Collision Tumors of the Cervix – A Case Series: Its Clinical Significance in the Management of an Early Stage Disease

Jimmy A. Billod[1] and Efren J. Domingo[2]

[1]*Baguio General Hospital and Medical Center*
[2]*University of the Philippines- Philippine General Hospital*

ABSTRACT

Majority of cervical cancer are squamous cell carcinoma and adenocarcinoma. The co-existence of two histologic types is rare. This article presents three cases of collision tumors of the cervix within a 10-year review. All underwent radical hysterectomy for an early stage disease. Likewise, it aims to review clinicopathologic features, management, response to treatment and prognosis of these types of tumor in the light of recent literature.

Key Words: cervical cancer, collision tumors of the cervix

INTRODUCTION

Cervical cancer is the second most common cancer among women, the third most common cause of cancer-related death, and the most common cause of mortality from gynecologic malignancy worldwide.[1] In the Philippines, it is the second most common site of cancer and is the second leading cause of cancer-related deaths among women. About 6,000 new cases and 4,349 deaths are expected to occur each year due to cervical cancer.[2] The overall 5-year survival rate was 44% and mortality rate was 1 per 10,000 women.[3] The vast majority of cervical cancers are squamous cell carcinomas (SCC), which comprises 80% to 85%, while 15% to 20% are from adenocarcinomas (ADC).[4-6] Invasive tumors of unspecified morphology constitute the remaining 5-10%.[7]

The simultaneous occurrence of different histologic types of cervical cancer has been rarely documented. In 1957, Melnick et al. first reported cases of coexistent SCC and ADC of the cervix; Dougherty and Cotten grouped them as combined or "mixed" carcinomas in 1964; and Abell, in 1973, classified them as a histologically distinct tumor. Rare tumors may contain areas of SCC and ADC at the same time and is considered as one of the unusual forms of cervical carcinoma. These types of tumors are usually termed as Collision Tumors.[8]

The objective of this article is to present cases of collision tumors of the cervix encountered in the Philippine General Hospital. Likewise, this paper reviews clinicopathologic features, risk factors, management, treatment and outcome and prognosis of collision tumor in an early stage disease in the light of recent literature.

Poster presented at the International Gynecologic Cancer Society Congress Lisbon, Portugal, October 2016, and awarded Second place at the SGOP Interesting Case Contest.

Corresponding Author: Jimmy A. Billod, MD
Baguio General Hospital and Medical Center
#1 Governors Pack Road, Baguio City
Telephone: + 63 09778344118
Email: jabillodmd@gmail.com

CASE REPORTS

Case 1

A 38-year-old, G6P4 (4024), presented with a 3-month history of intermenstrual vaginal bleeding lasting for 5 days. Her first coitus was at 22 years with 2 promiscuous sexual partners. She had a 2-year use of oral contraceptive pills (OCP). Pelvic examination revealed normal external genitalia, smooth vagina, the cervix was 3 x 3 cm nodular, corpus small with no adnexal masses or tenderness, bilateral parametria smooth and pliable. Transvaginal ultrasound (TV-UTZ) showed a hypoechoic cervical mass measuring 2.2 x 1.2 x 1.9 cm within its stroma. Both parametria were intact. The rest of metastatic workups were negative. Immunohistochemistry of the endocervical biopsy showed positive for cytokeratin, synaptophysin and chromogranin, which confirmed a small cell neuroendocrine carcinoma. The final impression was small cell neuroendocrine of the cervix, stage IB1. After neoadjuvant chemoradiation, she underwent exploratory laparotomy, radical hysterectomy with bilateral salpingo-oophorectomy with lymph node assessment. Histopathologically, the hysterectomy specimen showed two tumors in the cervix: the larger tumor is adenocarcinoma (1.5 cm), endometriod type, with infiltration of 1/3 of the cervical stroma. A small cell carcinoma is also present, at least 3 mm wide; the depth of invasion appears less than 1/3 thick. It was negative for lymphovascular invasion and no tumor seen on the endometrium, vaginal cuff, and bilateral parametria. Due to the presence of 1/3 stromal invasion and a histologic type of neuroendocrine carcinoma, the section decided to institute adjuvant chemotherapy in the form of Cisplatin-Paclitaxel every 3 weeks for 6 cycles. She was not able to comply with the chemotherapy. One year after the surgery, repeat ancillary laboratories and imaging studies showed no evidence of disease hence, the planned chemotherapy was not continued. She's presently in remission of the disease for 6 years.

Case 2

A 62-year-old, G3P3 (3003), complained of vaginal spotting. She had her first coitus at the age of 29 years to a single lifetime sexual partner. She had a history of OCP use for 10 years. TV-UTZ showed a cervical mass. Colposcopy and cervical punch biopsy revealed adenocarcinoma of the cervix, endometrioid type. On pelvic examination, she had normal external genitalia, smooth vagina, cervix was 3 x 3 cm, nodular with forniceal involvement, corpus was small with no adnexal masses or tenderness, bilateral parametria smooth and pliable. The initial impression was cervical adenocarcinoma, endometrioid type, stage IIA1. Metastatic workups were negative.

