

CASE REPORT

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Authorship acknowledgement: All authors declare that we have made contributions to the idea, study design, data collection, data analysis and interpretation, critical review of the intellectual content, and final approval of the manuscript we are submitting

Ethical responsibilities: Protection of persons. The authors declare that the procedures followed conformed to the ethical standards of the committee on responsible human experimentation and in accordance with the World Medical Association and the Helsinki Declaration of 1975 in its most current version

Data confidentiality: The authors declare that we have followed the protocols established by their respective health centers to access the data from the clinical records of the Hospital Central "Dr. Urquinaona", Maracaibo, Venezuela regarding the publication of patient data

Right to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article to carry out this type of publication for research/dissemination purposes on paper and on the Internet for the scientific community. This document is in the possession of the corresponding author

Funding: The authors certify that we have not received financial support, equipment, personnel, or in-kind support from individuals, public and/or private institutions for the realization of the study

Conflict of interest: The authors declare that they have no conflicts of interest

Received: 26 January 2022

Accepted: 12 May 2022

Online publication: 22 September 2022

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Cite as: Torres-Cepeda D, Rondon-Tapia M, Reyna-Villasmil E. Appendiceal goblet cell carcinoid tumor with endometrial metastasis. *Rev peru ginecol obstet.* 2022;68(4). DOI: <https://doi.org/10.31403/rpgo.v68i2441>

Appendiceal goblet cell carcinoid tumor with endometrial metastases

Tumor carcinoide de células calciformes apendicular con metástasis endometrial

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DOI: <https://doi.org/10.31403/rpgo.v68i2441>

ABSTRACT

Goblet cell carcinoid tumor is an almost exclusive mixed neoplasm of the appendix with neuroendocrine and mucinous differentiation. Endometrial metastatic involvement by extragenital carcinomas, especially the signet ring cell type, is rare. A case of appendiceal goblet cell carcinoid tumor with endometrial metastasis is presented. This was a 70-year-old female patient who presented with genital bleeding. The gynecological examination showed moderate red-brown genital bleeding and hardened cervix. Endometrial biopsy reported nests of signet ring cells. The provisional diagnostic impression was poorly differentiated carcinoma of probable intestinal origin. During surgery, the uterus had a stony consistency, the cecal appendix was fibrotic and thickened, and the omentum was thickened with tumor nodules. Anatomical sections of the cervix and uterine body showed tumor foci. In the cecal appendix, small clusters composed of goblet cells were found. Immunostaining was positive for synaptophysin, CDX-2, EMA, CK20, focal CD56. These findings confirmed the diagnosis of goblet cell carcinoid tumor, a tumor characterized by infiltration of the appendiceal wall by small nests or cords of goblet cells with intracytoplasmic mucin and focal expression of neuroendocrine markers. These neoplasms have a more aggressive behavior than neuroendocrine tumors. Endometrial metastasis is rare and can be mistaken for a primary signet ring cell carcinoma. It should be considered as a differential diagnosis after other primary tumors have been excluded.

Key words: Goblet cell carcinoid tumor, Appendix, Endometrium, Neoplastic metastasis

RESUMEN

El tumor carcinoide de células calciformes es una neoplasia mixta casi exclusiva del apéndice, con diferenciación neuroendocrina y mucinosa. La afección metastásica endometrial por carcinomas extragenitales, especialmente el tipo de células de anillo de sello, es rara. Se presenta un caso de tumor carcinoide de células calciformes apendicular con metástasis endometrial. Se trató de paciente femenina de 70 años quien presentó sangrado genital. El examen ginecológico mostró sangrado genital en moderada cantidad de color rojo-marrón y cuello uterino endurecido. En la biopsia endometrial se halló nidos de células de anillo de sello. La impresión diagnóstica provisional fue carcinoma mal diferenciado de probable origen intestinal. Durante la intervención, el útero tenía consistencia pétreo, el apéndice cecal era fibrótico y engrosado y el epiplón engrosado con nódulos tumorales. Las secciones anatómicas del cuello y cuerpo uterino mostraron focos tumorales. En el apéndice cecal se encontró acúmulos de pequeño tamaño compuestos por células calciformes. La inmunotinción fue positiva a sinaptofisina, CDX-2, EMA, CK20, CD56 focal. Estos hallazgos confirmaron el diagnóstico de tumor carcinoide de células calciformes, un tumor caracterizado por infiltración de la pared apendicular por pequeños nidos o cordones de células calciformes con mucina intracitoplasmática y expresión focal de marcadores neuroendocrinos. Estas neoplasias tienen un comportamiento más agresivo que los tumores neuroendocrinos. La metástasis endometrial es rara y puede ser confundida con un carcinoma primario de células de anillo de sello. Se debe considerar como diagnóstico diferencial después de excluir otros tumores primarios.

