Annals of Diagnostic Pathology 47 (2020) 151535

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Cytological-Pathologic Correlation

Histologic diagnosis of a case of anal duct carcinoma with cytological correlation and differential diagnoses

Alan Lu[a,*], Zihao Wu[b], Magda Esebua[a], Deepthi S. Rao[a]

[a] Department of Pathology and Anatomical Sciences, University of Missouri, United States of America
[b] Department of Surgery- Surgical Oncology, University of Missouri, United States of America

ARTICLE INFO

Keywords:
Anal duct carcinoma
Biopsy
Cytology
Differential diagnosis

ABSTRACT

Anal duct carcinoma is an uncommon malignancy of the glands of the anal duct. This entity poses a diagnostic challenge, both clinically and histologically. This article describes histopathologic findings in a case of anal duct carcinoma, including the initial diagnosis on biopsy and subsequent cytology specimens. Additionally, differential diagnoses of this neoplasm are discussed. With a high index of suspicion, and attention to histological and immunohistochemical features, anal duct carcinoma can be accurately diagnosed both on biopsy and on cytology.

1. Introduction

Anal carcinomas are rare malignancies of the gastrointestinal tract, and anal duct carcinomas comprise a small percentage of all anal carcinomas. These cancers were originally listed as “adenocarcinoma of anal glands” by the WHO, however it is possible that they originate from the ducts that lead from the anal glands, making “anal duct carcinoma” a more precise term [1,2]. The reported morphologic appearance of this tumor is variable, ranging from haphazard small glands with cuboidal epithelium to ductular structures with highly pleomorphic cells [3,4]. Due to the rarity of this malignancy, most of the information about this tumor is disseminated by case reports and case series [5]. To the best of our knowledge, cytology specimens of this malignancy have not been previously reported in the literature. In this article, we present histologic and cytologic findings of a case of anal duct carcinoma, and also the differential diagnosis of such a lesion.

2. Case report

We report a 54-year-old female patient who presented with a chief complaint of colicky abdominal pain for one month. This pain is associated with constipation, abdominal distension, and passing bright red blood when attempting to defecate. The patient endorsed nausea, and denied fevers, chills, and vomiting. At the emergency department, her laboratory studies and vital signs were notable for a hemoglobin of 5.6 g/dL, blood pressure of 95/75 mmHg, and heart rate of 90 beats per minute. Physical exam was significant for a large protruding rectal mass, believed to be a hemorrhoid. A CT scan of the abdomen revealed rectal wall thickening with fat stranding. Colonoscopy revealed large prolapsing hemorrhoids; however, the procedure was abandoned due to poor bowel prep. Surgical oncology was consulted for examination and biopsy under anesthesia. Digital rectal exam was significant for a stricturing rectal mass that was 4 cm from the anal verge, with normal overlying mucosa. The rectal mass was biopsied with a Tru-Cut biopsy device.

The biopsy slides showed normal overlying colonic-type mucosa. The underlying tissue had a prominent of fibrosis. There were single cells as well as tubular structures that are infiltrating through the fibrosis and between muscle fibers in the biopsy specimen (Fig. 1A–B). Due to the morphology of the cells, immunohistochemical stains were performed on the biopsy slides. The neoplastic cells were positive for cytokeratin (CK) 7, and were negative for CK20, CDX2, and P63 (Fig. 1C–F). Additional immunohistochemical stains were performed, including p16, TTF-1, estrogen receptor, progesterone receptor, S-100, PAX8, and GATA3, to rule out other entities in the differential diagnosis. These additional stains were negative. Overall consideration of the histologic features and immunophenotype led to a diagnosis of anal duct carcinoma.