She underwent exploratory laparotomy, radical hysterectomy with bilateral salpingo-oophorectomy, and bilateral lymph node dissection. The final histopathologic diagnosis was Collision tumor of the cervix, adenocarcinoma, moderately differentiated, endometrioid type and squamous cell carcinoma, large cell, non-keratinizing with more than 50% of cervical wall infiltration and to the superficial myometrium (less than 50%). Lymphovascular invasion was noted. The adnexa and all harvested lymph nodes were negative for tumor. The final diagnosis was Collision tumor; Adenocarcinoma, moderately differentiated, Squamous cell carcinoma, large cell, non-keratinizing, cervix, stage IIA1. She received adjuvant chemoradiation for the presence of lymphovascular invasion (LVSI) and more than 50% stromal invasion. She completed her pelvic external beam radiation (EBRT) concurrent with weekly Cisplatin. Presently, she is in remission for 5 years.

Case 3

A 45-years-old, G3P2 (2012), presented with a history of prolonged menstruation. She had her first coitus at 23 years old with 1 lifetime sexual partner with unknown promiscuity. She had a history of OCP use for 3 years. TV-UTZ showed endocervical polyp. She underwent polypectomy, which on biopsy revealed neuroendocrine tumor, grade 2. Immunohistochemistry was positive for chromogranin and synaptophysin, confirming a neuroendocrine tumor. On pelvic examination, she had normal external genitalia, smooth vagina, cervix measured 2 x 2.5 cm, nodular anteriorly, corpus was small, no adnexal masses or tenderness, bilateral parametria smooth and pliable. Metastatic workups were negative. She underwent radical hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node dissection, paraaortic lymph node sampling. The final histopathologic result revealed two different tumor histology, cervical adenocarcinoma, endocervical type, well-differentiated, and neuroendocrine tumor, with tumor size of 1 cm in greatest dimension and involving the upper third of the cervical stroma. No lymphovascular space invasion was seen. No tumor was seen on the endometrium, parametria, vagina, adnexa and lymph nodes. The final diagnosis was Collision tumor; Adenocarcinoma and Neuroendocrine, cervix stage IB1. Since there is involvement of the upper third of the cervical stroma and a component of neuroendocrine tumor, adjuvant chemotherapy was administered in the form of Oxaliplatin-Docetaxel every 3 weeks for 2 cycles followed by pelvic EBRT then another 3 cycles of systemic chemotherapy. Presently, she has no evidence of disease for 3 years. Table 1 presents the summary of the clinical and pathologic characteristics of the cases.

DEFINITION AND BACKGROUND

Collision tumor is defined as the coexistence of two adjacent but histologically different malignant neoplasms occurring in the same organ without histological admixture or an intermediate cell population zone. These tumors consist of components of different histogenesis and different tumorogenetic pathways representing a mosaic of two concurrent but independent tumors that have collided with

Table 1. Summary of the clinical and pathologic characteristics of the cases

Case	Age GP Score	Clinical Presentation / Risk factors	Initial Punch Biopsy Diagnosis	Gross Appearance	Final Diagnosis	Treatment	Present Status
1	38 G6P4 4024	Intermenstrual bleeding for 3 months (+) 2 sexual partners (+) OCP use	Small cell neuroendocrine carcinoma	1.5 x 1.5 x 1.0 cm firm mass at the posterior cervical lip with almost full thickness stromal invasion	Adenocarcinoma, endometrioid type with a small cell neuroendocrine carcinoma	Neoadjuvant chemotherapy with Cisplatin and Etoposide with pelvic EBRT followed by RHBSO, lymph node dissection	Alive in remission for 6 years
2	62 G3P3 3003	Post menopausal vaginal spotting for 3 weeks (+) OCP use	Adenocarcinoma, endometrioid type	2.5 x 1.9 x 0.8 cm necrotic mass on the anterior portion of the endocervical canal extending to the anterior lip of the ectocervix	Adenocarcinoma, moderately differentiated with squamous cell carcinoma, large cell, non-keratinizing	RHBSO, lymph node dissection followed by concurrent chemoradiation (LINAC)	Alive in remission for 5 years
3	45 G3P2 2012	Prolonged vaginal bleeding for 4 months (+) OCP use	Neuroendocrine tumor, grade 2	1.0 x 1.0 cm cervical mass at the anterior cervical lip which showed less than 1/3 stromal invasion	Cervical adenocarcinoma, endocervical type, well differentiated, and neuroendocrine tumor	RHBSO, lymphnode dissection followed by Adjuvant therapy with Oxaliplatin-Docetaxel x 2 cycles and pelvic EBRT (LINAC)	Alive in remission for 3 years

RHBSO – Radical hysterectomy with bilateral salpingo-oophorectomy; LINAC – Linear accelerator; EBRT – External beam radiotherapy

each other.[9] Because direct transition from once cell type to another is not seen, these tumors are best considered as separate neoplasms.[10]

The involvement of the same organ by more than one tumor can be classified on the basis of the manner of involvement by two tumors.[11]

1. Metastasis of one tumor in the substance of the other, the so- called cancer-to-cancer metastasis.
2. Presence of two histologically different tumors in the same organ with histologic admixture of the two tumors, called composite tumors.
3. Presence of two histologically distinct tumors without histologic admixture of the two entities, called collision tumors.