Palabras clave. Tumor carcinoide de células calciformes, Apéndice, Endometrio, Metástasis neoplásica

INTRODUCTION

Appendiceal goblet cell carcinoid (GCC) tumor is a rare and distinctive neoplasm occurring almost exclusively in the appendix and showing neuroendocrine and mucinous differentiation⁽¹⁾. It accounts for 5% of appendiceal tumors and characteristically is arranged in small clusters of goblet cells (signet ring cells) with some neuroendocrine cells. It can be difficult to diagnose, even after clinical, laboratory and imaging stud-

ies⁽²⁾. Proper characterization of these tumors is of fundamental clinical importance in prognosis and clinical management.

Genital metastases from primary extragenital carcinoma occur mainly in the ovaries and vagina. Uterine involvement is rarer due to the high fibrous content, pelvic lymphatic drainage, distal circulation blood flow and small anatomical site⁽³⁾. Metastasis of signet ring cell carcinoma, a form of adenocarcinoma, is extremely rare and can be seen in both invasive lobular breast carcinomas and gastrointestinal carcinomas. So far only one case of appendiceal goblet cell carcinoid tumor with endometrial metastasis has been observed⁽⁴⁾. A case of appendicular goblet cell carcinoid tumor with endometrial metastasis is presented.

CASE REPORT

This was a 70-year-old female patient who consulted for moderate genital bleeding of approximately 3 months of evolution. She denied abdominal pain, fever, nausea, diarrhea, vomiting and weight loss. The patient reported a history of dyslipidemia and hypertension for 20 years treated irregularly. She denied family history of intestinal or gynecological neoplasms.

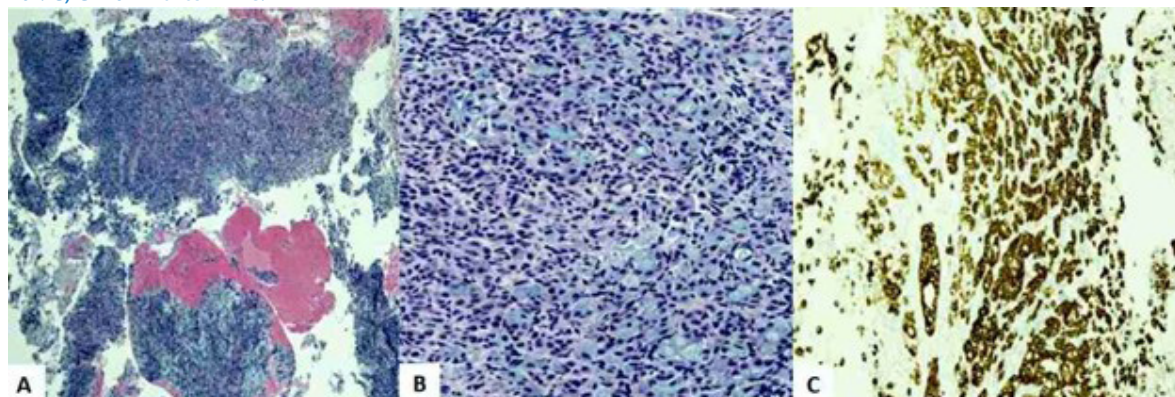
Physical examination revealed only mild pain on deep palpation in the right iliac fossa and hypogastrium with no defense or pain on decompression. The uterus was enlarged halfway between the umbilical scar and the pubis. Gynecological examination showed moderate amount of red-brown genital bleeding without pain on cervical mobilization and the cervix was hardened. Rectal examination showed palpation of the cervix

and uterine body and cervix with an irregular surface and no palpable tumors in the adnexa and fundus of Douglas.