An ultrasound of the abdomen performed the next day after the biopsy revealed portal tract prominence and moderate ascites. A paracentesis removed 240 mL of ascites fluid, which was sent to cytology. Review of a Papanicolaou-stained ThinPrep preparation and an

* Corresponding author at: University of Missouri, Pathology and Anatomical Sciences, Department of Pathology, One Hospital Drive, Columbia, MO 65212, United States of America.
E-mail address: ayl873@health.missouri.edu (A. Lu).

https://doi.org/10.1016/j.anndiagpath.2020.151535

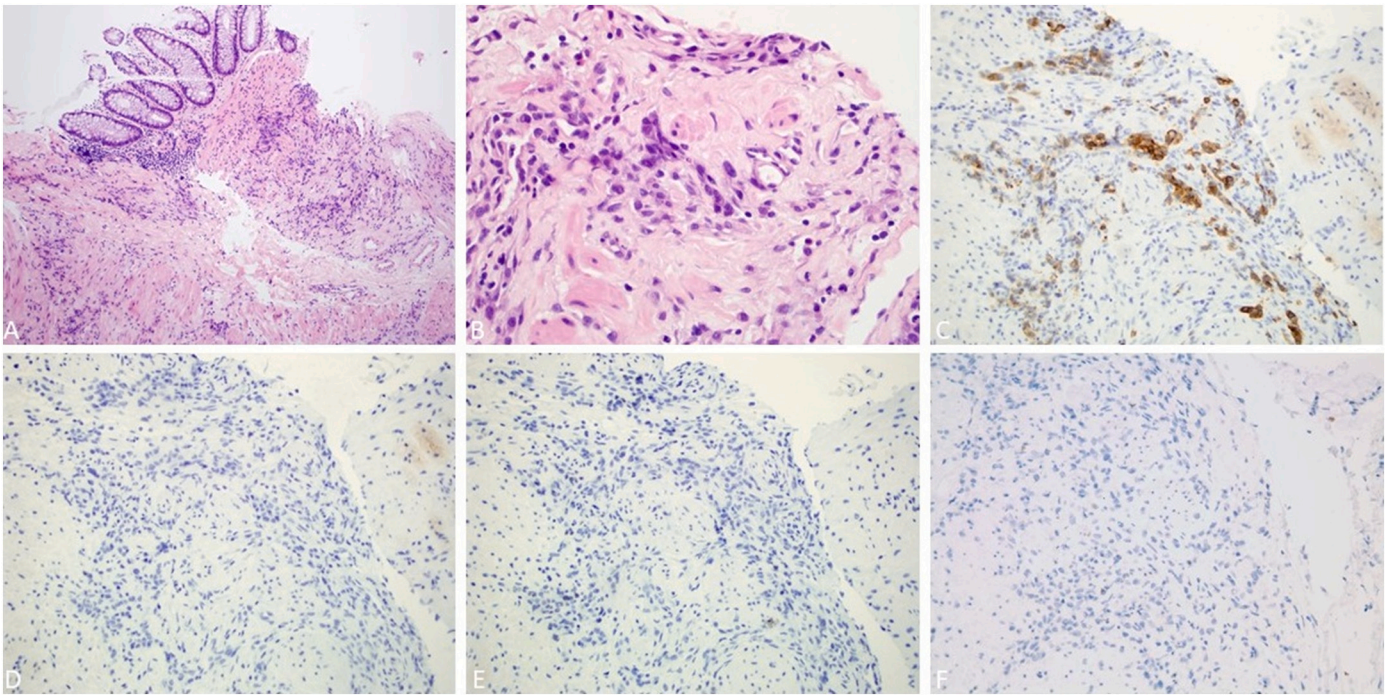

Fig. 1. A: H&E x100 Normal appearing colonic mucosa overlying prominent fibrosis with neoplastic cells infiltrating; B: H&E bland-appearing single cells and tubular structures with duct formation infiltrating into fibrosis and between muscle fibers; C: x200 CK7 is positive in neoplastic cells; D: x200 CK20 is negative in neoplastic cells; E: x200 CDX2 is negative in neoplastic cells; F: x200 P63 is negative in neoplastic cells.