There is no satisfactory explanation for the occurrence of collision tumors. Several hypotheses have been suggested as mechanism for such tumors. The simplest is that the two primary tumors occurred in continuity by a chance accidental "meeting". Two different tumors may develop contiguously because the region is altered by the same carcinogenic stimuli. Another hypothesis is that the presence of the first tumor alters the microenvironment making the development of the second adjacent tumor more likely or attracts a second primary.[11,12] More recent report suggests that stronger evidence for a multi- or monoclonal origin can be obtained from molecular genetic analysis, as genetic alterations will be retained during carcinogenesis, whereas phenotypic features may change.[13]

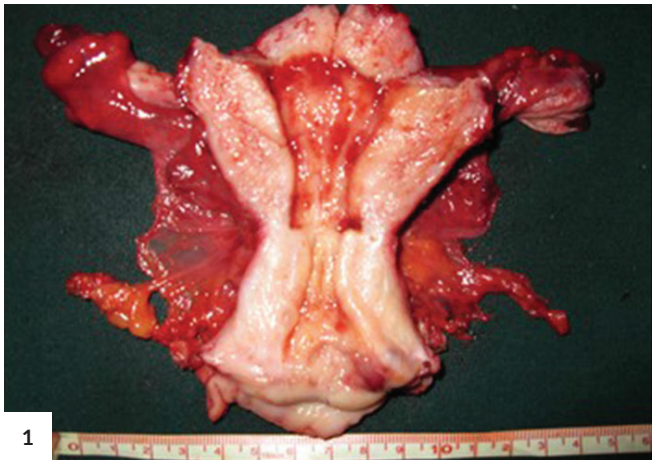
ETIOLOGY AND DIAGNOSIS

Epidemiologic studies as well as others indicate that Human Papilloma Virus (HPV) infection is the most important etiologic factor in the development of cervical cancer. Some co-factors for cervical carcinogenesis includes smoking, oral contraceptive pill use and fertility.[14,15] A common risk factor for the three cases in this paper is the OCP use. Oral contraceptive use is a well-established risk factor for cervical cancer. In line with the co-existence of two tumors and the different hypothesis on its occurrence, recent reports substantiated that HPV, particularly types 16 and 18 play a role in the etiology of cervical neuroendocrine (NEC) and mixed carcinomas.[16-20] Other authors concluded that the concurrent glandular and squamous lesions in collision tumors develop separately from the same type HPV.[21] Unfortunately, the HPV status of the presented cases was unknown. An attempt to employ HPV Genotyping on the paraffin tissue blocks was made but currently such analysis is not available in the local setting.

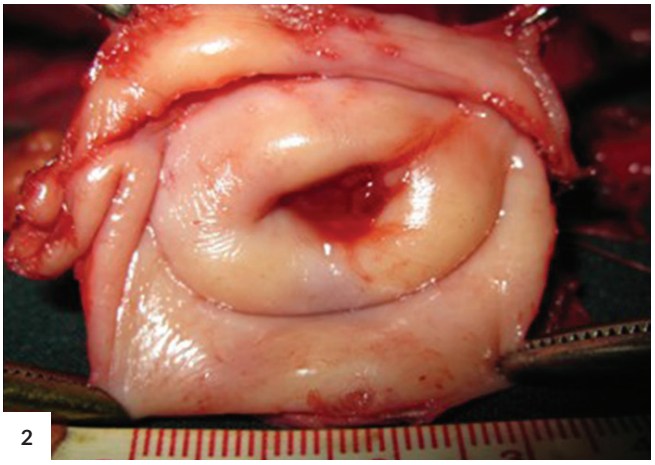
Given the similarities of the clinical and imaging features of any histologic type of cervical cancer, which is usually abnormal bleeding and a cervical mass, a preoperative diagnosis of dual pathological condition is definitely impossible. Based on the presented cases, diagnosis of collision tumor is not a one-time procedure. These tumors are never diagnosed by cytology or punch biopsy alone, but with a large chunk of cervical tissue and or a hysterectomy specimen (Figures 1-4). Without special or unique clinical features, such tumors are difficult to diagnose preoperatively and pathological identification of the dual components is often the only way to make a correct diagnosis.[8,9]

Recent reports and studies ventured on more sophisticated immunohistochemical and molecular studies to verify diagnosis and or histogenesis.[13,22] Chromogranin, synaptophysin, and CK stains were used to confirm neuroendocrine component of the two cases presented. Furthermore, in the diagnosis of such tumors, it is

Gross Hysterectomy Specimen (Case 3)

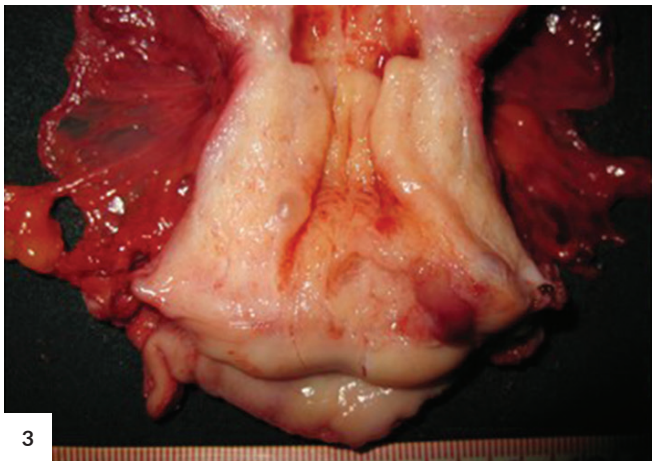


1

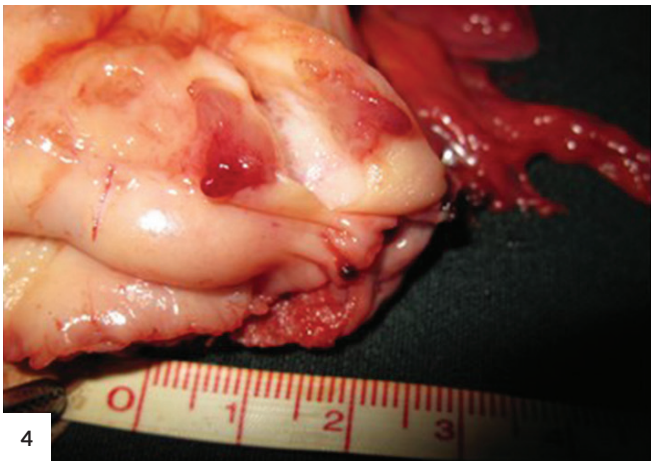


2

Figures 1 and 2. The uterus with smooth serosal surface invasion. The endometrium was smooth. The bilateral parametria and vagina were tumor-free grossly. The rest of the uterus and bilateral adnexae were grossly normal.