Pelvic ultrasound showed an enlarged uterus with irregular borders and slightly thickened endometrium (8 millimeters). In view of the findings, the patient was scheduled for cervical dilatation and endometrial biopsy, which yielded scant tissue material containing nests of mucinous cells with signet ring morphology. Immunostaining showed diffuse and strong reactivity to CK20, MUC5, CA19.9, CDX2 and carcinoembryonic antigen and was negative for CK7, estrogen receptor, p16, MUC6 and PAX8. The proliferative index was 20% in tumor cells stained with Ki-67 (Figure 1). The provisional diagnostic impression was poorly differentiated predominantly mucinous metastatic carcinoma of gastrointestinal origin.

Complete radiological evaluation was performed due to the possibility of primary tumor of gastrointestinal origin. Chest X-ray, cystoscopy, upper endoscopy, and colonoscopy findings were normal, as were hematology, liver and renal function, coagulation profile, blood count and tumor markers. Computed tomography images of the abdomen and pelvis showed an enlarged, irregular uterus with uneven thickening of the myometrium, numerous calcifications, and superficial cystic lesions, both adnexa without tumors. In addition, there was thickening of the omentum, peritoneal dissemination, and a small amount of free fluid in the pelvic cavity. No lesions were found in the thorax and the rest of the abdomen. In view of all these findings the patient was scheduled for surgery.

FIGURE 1. GROUP OF SIGNET RING CELLS IN THE ENDOMETRIAL BIOPSY SPECIMENS A) HEMATOXYLIN-EOSIN STAINING 10X. B) HEMATOXYLIN-EOSIN STAINING 40X. C) CK20 IMMUNOSTAINING.





During the operation, the uterus was observed to have a stony consistency and was strongly adherent to the rectum and sigmoid colon. Multiple extensive cystic implants were observed in the uterine body and cervix and in the cul-de-sac of Douglas. The cecal appendix was fibrotic, thickened and with firm adhesions to the abdominal wall and colon. The omentum was thickened with several tumor nodules. Total abdominal hysterectomy, bilateral oophorosalphin-gectomy, right hemicolectomy, partial omentec-tomy, pelvic-para-aortic lymphadenectomy and peritoneal fluid sampling were performed.

Anatomopathologic evaluation confirmed that the uterine cervix, isthmus and corpus uteri, along with the fallopian tubes and fibroadipose tissue, showed tumor cell infiltrates. Anatomic sections of the cervix and corpus uteri showed foci of signet ring cell adenocarcinoma partially infiltrating the stroma with no evidence of other primary carcinoma and/or tumor embolisms. The endocervical glands showed no signs of dys-plasia or neoplasia. In the cecal appendix, a tu-mor was found between the middle and upper third of approximately 1 centimeter in diameter formed by epithelial proliferation of small and irregular clusters that infiltrated the entire mu-cosa, submucosa and appendicular muscularis propria without focal invasion to serosa, meso appendix and surgical edge. These clusters were composed of large numbers of goblet cells

(signet ring cells) containing mucin along with sparse numbers of well-differentiated neuroen-docrine cells with pale, eosinophilic cytoplasm and round-ovate central nuclei mixed with mu-cosal cells. Tumor cells appeared singly and in small groups. Immunostaining was positive for synaptophysin, CDX-2, EMA, CK20, focal CD56, and negative for CK7, carcinoembryonic antigen (Figure 2). Goblet cell clusters that showed focal immunoreactivity to synaptophysin in the his-tological evaluation of the omentum were also found (Figure 3). These findings confirmed the diagnosis of GCC.

The patient was referred to medical oncology for chemotherapy and regular follow-up. She has shown no signs of recurrence 26 months after surgery.

