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Perianal goblet cell carcinoid with pagetoid spread

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Abstract

We present a case of perianal goblet cell carcinoid with pagetoid spread. Goblet cell carcinoid, also known as adenocarcinoid tumor, predominantly arises as a primary appendiceal tumor and contains nests of neuroendocrine and mucin-containing cells. When this tumor type is seen in other sites it usually represents a metastasis. We present the case of an 81 year old woman with a perianal mass. Histologic and immunohistochemical examination following surgical excision showed a goblet cell carcinoid demonstrating pagetoid spread along the perianal squamous mucosa. There was no evidence of a primary appendiceal tumor by history or imaging studies. To our knowledge, this is the first report of a goblet cell carcinoid presenting in this manner. The patient died due to complications of metastatic disease 26 months after initial diagnosis.

Keywords

goblet cell carcinoid; pagetoid spread; perianal

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

Introduction

Adenocarcinoid tumors or goblet cell carcinoid tumors are well described in the vermiform appendix.^{1–5} They are characterized by nests of cells with both neuroendocrine and intestinal goblet cell morphology.⁵ These tumors are typically more aggressive than classical carcinoid tumors of the appendix, but less aggressive than conventional adenocarcinoma.^{2,3} These tumors are staged and treated as adenocarcinomas rather than neuroendocrine tumors and recent papers have proposed changing the terminology to goblet cell carcinoma or crypt cell adenocarcinoma to better reflect the behavior of the tumor. Although goblet cell carcinoid tumors have occasionally been reported to occur outside of the appendix,^{8–13} they are categorized as appendiceal tumors by the WHO and most case series recognize goblet cell carcinoid outside the appendix as metastasis from an appendiceal primary.^{14–17} We present a unique case of a perianal goblet cell carcinoid demonstrating pagetoid spread in a patient without evidence of a primary appendiceal tumor.

Case Report

An 81 year old female with history of Paget's disease of the breast status post mastectomy 20 years ago presented to Mount Sinai Hospital with a red, indurated perianal mass measuring 1.2 cm in greatest dimension. The lesion was surgically excised and sent for pathologic evaluation. Histologic examination revealed neoplastic mucin-containing cells and neuroendocrine cells forming a mass involving the dermis and subcutaneous soft tissue (Figure 1A, 1B) and extending along the squamous epithelium in a pagetoid fashion (Figure 1C). Immunohistochemical stains showed that the tumor was positive for synaptophysin (Figure 1D, 1E), chromogranin, CK20, CDX-2 (Figure 1F) and CK-7 and the diagnosis of perianal goblet cell carcinoid tumor with pagetoid spread was made. Tumor was present at multiple lateral margins and was within 0.1 cm of the deep margin. A wider excision was performed three months later showing residual pagetoid tumor, but now with negative margins. Nine months after the initial surgery, an enlarged left inguinal lymph node was identified and biopsy showed metastatic goblet cell carcinoid. She then developed a 15 cm left inguinal mass, presumed to be regional spread of disease. Her care was transferred to Memorial Sloan Kettering Cancer Center for chemotherapy. CT and MRI studies showed hepatic and pulmonary masses in addition to the pelvic lymphadenopathy. Twenty-one months after her initial surgery she was started on irinotecan 140mg/m² q 2 weeks. The dose was reduced to 125mg/m² due to grade 2 diarrhea. CT scan showed mild reduction in lymphadenopathy and reduction in size of liver lesions as well as thickening of the bladder wall, presumably secondary to involvement by tumor. Subsequent MRI 25 months after initial surgery showed further mild reduction in lymphadenopathy as well as iliac and vertebral lesions suspicious for metastatic lesions. She died due to complications of the pelvic mass the following month, 26 months following initial surgery.

Discussion

We present a case of a perianal goblet cell carcinoid tumor with pagetoid spread, an unusual presentation of a rare tumor of the perianal region. The clinical differential diagnoses in this case were Paget's disease of the anus, adenocarcinoma, squamous cell carcinoma, and

