

Case Report

A Case of Cervical Carcinoid and Review of the Literature

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Keywords

Uterine cervix carcinoid · Neuroendocrine tumors · Radical hysterectomy

Abstract

Uterine cervix carcinoids are distinct neuroendocrine cervical tumors, representing a comparatively small percentage of them. These well-differentiated neoplasms are far less prevalent than small- and large-cell carcinomas, characterized by a more favorable biological course. We report a case of a 43-year-old woman with a nonmetastatic cervical carcinoid, managed with radical hysterectomy. She still remains free of disease. Scant reports in the literature prohibit any reliable prediction of cervical carcinoid prognosis. Thus, prompt identification of the disease and subsequent therapeutic intervention could alter the final outcome.

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Introduction

Cervical carcinoid is the least common type of neuroendocrine neoplasm arising in cervix uteri, in contrast to the more common small cell neuroendocrine carcinoma and to the large cell variant [1]. Well-differentiated cervical carcinoid tumors exhibit the typical carcinoid features found elsewhere in the body, i.e. absent or minimal cytological atypia, low mitotic score, no necrosis. Overall, cervical neuroendocrine tumors represent about 2% of all cervical malignancies. A standardized terminology for neuroendocrine tumors of the uterine cervix was created in 1997 by a workshop sponsored by the College of American Pathologists and the National Cancer Institute [2]. Carcinoids and small-/large-cell carcinomas have different natural histories and treatment. The former are characterized by significantly better prognosis than the latter, while their treatment could resemble that of gastroenteropancreatic neuroendocrine tumors. Small-cell cervical carcinomas represent an extrapulmonary variant of small cell cancer, and their outcome is associated with disease extent [3]. There are still limited data to guide specific treatment of cervical carcinoids, given their rarity. The published literature contains few patients [4], and there are no prospective trials.

Case Presentation

A 43-year-old woman was admitted to the Gynecology Department in March 2007 complaining of vaginal bleeding. Initial gynecological examination revealed a cervical uterine polyp, while Pap smear was negative for malignancy. Subsequently, the patient was submitted to a removal of the cervical polyp and to a diagnostic curettage at the same time.

Histopathological examination of the cervical polyp, which exhibited a maximum diameter of 2 cm, showed that it was occupied in a large part by a neoplastic lesion, characterized by organoid arrangement, with nested, trabecular, or cord-like growth patterns, and uniform cells, with minimal nuclear atypia and rare mitoses (Fig. 1). Necrosis was not observed. The Ki-67 labeling index was low, estimated at 1–2%. Immunohistochemistry showed positivity for synaptophysin (Fig. 2) and chromogranin A (CgA). Thus, the lesion was diagnosed as a neuroendocrine tumor of the uterine cervix with carcinoid features.

Serum CgA and 24-h urinary 5-hydroxyindolacetic acid (5-HIAA) were measured and found within normal values. A radical hysterectomy with lymphadenectomy was then performed, which showed a small residual cervical lesion with similar histopathological characteristics, and a stromal invasion 2 mm in depth, but none of the 23 lymph nodes were involved. An octreoscan failed to demonstrate any abnormal uptake, and postsurgical computed tomographies were negative for evident disease or secondary lesions. The patient was staged as having stage IB1 disease, and since then she remains free of disease under periodic follow-up.

Discussion

Cervical carcinoids are diagnosed at a mean age of 50 years, and the morphological features of these neoplasms resemble those described in a variety of endocrine tumors, such as gastroenteropancreatic neuroendocrine tumors. It is suggested that they represent a specific type of cervical neoplasia derived from the argyrophil cells, normally found in small num-

bers among the linings of the endocervical glands and the cervical squamous epithelium. Lymphovascular space invasion (LVI) is not a prominent feature of well-differentiated tumors, in contrast to high-grade neoplasms, in which 80% of cases exhibit LVI [5].

Cervical carcinoids are extremely rare and, despite improvements in their identification, they are frequently misdiagnosed and mismanaged. Immunohistochemistry with neuroendocrine markers, such as chromogranin and synaptophysin, significantly enhances the diagnosis of neuroendocrine tumors, while testing for serum CgA and 24-h urinary 5-HIAA may be useful in these cases. Urinary levels of 5-HIAA are most frequently elevated in patients with primary midgut carcinoids, as other carcinoid tumors only rarely secrete serotonin (they lack the enzyme DOPA decarboxylase, cannot convert 5-hydroxytryptophan to serotonin and therefore to 5-HIAA). CgA is contained in the neurosecretory vesicles of neuroendocrine tumor cells and is detectable in the plasma of such patients. Serum CgA is a more sensitive and broadly applicable tumor marker for neuroendocrine tumors than is urinary 5-HIAA, but it is less specific. CgA levels are higher in patients with diffuse metastases than localized disease or isolated hepatic involvement and higher levels may be associated with a poorer prognosis [6]. Data on the correlation of plasma CgA levels with treatment response and on their prognostic value are not available for cervical carcinoids.