DISCUSSION

GCC, also described as appendiceal adenocarci-noid tumor, mucinous carcinoid, crypt cell car-cinoma, is one of the most common malignant neoplasms of the cecal appendix, different from carcinoid tumors and adenocarcinoma⁽³⁾. It is a tumor of two histological types, with neuroen-docrine differentiation and goblet cell differen-tiation (signet ring cells), and a metastasis rate (15% to 30% of cases) higher than conventional appendiceal carcinoid tumor^(5,6). Although it is almost exclusive to the cecal appendix, in rare

FIGURE 2. GLOBLET CELL CARCINOID TUMOR. ISOLATED GROUPS OF NEUROENDOCRINE CELLS AND GLOBLET CELLS WITH ABUNDANT INTRACYTOPLASMIC MUCIN IN THE WALL OF THE CECAL APPENDIX AND CONCENTRIC GROWTH PATTERN. A) HEMATOXYLIN-EOSIN STAINING 100X. B) POSITIVE IMMUNOSTAINING FOR SYNAPTO-PHYSIN.

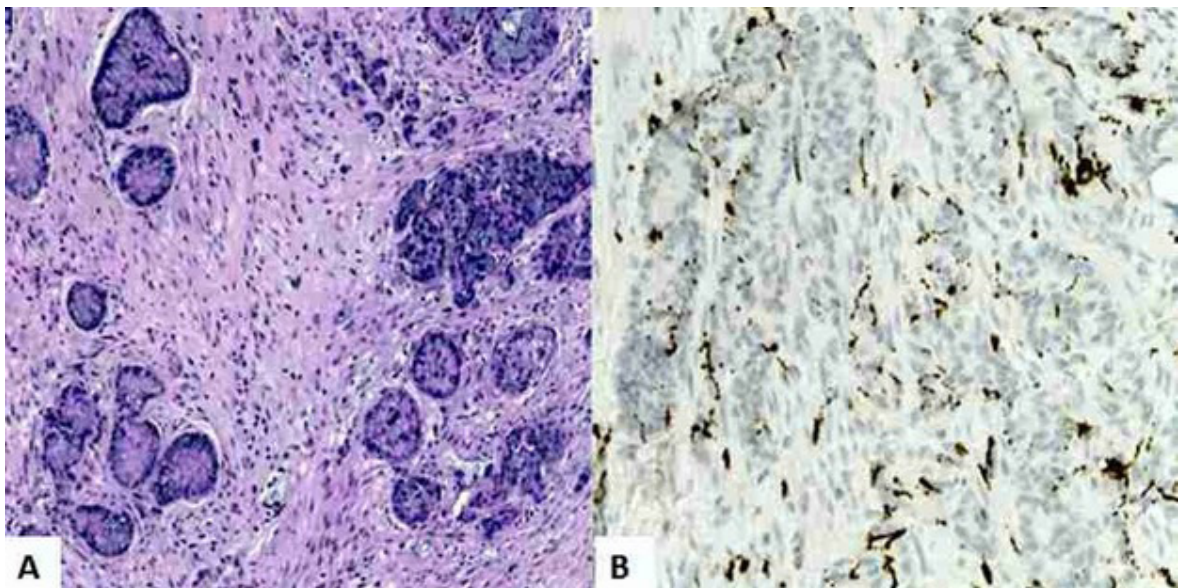
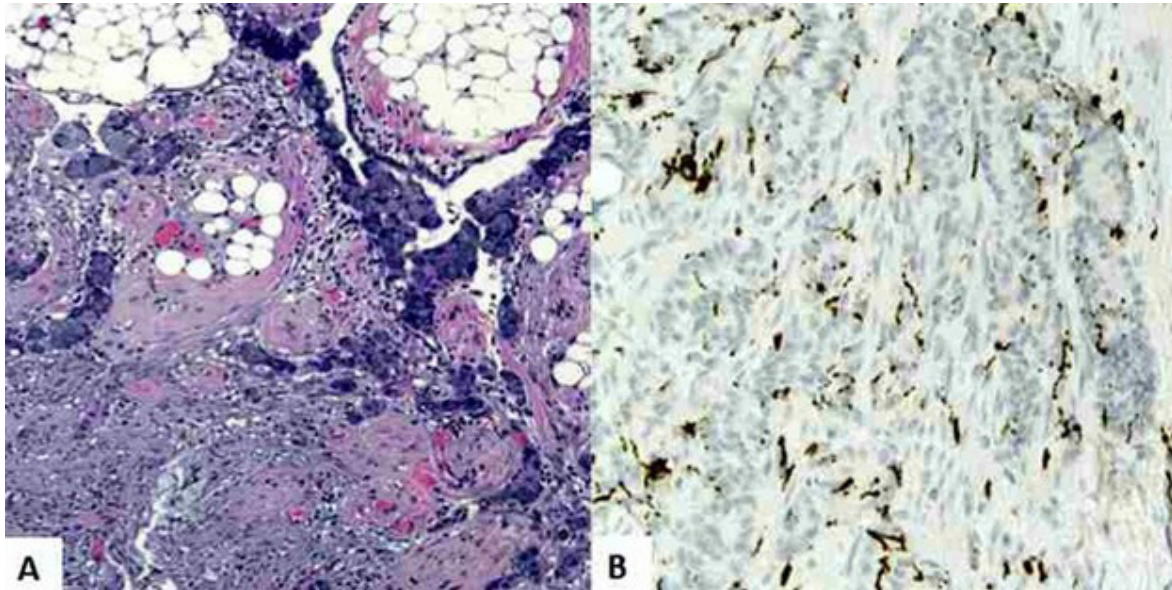




