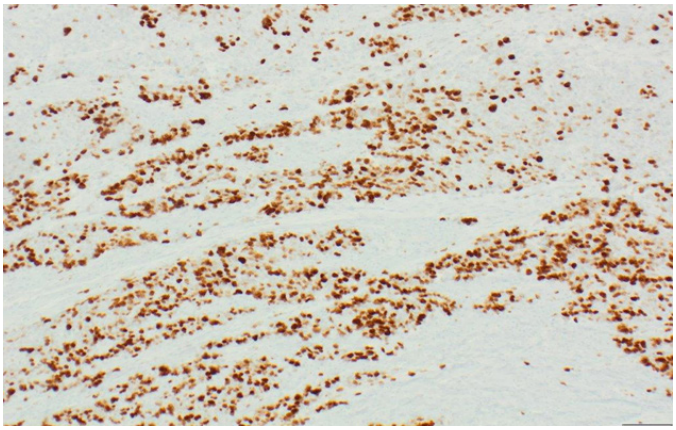

Figure 4: Ki67 immunohistochemistry of the neuroendocrine component of the tumor. The proliferation index is >50% (×10).

DISCUSSION

Mixed colorectal tumors with neuroendocrine and squamoid features as seen in this case are exceptionally rare. The pathologic findings, especially in terms of the squamoid component of this carcinoma, were unusual. The squamoid cells did not demonstrate positive reactions for all immunohistochemical markers of

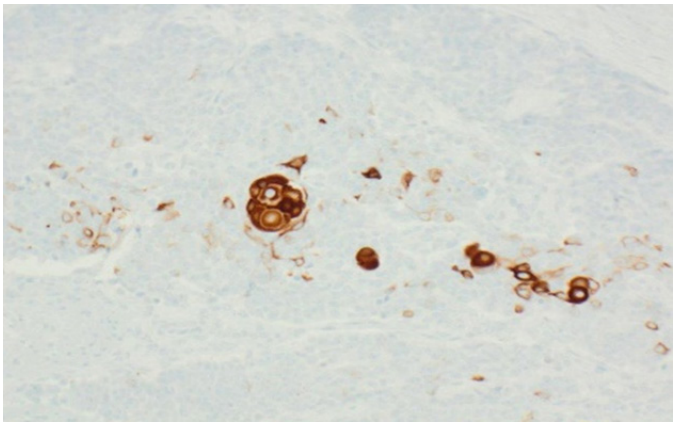

Figure 5: Squamoid component highlighted by CK5/6 (×100).

squamous cell carcinoma. Squamous cell carcinomas can be identified by staining for cytokeratin 5/6 (CK5/6), p40, and p63. These markers are highly specific in identifying squamous cell carcinoma [3, 4]. In this case, the squamoid cells showed positive reaction only with CK5/6 and were negative for both p63 and p40. Cytokeratin 7 and cytokeratin 20 are sensitive markers in identifying colorectal adenocarcinoma. In this case these markers were consistently negative in both components, in keeping with the morphology which did not show any features of adenocarcinoma.

The neuroendocrine component of the tumor displayed a diffuse positive reaction for typical markers of neuroendocrine carcinoma synaptophysin, CD56, and chromogranin. Focal nuclear CDX2 staining was noted, consistent with a primary of intestinal origin. The neuroendocrine cells also exhibited nuclear positivity for TTF-1. Thyroid transcription factor-1 is regarded as being highly specific for distinguishing neoplasms of pulmonary and thyroid origin. It is usually negative in small cell neuroendocrine carcinomas of extra pulmonary origin [5] however in one study which examined three cases of small cell neuroendocrine carcinoma of the rectum, TTF-1 staining was positive in all three cases [6].

Mixed colorectal tumors usually contain an adenocarcinoma component. In the case of our patient, as described, there was no evidence of glandular differentiation in the tumor. WHO 2010 classification of neuroendocrine tumors of the colorectum describes that a squamous component can occur though it is very rare. In our case, given the immunophenotype of the squamoid cells, we prefer the designation of "neuroendocrine carcinoma with squamoid differentiation." There are very few reported cases of mixed neuroendocrine and squamous cell colorectal carcinomas [7–9].

Neuroendocrine carcinomas account for less than 1% of colon and rectal cancers [8]. They exhibit typical morphological and immunohistochemical features. They are usually highly aggressive due to the high degree of mitotic activity as seen in this case. Prognosis is poor with many patients presenting with metastatic disease. Median survival is 10–14 months. Metastatic disease and poor performance status are associated with worse outcomes [10, 11].

CONCLUSION

This case demonstrated a rare histopathological subtype of colorectal cancer. The absence of any adenocarcinoma component is an extremely rare finding in rectal cancer. The squamoid cell population did not display the full range of immunohistochemical markers of typical squamous cell carcinoma and the tumor also stained positive for nuclear staining for TTF-1 in the neuroendocrine population. This rare mixed tumor metastasized at a rapid rate and evaded conventional staging investigations. It is important to consider alternative carcinoma subtypes in rectal cancer and how this may impact patient prognosis.

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Author Contributions

Radha Senaratne – Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Stephanie Curran – Conception of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

William Joyce – Conception of the work, Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

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Consent Statement

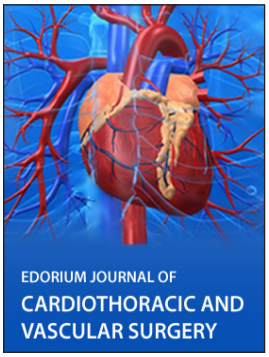
Written informed consent was obtained from the patient's next-of-kin for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.



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