3



4

Figures 3 and 4. On cut section, there was a cervical mass at the anterior cervical with less than 1/3 stromal invasion.

important to exclude rare tumors resulting from one cancer metastasizing to one another or just a mere a differentiation of a primary histologic type.[11,21]

SCC and ADC *(Figures 5-8)*

Co-existence of SCC and ADC is the most common reported collision cervical tumor. They arise from a common precursor cell which is the multipotential subcolumnar reserve cell found in the transformation zone.[8,22,23]

ADC and NEC *(Figures 9-16)*

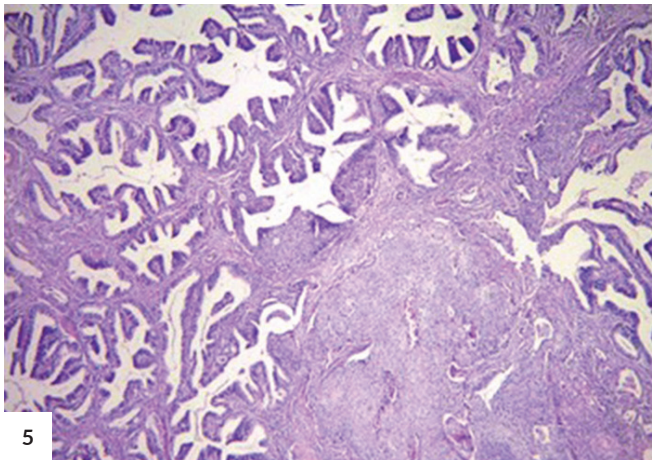
All histologic categories of endocrine tumors mostly occur in pure form but sometimes can also be associated with SCC or ADC.[19] NET co-existing with ADC and neuroendocrine differentiation in cervical carcinomas is unusual. The exact cellular origin of neuroendocrine tumors of the cervix is still unresolved. Argyrophil and argentaffin cells are well described in the female genital tract. These neuroendocrine cells within the normal cervix have been suggested to give rise to neuroendocrine tumors.[24,25]

TREATMENT AND PROGNOSIS

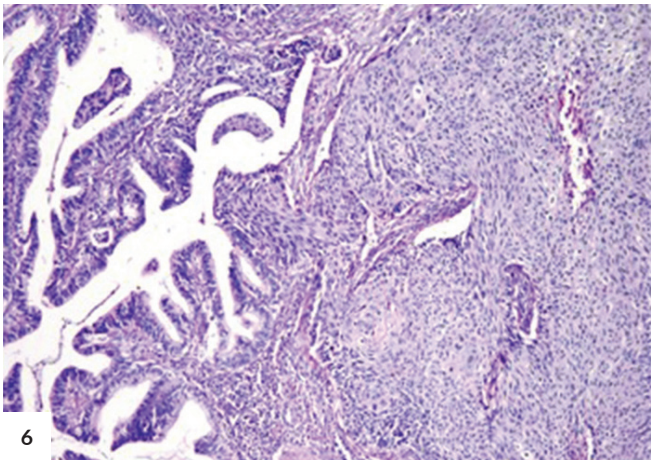
Due to the infrequency of such lesions, the biological behavior of colliding tumors is difficult to ascertain in the context of which component will determine the final outcome in terms of disease free survival. It is debatable whether such outcomes are dependent on either the most predominant component of the collision and/or the more histologically aggressive component of the collision tumor.[9]

Generally, in early stage cervical carcinoma, both the size of the lesion and the depth of stromal invasion affect survival. The lesion diameter is the most prognostic factor in early-stage cervical carcinoma.[26-28] Several authors did not find differences in the 3-year survival rates among patients with ADC or SCC.[29] In contrast, other reports emphasized that occurrence of two tumors is more aggressive than ADC or