H&E-stained cell block showed a distinct population of relatively bland neoplastic cells with duct formation, that were morphologically similar to those seen in the biopsy specimen (Fig. 2A–B). On the ThinPrep, the groups of neoplastic cells appeared three-dimensional with smooth contours. The cells themselves were large and pleomorphic, with high N:C ratios. The nuclear membranes were slightly irregular, and the nuclei either had single or multiple prominent nucleoli. These clusters of cells were in a background of heavy histiocytic inflammation. On the cell block, the clusters of neoplastic cells had more irregular borders, and had irregular nuclear membranes. Immunohistochemical stains for BerEP4, CK7, CDX2, CD68, Calretinin, and D2-40 were performed on the cell block. The neoplastic cells were strongly positive for BerEP4, and were positive for CK7 (Fig. 2C–D). The remainder of the panel was either negative or non-contributory.

Due to the finding of malignant ascites, the patient was not a candidate for abdominal-perineal resection. Because of the paucity of literature on anal duct carcinoma, it was recommended that the patient be referred to a specialized institution with experience treating this condition. The patient was lost to follow-up and did not receive treatment for her cancer. Four months later, the patient presented to the emergency department with increasing abdominal pain and constipation, with unknown last time of bowel movement. At this time, CT scan was significant for large-volume ascites and peritoneal carcinomatosis. Paracentesis was performed, and 550 mL of straw-colored fluid was removed, and sent to cytology. This second cytology specimen showed an increased number of bland neoplastic cells with duct formation, again similar in morphology to the neoplastic cells in the biopsy specimen and in the first cytology specimen. In this sample, the neoplastic cells were again strongly positive for BerEP4, and were positive for CK7.

The clinical team discussed these findings with the patient, who understood the prognosis, and expressed desire for comfort care. She was discharged several days later on hospice care.

3. Discussion

Anal duct carcinoma is a very rare malignancy that originates in the anal glands that produce mucus, or the ducts that transport the mucus to the crypts of Morgagni [1]. The normal anal glands are lined by basal cells, over which cuboidal to columnar cells form a transitional-type epithelium. The thickness of the epithelium decreases in the ducts. [3]. A 1993 survey of the American Society of Colon and Rectal Surgeons found that the average age of patients with anal duct carcinoma was 54.6 years old, with a slightly higher incidence in males [5]. This malignancy presents most commonly with symptoms of anal pain, rectal bleeding, and as an anal mass, induration, stricture, or fistula. These symptoms and findings overlap with many benign entities, which may cause delay in diagnosis and treatment. Indeed, between 13.5 and 62% of cases have metastasis at time of presentation [5,6].

Anal duct carcinoma is difficult to treat for several reasons. First, the delay in diagnosis leads to presentation at later stages [6]. Also, the tumor is highly infiltrative and aggressive, and tends to recur locally as well as metastasizing [4]. Reported five-year survival rates range from 4.8% in some case series to 42.8% [5,12]. Finally, the rarity of the diagnosis means that there are not well-established guidelines for treatment. Therapies vary widely, including limited and radical surgical resection, along with chemoradiation, with some evidence that combined modality treatments with preoperative chemotherapy and radiotherapy followed by resection being the most reasonable approach [5,13,14]. An interesting recent development has been the observation that a large percentage (approximately 50% in one study) of glandular neoplasms arising from the anal glands/transitional zone are linked to infection with high-risk HPV, and that only glandular neoplasms from the transition zone were found to be infected with high-risk HPV [15]. Although this tumor was negative for p16, it is important to investigate anal duct carcinomas for HPV infection due to potential treatment or prognostic significance.

Microscopically, these tumors are often described as small ductal structures and tubules infiltrating into the anorectal wall with possible production of mucin. They should be haphazardly distributed without