melanoma. The histology and immunohistochemical staining pattern were incompatible with a squamous lesion or melanoma,^{18,19} while the positive staining for neuroendocrine markers (synaptophysin, chromogranin) and intestinal markers (CK20, CDX-2) indicate a tumor with mixed features. The clustering of mucin-containing cells and neuroendocrine cells seen in this tumor is characteristic of a goblet cell carcinoid tumor, which typically arise in the appendix. Though the appendix was never examined pathologically, we believe that our case represents a primary perianal lesion for two reasons. First, the patient underwent multiple imaging studies in the two years following initial diagnosis, none of which revealed appendiceal changes or mass. These normal imaging findings alone; however, do not entirely rule out an appendiceal lesion. Lee et al. studied the pre-operative CT imaging characteristics of patients with pathology- proven goblet cell carcinoid tumor of the appendix and found that 2 of 27 cases showed normal appendix, while 9 showed appendicitis, 9 showed prominent appendices without peri-appendiceal infiltration and 7 showed mass lesions.²⁰ Second, the perianal tumor was located in the dermis and subcutaneous soft tissue without evidence of peritoneal involvement at time of diagnosis. Appendiceal goblet cell carcinoids generally spread through peritoneal dissemination or to the ovaries.⁴ It would be unusual for a primary appendiceal goblet cell carcinoid to spread to the dermis and subcutaneous soft tissue as a first site of metastasis.

A further unusual feature of this tumor is its pagetoid spread. While the perianal region is a common site for extramammary Paget's disease, pagetoid spread of a goblet cell carcinoid tumor has not to our knowledge been reported. While mammary Paget's disease is nearly always associated with an underlying invasive or in situ tumor, 80–96% of cases of extramammary Paget's disease do not have an associated tumor.²¹ Classic extramammary Paget's disease is considered an adenocarcinoma involving the squamous mucosa and it is generally positive for CK7 and negative for CK20 as well as neuroendocrine markers.²²

Pagetoid spread of a neoplasm has been postulated to occur through local lymphatics²³ or may represent an epidermal metastasis.²⁴ Interestingly, this patient had a remote history of Paget's disease of the breast. Tissue from the prior mastectomy was not available for comparison; however, the morphology and immunohistochemical profile of the perianal lesion makes it unlikely to be a metastatic breast lesion.

Though collision tumors have been described in multiple sites in the gastrointestinal tract²⁵ and both endocrine and exocrine components are present in the anus,²⁶ to our knowledge, only one case report has described a combined carcinoid-adenocarcinoma tumor in the anus.¹⁶ The presentation was similar; an elderly patient presented with a rectal mass which was excised and the histologic images provided show a tumor with similar morphology to our case. In their case, metastatic foci involving inguinal lymph nodes and genital skin were identified one month after surgery and the patient died due to metastatic disease 6 months after surgery.

The perianal region is a very unusual site for goblet cell carcinoid. Further, this tumor shows pagetoid spread, which has not, to our knowledge been described with this tumor. It well illustrates that though goblet cell carcinoid is described formally as an appendiceal tumor,³

goblet cell carcinoid tumors have been described throughout the gastrointestinal tract, including the perianal region,^{16,26,27} and that pagetoid spread can also rarely occur.