Squamous Cell Carcinoma and Adenocarcinoma

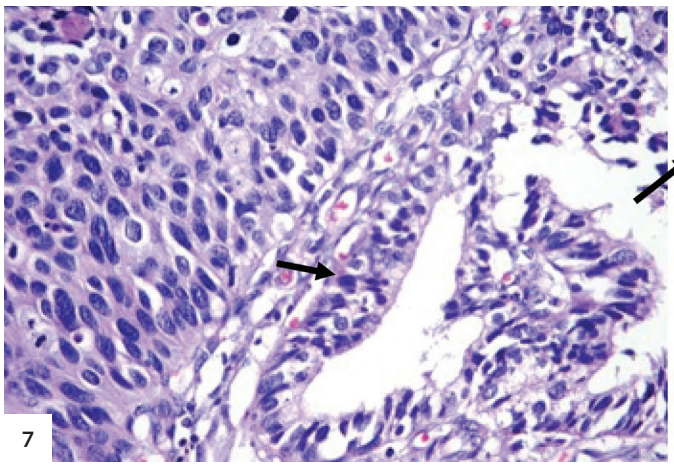


5

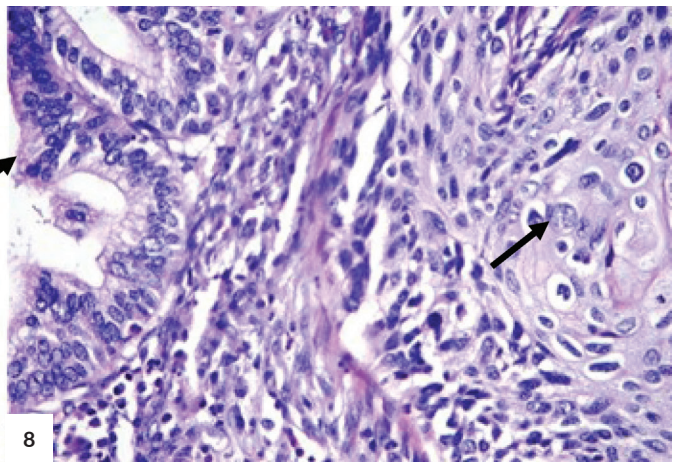


6

Figures 5 and 6. Scanning view (H&E, 40x) and LPO view (H&E, 100x). On scanning view (Figure 5), cut sections of the cervical stroma showed two different histologic types of cancer adjacent to each other. The first is a moderately differentiated adenocarcinoma and the other one is a well-differentiated squamous cell carcinoma.
On low power view (Figure 6), the area with adenocarcinoma is composed of well-formed, tortuous glands. The glands are closely arranged to one another and almost similar to endometrial glands. There is a note of budding of the smaller glands from the larger glands. In the area with squamous cell carcinoma, there are islands of neoplastic squamous cells arranged in tongues or sheets. The contours of the infiltrating nests are irregularly shaped.



7



8

Figures 7 and 8. HPO view (H&E, 400x). On high power view (Figures 7 and 8), the glands are lined by tall columnar epithelium. There is marked cellular nuclear pleomorphism and hyperchromatism. This is a moderately differentiated type due to the nuclear atypia. In the area of the squamous cell carcinoma, there are whorls of squamous epithelium with moderate to abundant eosinophilia and individual keratinization. The squamous cells are arranged in a pavement-like or mosaic pattern. There is no evidence of extracellular keratinization, hence it was signed out as squamous cell carcinoma, large cell, non-keratinizing.

SCC, with frequent lymph node metastasis at diagnosis, and a poor prognosis.[30,31] The poor prognosis can be attributed to high frequency of LVSI, persistence of tumor following preoperative radiotherapy, and metastasis to distant site. These groups of patients had a worse survival rate, mainly because of the higher incidence of uncontrolled local disease.[32]

Surgery was found to be the treatment of choice for patients with stage I cervical cancer as judged by better survival.[29] However, for patients with co-existence of these two histologic types, combined surgery and radiation resulted in higher rates of cure.[31] Similarly, the second case was managed based on the standard clinical practice guideline for early stage cervical cancer.[33] She underwent radical hysterectomy followed by pelvic radiation for the positive LVSI, a tumor size more than 2 cm and coexistence of two tumors.

Adenocarcinoma and Neuroendocrine Carcinoma

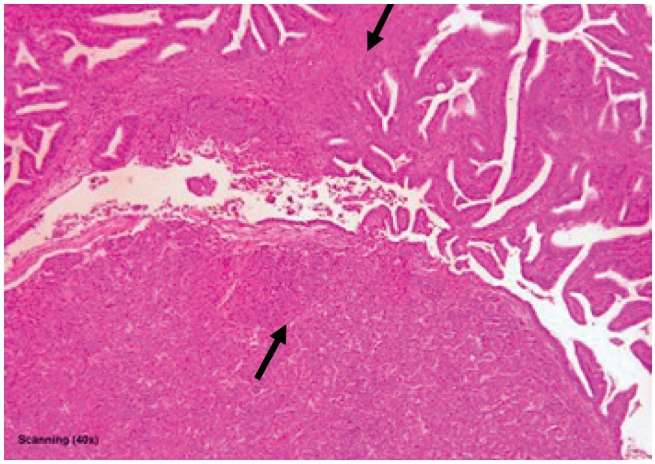


Figure 9. Tumor shows two architectural morphologies. The upper portion shows a glandular differentiation, while the lower portion shows a more solid tumor in sheets (H&E,40x).

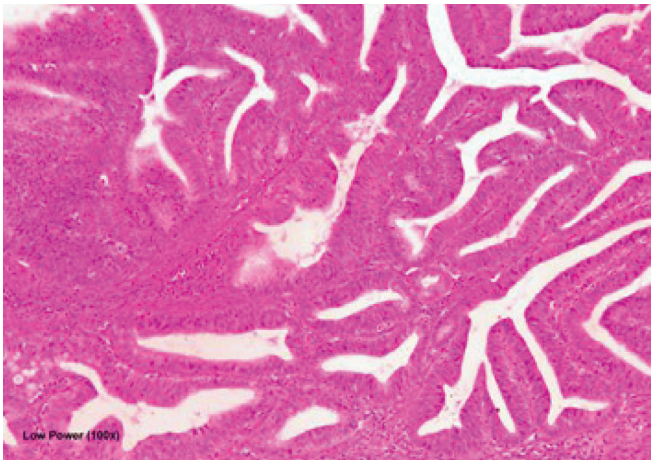


Figure 10. The glandular portion of the tumor, showing papillary fronds with fibrovascular cores. (H&E,100x).