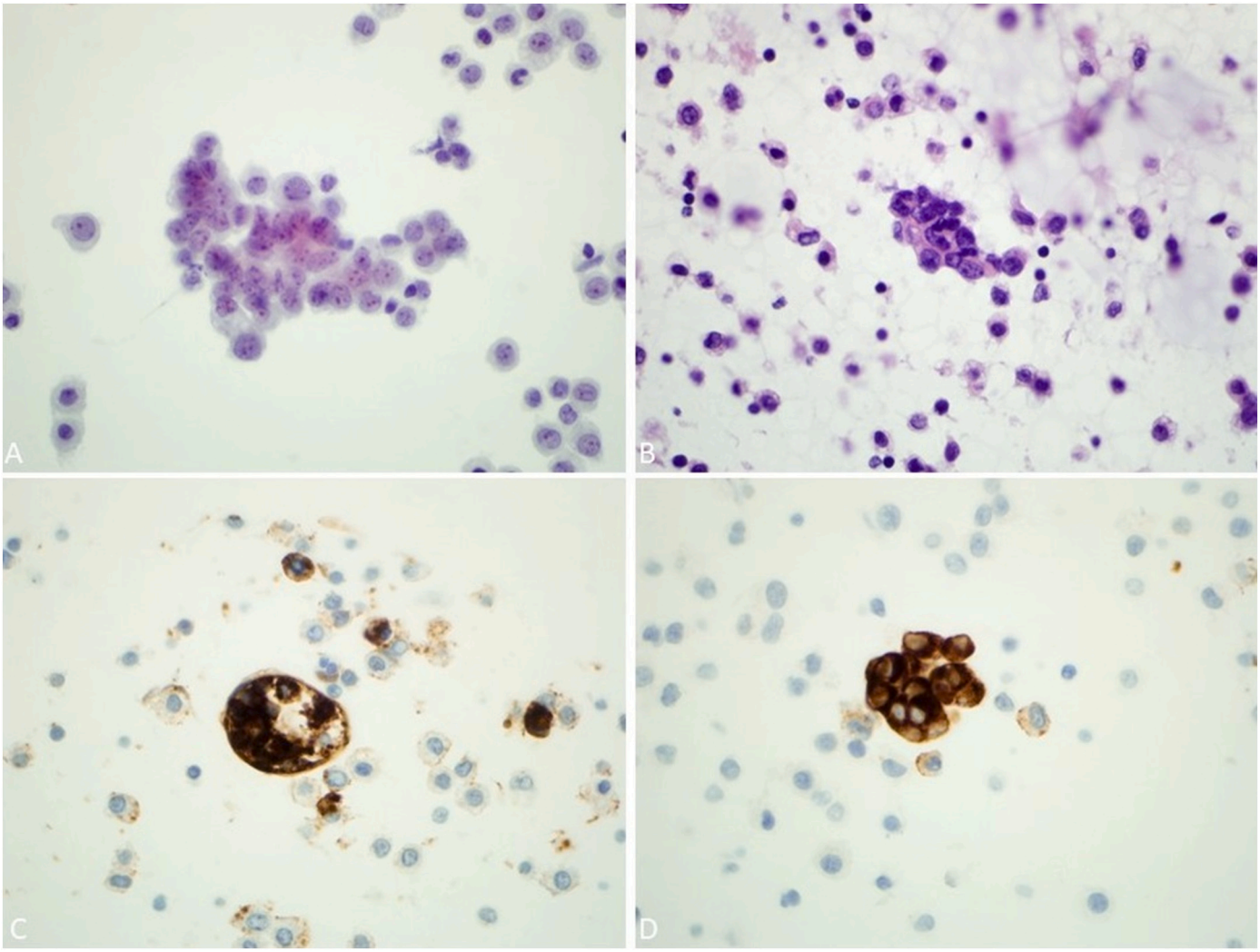

Fig. 2. A: Papanicolaou x600 ThinPrep of ascites fluid demonstrates distinct population of malignant cells; B: H&E x600 Cell block shows groups of malignant cells with duct formation, similar to neoplastic cells seen in biopsy specimen; C: x600 neoplastic cells are strongly positive for BerEP4; D: x600 neoplastic cells are positive for CK7.

intraluminal component [8,9]. Typically, the overlying epithelium is normal. Anal duct carcinoma can be differentiated morphologically from mucosal-type anal adenocarcinoma on the basis that the mucosal-type anal adenocarcinomas have histological features indistinguishable from rectal adenocarcinoma.