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References

1. Subbuswamy SG, Gibbs NM, Ross CF, Morson BC. Goblet cell carcinoid of the appendix. *Cancer* 1974;34:338–44. [PubMed: 4852178]
2. Gallegos NC, Milroy C, Linehan IP, Boulos PB. Crypt cell carcinoma of the appendix. *Eur J Surg Oncol* 1992;18:386–7. [PubMed: 1521632]
3. Butler JA, Houshiar A, Lin F, Wilson SE. Goblet cell carcinoid of the appendix. *Am J Surg* 1994;168:685–7. [PubMed: 7978019]
4. Pahlavan PS, Kanthan R. Goblet cell carcinoid of the appendix. *World J Surg Oncol* 2005;3:36. [PubMed: 15967038]
5. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol* 2008;32:1429–43. [PubMed: 18685490]
6. Wen KW, Hale G, Shafizadeh N, Hosseini M, Huang A, Kakar S. Appendiceal goblet cell carcinoid: common errors in staging and clinical interpretation with a proposal for an improved terminology. *Hum Pathol*. 2017;65:187–93. [PubMed: 28551326]
7. Nonaka D, Papaxoinis G, Lamarca A, Fulford P, Valle J, Chakrabarty B. A study of appendiceal crypt cell adenocarcinoma (so-called goblet cell carcinoid and its related adenocarcinoma). *Hum Pathol*. 2018;72:18–27. [PubMed: 28823572]
8. Levendoglu H, Cox CA, Nadimpalli V. Composite (adenocarcinoid) tumors of the gastrointestinal tract. *Dig Dis Sci* 1990;35:519–25. [PubMed: 2180655]
9. Cary NR, Barron DJ, McGoldrick JP, Wells FC. Combined oesophageal adenocarcinoma and carcinoid in Barrett's oesophagitis: potential role of enterochromaffin-like cells in oesophageal malignancy. *Thorax* 1993;48:404–5. [PubMed: 8511743]
10. Caruso ML, Pilato FP, D'Adda T, et al. Composite carcinoid-adenocarcinoma of the stomach associated with multiple gastric carcinoids and nonantral gastric atrophy. *Cancer* 1989;64:1534–39. [PubMed: 2776113]
11. Adhikari D, Conte C, Eskreis D, Urmacher C, Ellen K. Combined adenocarcinoma and carcinoid tumor in atrophic gastritis. *Ann Clin Lab Sci* 2002;32:422–7. [PubMed: 12458898]
12. Tsujii T, Kambara T, Shimizu K, et al. Adenocarcinoma with extensive neuroendocrine differentiation arising in an ileal diverticulum: report of a case. *Surg Today* 2002;32:439–42. [PubMed: 12061697]
13. Alex WR, Auerbach HE, Pezzi CM. Adenocarcinoid tumor of the ampulla of Vater. *Am Surg* 1998;64:355–9. [PubMed: 9544149]
14. Ikeda E, Tsutsumi Y, Yoshida H, Yanagi K. Goblet cell carcinoid of the vermiform appendix with ovarian metastasis mimicking mucinous cystadenocarcinoma. *Acta Pathol Jpn* 1991;41:45560.
15. Heisterberg L, Wahlin A, Nielsen KS. Two cases of goblet cell carcinoid tumor of the appendix with bilateral ovarian metastases. *Acta Obstet Gynecol Scand* 1982;61:153–6. [PubMed: 7113691]
16. Anagnostopoulos GK, Arvanitidis D, Sakorafas G, et al. Combined carcinoid-adenocarcinoma tumour of the anal canal. *Scand J Gastroenterol* 2004;39:198–200. [PubMed: 15000285]
17. Avcu S, Ozen O, Bulut MD, Bora A. Hepatic metastases of primary jejunal carcinoid tumor: A case report with radiological findings. *N Am J Med Sci* 2009;1:305–8. [PubMed: 22666712]
18. Garrett K, Kalady MF. Anal neoplasms. *Surg Clin North Am* 2010;90:147–61. [PubMed: 20109639]
19. Henquet CJ. Anogenital malignancies and pre-malignancies. *J Eur Acad Dermatol Venereol* 2011;25:885–95. [PubMed: 21272092]

20. Lee KS, Tang LH, Shia J, et al. Goblet cell carcinoid neoplasm of the appendix: clinical and CT features. *Eur J Radiol* 2013;82:85–9. [PubMed: 23088880]
21. Lopes Filho LL, Lopes IM, Lopes LR, Enokihara MM, Michalany AO, Matsunaga N. Mammary and extramammary Paget's disease. *Anais brasileiros de dermatologia* 2015;90:225–31. [PubMed: 25830993]
22. Mengjun B, Zheng-Qiang W, Tasleem MM. Extramammary Paget's disease of the perianal region: a review of the literature emphasizing management. *Dermatol Surg* 2013;39:69–75. [PubMed: 23127181]
23. Fisher ER, Beyer FD Jr. Extramammary Paget's disease. *Am J Surg* 1957;94:493–8. [PubMed: 13458619]
24. Koss LG, Brockunier A Jr. Ultrastructural aspects of Paget's disease of the vulva. *Arch Pathol* 1969;87:592–600. [PubMed: 4181366]
25. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85:1686–93. [PubMed: 10223561]
26. Horsch D, Fink T, Goke B, Arnold R, Buchler M, Weihe E. Distribution and chemical phenotypes of neuroendocrine cells in the human anal canal. *Regul Pept* 1994;54:527–42. [PubMed: 7716284]
27. Lewin K. Carcinoid tumors and the mixed (composite) glandular-endocrine cell carcinomas. *Am J Surg Pathol* 1987;11 Suppl 1:71–86. [PubMed: 3544888]

Figure 1.

Perianal goblet cell carcinoid with pagetoid spread. The tumor is centered in the dermis and subcutaneous soft tissue of the perianal skin (A; hematoxylin and eosin, original magnification 20X) and consists of nests of mucin-containing and neuroendocrine cells (B; hematoxylin and eosin original magnification 600X) with pagetoid spread into the perianal squamous mucosa (C; hematoxylin and eosin original magnification 100X). Immunohistochemical stain shows that the dermal tumor (D; original magnification 200X) and its pagetoid spread (E; original magnification 100X) are positive for synaptophysin and

that the tumor is also positive for CDX-2 (F; original magnification 100X; the pagetoid spread is also positive for CDX-2 – not shown).

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