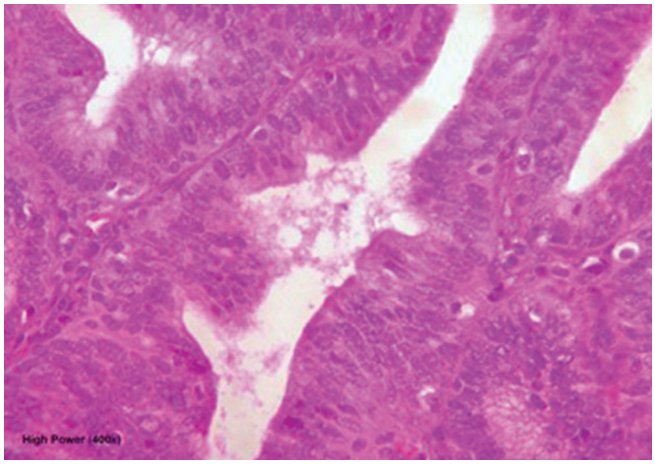


Figure 11. The epithelial cells attached to the fibrovascular core are columnar, with pseudostratification of the nuclei, which are ovoid, hyperchromatic, and with coarse chromatin (H&E,400x)

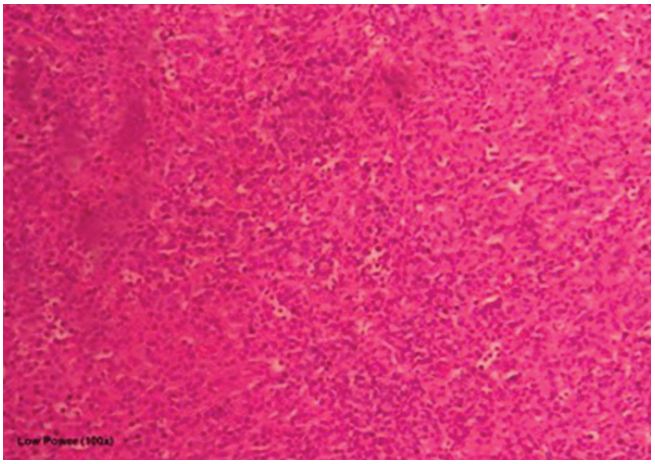


Figure 12. The other portion of the tumor shows a cellular mass in sheets (H&E,100x).

Neuroendocrine carcinoma of the cervix whether as primary, differentiation and/or co-existence demonstrated poor prognosis even in Stage 1 disease. Early adjuvant chemotherapy is therefore advocated in such cases. Pelvic radiation and/or radical hysterectomy usually controls local disease.[34,35] The tendency of this tumor to disseminate via hematogenous and lymphatic routes emphasizes the need for systemic therapy.[24,36-39] Both cases were managed with combination of surgery, radiation and chemotherapy.

Dual tumors and NEC may have a significant effect on survival. Response to treatment showed good outcome despite co-existence of two tumors and/or with poor histologic type probably because 1. All were at early clinical stage and 2. Adjuvant therapy was instituted before and after the surgery.

SUMMARY AND CONCLUSION

Collision tumor of the cervix is a well-established histopathologic entity but diagnosed uncommonly. The diagnosis of collision tumors requires a substantial portion of cervical tissue. Accurate diagnosis may require additional immunohistochemical studies. The relative rarity of this type of tumors in relation to the cervix may be affected by the fact that they are precisely diagnosed with significant tissue sample and early stage cervical cancer which surgery can be applied is diagnosed less often. It has been shown that collision tumors share the same co-factors as those with single histologic type cervical cancer; Likewise, HPV infection is strongly implicated.

Immunohistochemical Studies

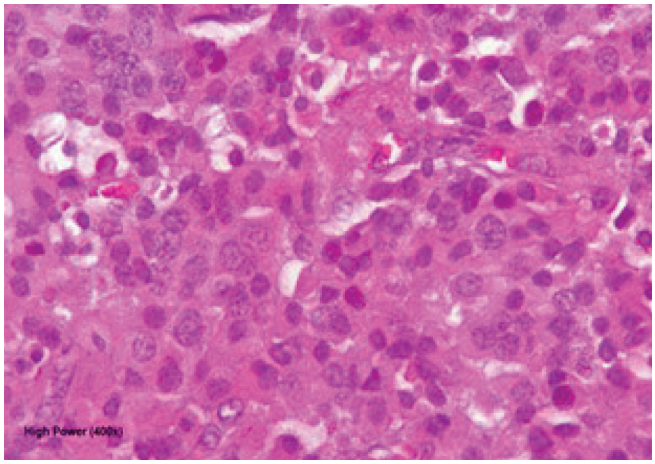


Figure 13. The solid tumor is composed of round cells with moderate eosinophilic cytoplasm. The nuclei are slightly pleomorphic, some of which are small, hyperchromatic, while the others are large with open chromatin pattern (H&E, 400x).