The immunohistochemical phenotype of the tumor is reported by Hobbs, et al., as being cytokeratin (CK) 7 +, CK20 – [9]. Further immunophenotyping by Lisovsky, et al. showed that normal anal glands and anal duct carcinomas are negative for CDX2. Anal duct carcinoma is negative for p63 and CK 5/6, while normal anal glands are positive for p63 and CK 5/6 in basal and parabasal cells [3]. Additionally, there are other extramucosal-type anal canal adenocarcinomas that may have an anal gland-like immunophenotype. These include fistula-associated adenocarcinoma; and extramucosal anal canal adenocarcinomas that are non-anal gland type and non-fistula-associated [2]. Due to the fact that no fistula was clinically present, the fistula-associated extramucosal anal adenocarcinoma was not included in the differential diagnosis of this tumor.

The differential diagnosis of anal duct carcinoma is broad. Entities that may have similar morphology and infiltrative pattern should be considered.

1. Poorly differentiated rectal adenocarcinoma

Rectal adenocarcinoma is a malignancy with a male predominance, and can present with symptoms of microcytic anemia, hematochezia, and constipation. It will be seen as a lesion with raised edges and ulcerated center. Poorly differentiated rectal adenocarcinomas can be seen microscopically as gland structures with loss of nuclear polarity, or even without glands. On cytology of a malignant effusion, cells will often be columnar with elongated nuclei. Clusters of cells and necrosis can be seen [11]. These cancers are usually negative for CK7, positive for CK20, and positive for CDX2. Occasionally, they may express CD7, but will retain CK20 and CDX2, allowing for differentiation from anal duct carcinoma [10].

2. Squamous cell carcinoma

Anal squamous cell carcinoma is seen more frequently in women, and commonly presents with anal bleeding, pain, or as a palpable mass. Risk factors include human papillomavirus (HPV) infection and smoking. They are often seen endoscopically as a small mobile lesion, and can become ulcerated or indurated with a large fungating mass. Microscopically there may be invasive nests of pale eosinophilic cells that may or may not be keratinized. There may also be basaloid features such as peripheral palisading [10]. On cytology of a malignant effusion, it will appear as clusters or single cells that have orange dense

cytoplasm and hyperchromatic nuclei. Immunohistochemical staining for P63 and CK5/6 will be positive in squamous cell carcinoma, and CD7 will generally be negative [11].

3. Melanoma

Anal melanoma is usually seen as a pigmented, painful, ulcerated and bleeding lesion. They are highly aggressive and require wide local excision. The microscopic appearance is highly variable, and can range from epithelioid cells with prominent central nucleoli and nuclear pseudoinclusions, to spindled or highly pleomorphic cells. On cytology, melanoma cells will appear malignant, and will classically have pigment and intranuclear cytoplasmic inclusions. However the appearance, like on histology, is highly variable, and immunohistochemistry is useful for aiding the diagnosis [7]. Neoplastic cells will stain positive for Melan-A, HMB-45, S-100, and SOX 10. These are often most useful as part of a panel of immunohistochemical stains. A high index of suspicion is needed to diagnose malignant melanoma in the gastrointestinal tract.

4. Neuroendocrine tumor

Neuroendocrine tumors are known to occur in the anal canal. When well-differentiated, they are believed to be fairly indolent. High grade lesions such as small-cell carcinoma tend to have poor prognosis. Certain anorectal carcinoid tumors in the anorectal area are known to have a tubular and trabecular patterns microscopically [1]. The cells will have round, regular nuclei that have stippled chromatin, and moderate amounts of cytoplasm. These tumors will tend to stain with neuroendocrine markers such as synaptophysin, chromogranin A, and CD56.

5. Metastasis from other primary

Due to positivity of CK7, the possibility of metastasis from a poorly differentiated carcinoma of unknown primary must be excluded in the diagnosis of anal duct carcinoma. A wide panel of immunohistochemical stains can be helpful. In this case, stains for P63, p16, TTF-1, estrogen receptor, progesterone receptor, S-100, GATA-3 and PAX8 were used to rule out metastasis.