Cross-sectional imaging including either a triphasic CT or an MRI are appropriate imaging techniques and should be performed to evaluate the extent of the disease. Somatostatin receptor scintigraphy (SRS) represents an important method for localizing well-differentiated neuroendocrine neoplasms, with an overall sensitivity reported to be as high as 90%. Baseline SRS may also be useful as the uptake of radiolabeled octreotide is predictive of a clinical response to therapy with somatostatin analogues. The absence of a positive octreoscan result does not preclude the possibility of octreotide's efficacy in metastatic carcinoids, as seen in intestinal carcinoids. It is not known whether this is also true for cervical carcinoids. On the other hand, PET/CT does not provide any meaningful information, with the exception of clinicopathologically aggressive tumors.

Characteristic endocrine syndromes associated with low-grade neuroendocrine tumors of the cervix virtually do not exist, with the carcinoid syndrome being extremely unusual [7]. Carcinoid syndrome is a term applied to a constellation of symptoms mediated by various humoral factors that are elaborated by carcinoid tumors, such as serotonin, kinins, histamine, kallikreins and other. Flushing and diarrhea are the most common manifestations, while valvular lesions (Hedinger syndrome) and bronchoconstriction are less frequent. Carcinoid syndrome usually occurs with carcinoids of the small intestine, appendix and proximal colon, with metastatic liver involvement. In the absence of hepatic metastases, the occurrence of carcinoid syndrome is rare and depends on the release of mediators directly into the systemic circulation rather than the portal circulation, as in the case of bronchial or ovarian carcinoids. The secretion of multiple hormones or bioamines, such as adrenocorticotropic hormone, β -melanocyte-stimulating hormone, serotonin, histamine, somatostatin, calcitonin, gastrin, vasoactive intestinal polypeptide, pancreatic polypeptide, have been reported in cervical neuroendocrine tumors, although not related to clinical symptoms.

Carcinoid tumors possess distinct histological, clinical, and biological properties, while their presentation is often obscure. For the most part, they tend to be associated with the gastrointestinal tract and the bronchial tree, but they can arise less commonly in other sites, such as the ovaries, the gallbladder, the testis, the larynx, the middle ear, the breast, the liver, and the uterine cervix [8]. Among the unusual sites of primary carcinoids, the latter remains one of the rarest locations. Their rarity and underdiagnosis or misdiagnosis may contribute to the paucity of published data. The majority of cervical neuroendocrine neoplasms display

an aggressive behavior, with scant reports of benign presentations. Cervical carcinoids most commonly present as a stage 1 disease, in contrast to squamous cell carcinoma which usually is diagnosed as a stage 2 disease. Prognosis is mainly dependent on tumor stage. On the other hand, the relationship between size and metastatic propensity has not been established, in contrast to gastrointestinal tract carcinoids wherein tumor size >2 cm increases the risk for metastases. The impact of the mitotic rate per 10 HPF and Ki-67 labeling index on the prognosis of neuroendocrine tumors has been evaluated in multiple studies, but these tumors were of gastroenteropancreatic [9] or bronchopulmonary origin. The same might be true for cervical carcinoids, but the overall small sample size prohibits any reliable generalization of patient outcome. The pattern of disease recurrence in cervical neuroendocrine tumors is strikingly different from that in squamous cell carcinomas. Most patients with recurrent neuroendocrine disease exhibit metastatic involvement, even in the earlier stages during diagnosis, whereas most patients with squamous cell tumors of the same stage are found with pelvic disease at relapse.

Most reported cases with a cervical carcinoid diagnosis were diagnosed as postoperative pathological findings [10]. Most carcinoid tumors demonstrate a remarkable tropism for the liver. Liver lesions should be considered for resection to control tumor burden and those lesions that are not resectable should be considered for regional embolization, radiofrequency ablation or cryotherapy [11]. In advanced stages, where curative surgical procedures are not possible, chemotherapy does not have an established role. The utility of somatostatin analogues has only been described in the case of systemic manifestations of the carcinoid syndrome [7]. Proof of octreotide's antiproliferative effects is already available for functionally active or inactive metastatic neuroendocrine midgut tumors. The inhibitory effects of somatostatin analogues on cervical carcinoid proliferation are extremely difficult to confirm, due to the rarity of the disease. For the same reason, therapeutic options existing for advanced gastroenteropancreatic carcinoid tumors, such as interferon α -2b [12], everolimus [13], or sunitinib [14], have not yet been evaluated in metastatic cervical neuroendocrine neoplasms. Chemotherapeutic agents, including streptozocin, 5-fluorouracil, doxorubicin [15], and temozolomide, are efficacious mainly in advanced pancreatic neuroendocrine tumors. Data concerning the response of cervical carcinoids to chemotherapy are still missing. The use of conventional cytotoxic chemotherapy should be restricted primarily to patients with poorly differentiated tumors, where objective response rates are higher. Similarly, the effect of radiotherapy on these tumors has not been established.