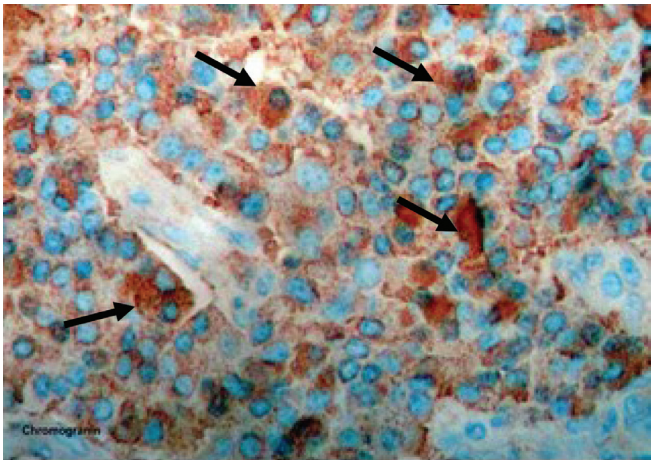


Figure 14. Moderate to strong coarse cytoplasmic staining of the round cells with Chromogranin. This is interpreted as positive.

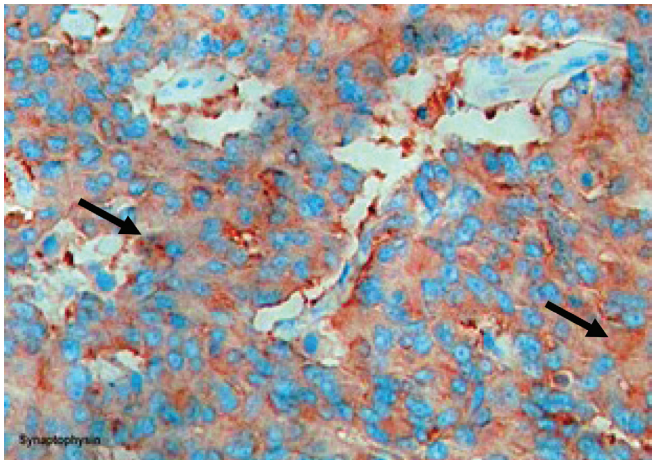


Figure 15. Moderate granular cytoplasmic staining with Synaptophysin. This is interpreted as positive.

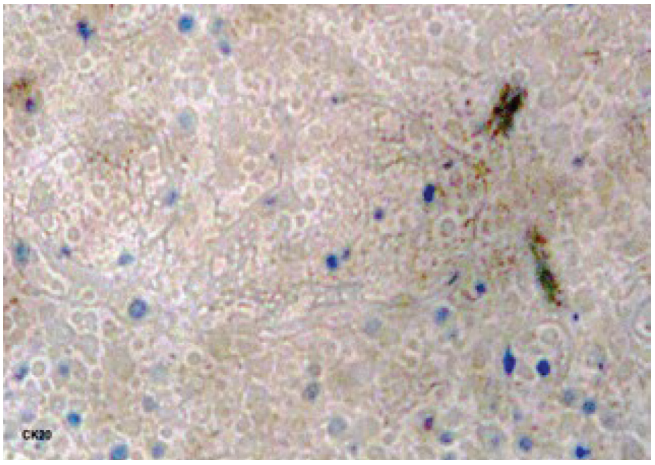


Figure 16. This round cells (solid sheet) portion of the mass was negative for CK20.

In the pathologist point-of view, there may be no significant inference of collision tumors, it only may depict co-existence of two different tumors in one organ. However, when such double lesions occur, they do influence the mode of treatment. The advent of genetic and molecular analysis should shed more light on the histogenesis and eventually lead to development of appropriate and accurate treatment to improve patient survival.

Based on these reports and review of literature, due to poorer prognosis of collision and composite tumors, chemotherapy with concurrent pelvic radiation therapy or systemic chemotherapy is administered in the adjuvant setting after appropriate radical hysterectomy for early stage disease. This multimodal therapy may increase patient survival and possibly cure some patient with early clinical stage despite the tendency for early distant metastasis. Due to its rarity, there is still no standard concept on the treatment, however collection of experience on these rare entities may soon deliver a standard protocol.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

All authors declared no conflict of interest.

Funding Source

No funding.