In summary, we report a rare case of anal duct carcinoma, with metastasis to the peritoneum. The initial biopsy specimen that we received had morphology consistent with anal duct carcinoma, with small ductal structures and single cells infiltrating into the anorectal wall. Additionally, the immunophenotype of the initial biopsy was consistent with prior reports of anal duct carcinoma. The initial ascites specimen that was received showed malignant cells, and morphology of the cells was similar to those in the biopsy specimen. Furthermore, the patient did not have evidence of any other malignancy on CT imaging, meaning that the ascites represented metastatic anal duct carcinoma. These metastatic neoplastic cells were identified on cytology and confirmed with BerEP4 positivity and CD7 positivity. As this is the first report of a malignant cytology specimen, further reports are needed to better characterize the immunophenotype of metastatic anal duct carcinoma cells.

Disclaimers

None.

Acknowledgments

- This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
- AL contributed to the study design, manuscript preparation, and critical revision of the manuscript. ZW contributed to the study design, manuscript preparation, and critical revision of the manuscript. ME contributed to the study design, manuscript preparation, and critical revision of the manuscript. DR contributed to the study design, manuscript preparation, and critical revision of the manuscript.

References

[1] Shia Jinru. An update on tumors of the anal canal. Arch Pathol Lab Med 2010;134:1601–11.
[2] Bosman FT, et al. Bosman Fred T, editor. WHO classification of tumours of the digestive system. International Agency for Research on Cancer; 2010.
[3] Lisovsky M, Patel K, Cymes K, Chase D, Bhuiya T, Morgenstern N. Immunophenotypic characterization of anal gland carcinoma: loss of p63 and cytokeratin 5/6. Arch Pathol Lab Med 2007;131:1304–11.
[4] Meriden Z, Montgomery EA. Anal duct carcinomaZ: a report of 5 cases. Hum Pathol 2012;43(2):216–20.
[5] Abel ME, Chiu YS, Russell TR, Volpe PA. Adenocarcinoma of the anal glands: results of a survey. Dis Colon Rectum 1993;36:383–7.
[6] Biggs RL, Lucha PA, Stoll PM. Anal duct carcinoma: report of case and a survey of the experience of the American Osteopathic College of Proctology. J Am Osteopath Assoc 2001;101:450–3.
[7] Murali R, Loughman NT, McKenzie PR, et al. Cytological features of melanoma in exfoliative fluid specimens. J Clin Pathol 2009;62:638–43.
[8] Kulkarni MP, Momin YA, Pandav AB, Sulhyan KR. Adenocarcinoma of the anal canal: a report of two cases with review of literature. Indian J Pathol Microbiol 2016;59:404–6.
[9] Hobbs CM, Lowry MA, Owen D, Sobin LH. Anal gland carcinoma. Cancer 2001;92:2045–9.
[10] Hoff PM, Coudry R, Venchiarutti Moniz CM. Pathology of anal cancer. Surg Oncol Clin N Am 2017;26:57–71.
[11] Coffey DM, Thrall MJ. Malignant effusion, carcinomas. ExpertPath. https://app.expertpath.com/document/malignant-effusion-carcinomas/87ee80e1-6d26-482d-85b2-402384225b60; 2020.
[12] Jensen SL, Shokouh-Amiri MH, Hagen K, Harling H, Nielsen OV. Adenocarcinoma of the anal ducts. A series of 21 cases. Dis Colon Rectum 1988;31(4):268–72.
[13] Chang GJ. A twenty-year experience with adenocarcinoma of the anal canal. Dis Colon Rectum 2009;52(August (8)):1375–80.
[14] Mori M, Koda K, Hirano A, et al. Early anal gland adenocarcinoma with a characteristic submucosal tumor-like appearance: a case report. World J Surg Oncol 2018;16(148).
[15] Herfs M, Roncarati P, Koopmansch B, et al. A dualistic model of primary anal canal adenocarcinoma with distinct cellular origins, etiologies, inflammatory microenvironments and mutational signatures: implications for personalised medicine. Br J Cancer 2018;118:1302–12.