FIGURE 3. GOBLET CELL CARCINOID TUMOR. THE TUMOR CELLS ARE ARRANGED IN CLUSTERS IN THE OMENTUM. THE SIGNET RING CELLS CONTAIN INTRACELLULAR MUCIN VACUOLES FORMING SMALL CLUSTERS. A) HEMATOXYLIN-EOSIN STAINING, 100 X. B) POSITIVE IMMUNOSTAINING FOR SYNAPTOPHYSIN.



cases it can be found in the rectum, ileum or colon. It has a similar distribution among men and women and has been diagnosed in patients between 18 and 89 years of age⁽²⁾.

GCC is considered an amphicrine tumor, with both exocrine and endocrine features that apparently arises from pluripotent crypt cells with divergent differentiation⁽³⁾. Ultrastructural analysis of tumor cells shows that they contain mucinous vacuoles of variable size and occasional membrane-bound granules⁽⁵⁾. TP53, KRAS, BRAF and APC mutations, frequent in colorectal adenocarcinomas, are rare or absent in these tumors. The neoplasms show alterations in genes associated with Wnt signaling (USP9X, NOTCH1, CTNNA1, CTNBNB1, TRRAP). In addition, they show mutations in the chromatin remodeling genes ARID1A and ARID2, CDH1, RHPN2, MLL2, SOX9 and RHOA⁽¹⁾.

Tumors may be symptomless, but most cases may present with symptoms of acute appendicitis (due to luminal obstruction) or acute peritonitis (due to appendicular rupture). Some cases may have recurrent episodes of abdominal pain, palpable tumor in the lower hemiabdomen, intestinal obstruction, gastrointestinal bleeding, and secondary genitourinary complications^(7,8). They can also spread to the peritoneal cavity without causing tissue destruction, tumor formation and/or significant gastrointestinal symptoms. Apart from the present case there is only

one previous report of genital hemorrhage as an initial manifestation of the tumor⁽⁴⁾. The diagnosis is accidental during surgery, as the tumor may be difficult to discover, even after different clinical studies. Some cases with advanced disease may show ovarian tumors that may lead to the preoperative diagnosis of primary ovarian neoplasia or Krukenberg's tumor^(8,9). The most common metastatic sites are peritoneum, omentum, ovaries, colon, and right ileum. Metastases to costal arches, vertebrae, lymph nodes, liver, brain, and prostate are rare^(7,10).

The definitive diagnosis of GCC is based on histologic features. Appendiceal carcinoids can be divided according to their histologic patterns: typical argentaffin and enterochromaffin cell carcinoid, non-argentaffin L-cell carcinoid, and goblet cell carcinoid. In the latter, the cecal appendix may be normal or cause wall thickening with circumferential involvement and extend longitudinally along the cecal appendix. The size of the tumor, therefore, should be determined by measuring the extent of the tumor along the appendix and is estimated to be greater than 2 centimeters in most cases. The tumors do not produce adenomatous, dysplastic, or neoplastic changes suggestive of a mucinous tumor, except in areas where the tumor cell clusters are connected to the base of the crypts. The tumor cells are arranged in patterns of intestinal crypts, nests, rosettes, or clusters without distinct lumens⁽⁴⁾. After extensive infiltration, the



appendiceal wall appears hardened and the intraluminal lumen may disappear secondary to diffuse fibrosis⁽⁹⁾. Because it arises within the inferior lamina propria, and generally there is no tissue destruction or well-defined tumor, imaging studies show only a slight thickening of the appendicular wall⁽⁴⁾.