Conclusion

In conclusion, the most effective treatment modalities for cervical carcinoids remain uncertain, because of the small number of reported cases. We have reported a case of cervical carcinoid treated successfully with radical hysterectomy. Diagnosis of low-grade neuroendocrine tumors of cervix uteri, which are characterized generally by an indolent biological course, could contribute to the diminution of metastatic disease and consequently to the improvement of their prognosis.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure Statement

We have read and understood *Case Reports in Oncology* policy on disclosing conflicts of interest and declare that we have none.

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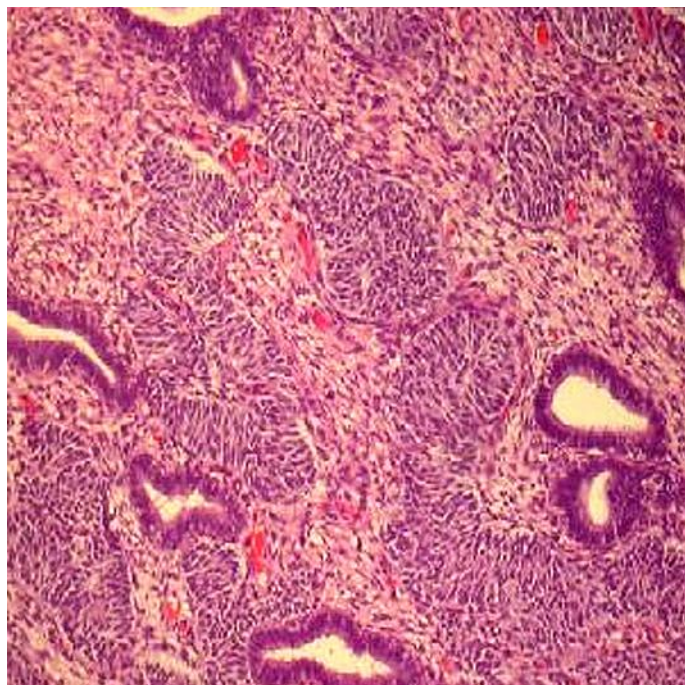


Fig. 1. The cervical polyp was occupied by a neoplastic lesion exhibiting arrangements of relatively uniform tumor cells between endocervical glands. Hematoxylin-eosin staining. Original magnification $\times 200$.

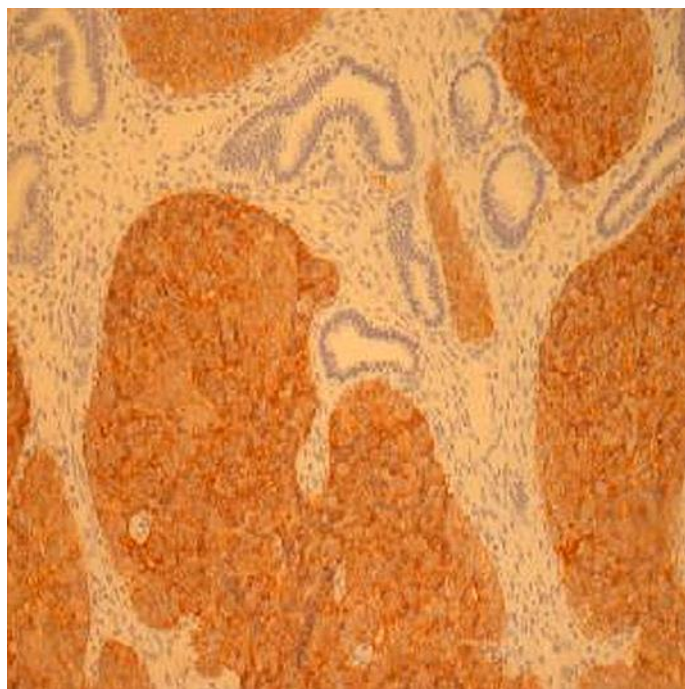


Fig. 2. The tumor cells showed positivity for synaptophysin.