Although it can often be confused with signet ring cell carcinoma, GCC has typical characteristics, such as two types of cells arranged in small nests: neuroendocrine cells with eosinophilic granular cytoplasm and gastrointestinal goblet cells. The tumor consists of glands with varying degrees of mucinous differentiation. Neuroendocrine cells are mixed with mucinous cells and their proportion is lower than in the classic carcinoid tumor. The glands infiltrate adjacent structures without destroying or causing a desmoplastic reaction of the stroma. There is no standard immunohistochemical staining for these tumors. Most cases show strong and diffuse positivity for CK20 and are CK7 positive in 70% to 75% of cases (positivity varying from focal to diffuse)⁽¹¹⁾. They also show focal and patchy expression to neuroendocrine markers such as synaptophysin, somatostatin, serotonin, neuron-specific enolase, and pancreatic polypeptide. Periodic acid-Schiff-diastase and mucicarmine staining highlight the presence of abundant intracellular mucin within goblet cells⁽⁷⁾.

Differential diagnoses include mucinous adenocarcinoma, signet ring adenocarcinoma and mixed carcinoid-adenocarcinoma tumor. Neuroendocrine tumors lack goblet cells, show diffuse immunoreactivity to synaptophysin and chromogranin and are negative for CK7 and CK20. The presence of focal goblet cell clusters, nuclear pleomorphism and mitotic activity, with solid or cribriform areas and destruction of stroma or smooth muscle are characteristic of colorectal appendiceal adenocarcinoma⁽¹²⁾. In cases of unusual endometrial adenocarcinomas with prominent signet ring cells, metastatic appendiceal GCC should be considered in the differential diagnosis, especially after excluding the more common gastrointestinal and ovarian tumors⁽¹³⁻¹⁶⁾. The immunostaining of endometrial tissue in this case was like that found in previous cases with metastases to neighboring organs.

As practiced in the present case, surgery is the treatment of GCC. It is not clear in which situa-

tions it is necessary to perform simple appendectomy or right hemicolectomy since it is a more aggressive tumor than carcinoid and with a higher risk of metastasis. Right hemicolectomy is recommended when there is involvement of the appendiceal base and/or cecum, positive resection margins, tumor size greater than 2 centimeters, severe atypia and more than 2 mitoses per field. The finding of lymphatic-perineural invasion is not an indication to perform hemicolectomy^(10,12). Prophylactic oophorosalingectomy may also be necessary due to the high risk of ovarian metastasis. Even in cases of Krukenberg's tumor of unknown origin it is advisable to perform appendectomy to rule out a possible GCC⁽⁷⁾. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy have been used in cases of peritoneal carcinomatosis. However, the effectiveness of these chemotherapy regimens remains controversial^(1,17). The role of chemotherapy is not clearly established, although cases with stage IV disease may be treated with adjuvant 5-fluorouracil-based chemotherapy, like colorectal adenocarcinomas^(18,19). The patient in the present case underwent chemotherapy with favorable results.

The prognosis is intermediate between carcinoid and well-differentiated adenocarcinoma of the cecal appendix, with 5-year survival that can reach 76%^(3,8). In addition to the established prognostic factors, such as size and location of the tumor or presence of metastasis, there are other markers that can have prognostic value, such as incomplete resection at the base of the appendix, extra-appendiceal dissemination, tissue invasion and cellular atypia^(5,6,20). The patient in this case has remained free of tumor recurrence for more than two years.

In conclusion, GCC is a rare entity with typical histologic features, with both mucinous and neuroendocrine cells, and a more aggressive behavior than conventional appendiceal carcinoid tumor. Unusual endometrial adenocarcinomas with large numbers of signet ring cells should be considered as metastases of appendiceal GCC, after excluding the presence of other more common primary tumors. Diagnosis is based on specific anatomopathologic and immunohistochemical findings. Surgery is essential to increase the overall survival rate.



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