REFERENCES

1. WHO/ICO Information Center on HPV and Cervical Cancer (HPV Information Center). Summary Report on HPV and cervical cancer statistics in the Philippines, 2007.
2. Domingo E. Clinical Practice Guidelines for the Obstetrician-Gynecologist. Society of Gynecologic Oncologists of the Philippines (Foundation), Inc. 2nd Edition, November 2010.
3. Kurman R, Ellenson L, Ronnett B. Blaustein's Pathology of the Female Genital Tract (6th ed.). doi:10.1007/978-1-4419-0489-8_6.
4. Katz V, Lentz, G, Lobo R. Gershenson, D. Comprehesive Gynecology, 5th Edition. Philadelphia, Mosby-Elsevier, 2007. pp. 743-77.
5. Fu Y, Reagan J. Pathology of the Uterine Cervix, Vagina and Vulva. Saunders Company, 1989. Vol 21:313.
6. Andersson S, Hellstrom AC, Angstrom R, Stendahl U, Auer G, and Wallin KL. The clinicopathologic significance of laminin-5 c 2 chain expression in cervical squamous carcinoma and adenocarcinoma. Int J Gynecol Cancer. 2005;15:1065-72. https://doi.org/10.1111/j.1525-1438.2005.00263.x
7. Beckmann C, Ling F, Barzansky B, Herbert W, Laube D, Smith R. Obstetrics and Gynecoogy, 6th Edition. Philadelphia, Lippinncot Williams & Wilkins, 2010. pp. 375-87.
8. Kersemaekers, F, van de Vijver M, Fleuren G. Comparison of the Genetic Alterations in Two Epithelial Collision Tumors of the Uterine Cervix. A Report of Two Cases. Int J Gynecol Pathol. 2000;19:225-30.
9. Brahmania M, Kanthan C and Kanthan R. Collision tumor of colon-colonic adenocarcinoma and ovarian granulose cell tumor. World J Surg Oncol. 2007;5:118.
10. Kurman, RJ. Blaustein's Pathology of the Female Reproductive Genital Tract. 2002. 5th edition. pp. 325-81.
11. Vyas M, Menon S. Collision tumor of kidney: A cases of renal cell carcinoma with metastasis of prostatic adenocarcinoma. Indian J Med Paediatr Oncol. 2013 Jan-Mar;34(1):21-3.
12. Kraus D. Collision Tumor of the Thyroid. Head Neck. 2004:637-40.
13. Bartley A, Rashid A, Fourbier K, Abraham S. Neuroendocrine and mucinous differentiation in signet ring cell carcinoma of the stomach: evidence for a common cell of origin in composite tumors. Hum Pathol. 2011;42:1420-9.
14. Domingo E, Dy Echo A. Epidemiology, prevention and treatment of cervical cancer in the Philippines. J Gynecol Oncol. 2009;20:11-6.
15. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12-9.
16. Green J, Berrington A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20–44 years: the UK National Case – Control Study of Cervical Cancer. Br J Cancer. 2003;89:2078-86.
17. Yamakawa Y, Forslund O, Teshima H et al. Human Papillomavirus DNA in adenocarcinoma and Adenosquamous Carcinoma of the Uterine Cervix Detected by Polymerase Chain Reaction. Gynecol Oncol. 1994;53:190-5.
18. Grayson W, Taylor L, et al. Detection of human papillomavirus in large cell neuroendocrine carcinoma of the uterine cervix: a study of 12 cases. J Clin Pathol. 2002;55:108-14.
19. Abeler V, Holm R, Nesland J, et al. Small cell carcinoma of the cervix. Cancer. 1994;73:672-7.
20. Eichhorn J, Young R. Neuroendocrine Tumors of the Genital Tract. Am J Clin Pathol. 2001;115:S94-S112.
21. Ueda Y, Miyataki T, Okazawa M, et al. Clonality and HPV Infection Analysis of Concurrent Glandular and Squamous Lesions and Adenosquamous Carcinomas of the Uterine Cervix. Am J Clin Pathol. 2008;130:389-400.
22. Choo YC, Naylor B. Coexistent Squamous Cell Carcinoma and Adenocarcinoma of the Uterine cervix. Gynecol Oncol. 1984;17:168-74.
23. Yajima A, Fukuda M, Noda K, et al. Histopathological Findings Concerning the Morphogenesis of Mixed Carcinoma of the Uterine Cervix. Gynecol Oncol. 1984;18:157-64.
24. Savargaonkar P, Hale R, Mutton A, et al. Neuroendocrine differentiation in cervical carcinoma. J Clin Pathol. 1996;49:139-41.
25. Ichimura H, Sakashita N, Iida T, et al. Differentiation of a Cell Line of Human Cervical Argyrophil Small Cell Carcinoma to Macrophage Lineage Cells. Jpn J Cancer Res. 1999;90:523-9.
26. Behtash N, Nazari Z, Ayatollahi, et al, Neodjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage IB-IIA cervical cancer. EJSO. 2006;32:1226-30.
27. Pagkatipunan M, Limson G, Manalo A. Prognostic factors in the recurrence of Cervical Cancer after Radical Hysterectomy with Bilateral Lymphnode Dissection. Acta Med Philipp. 1993;29(1):18-27.
28. Hoskins P, Swenerton K, Pike J, et al. Small-Cell Carcinoma of the Cervix: Fourteen Years of Experience at a Single Institution Using a Combined-Modality Regimen of Involved-Field Irradiation and Platinum Combination Chemotherapy. Journal of Clinical Oncology. 2003:3495-501.
29. Shingleton H, Bell M, Fremgen A, et al. Is there really a Difference in Survival of Women with Squamous Cell Carcinoma, Adenocarcinoma, and Adenosquamous Cell Carcinoma of the cervix? Cancer. 1995;76(10):1948-55.
30. Bastide K, Ugolin N, Levalois C, et al. Are adenosqouamous lung carcinoma a simple mix of adenocarcinomas and squamous cell carcinoma, or more complex at the molecular level? Lung Cancer. 2010;68:1-9.
31. Huang Y, Wang C, Tsai C, et al. Clinical Behaviors and Outcome for Adenocarcinoma or Adenosquamous carcinoma of Cervix Treated by Radical Hysterectomy and Adjuvant Radiotherapy or Chemoradiotherapy. Int J Radiation Oncol Biol Phys. 2012;84(2);420-7.
32. Hong JH, Tsai CS, Wang CC, et al. Comparison of clinical behaviors and responses to radiation between squamous cell carcinomas and adenocarcinomas/adenosquamous carcinomas of the cervix. Chang Gung Med J. 2000 Jul;23(7):396-404. (Abstract)
33. Domingo E. Society of Gynecologic Oncologists of the Philippines Clinical Practice Guidelines, 6th Edition. 2012. Page 11.
34. Seidel R, Steinfeld A. Carcinoid tumor: Natural History and Implications of Therapy. Gynecol Oncol. 1988;30:114-9.
35. Rehki B, Patil B, Deodhar KK, et al. Spectrum of neuroendocrine carcinomas of the uterine cervix, including histopathologic features, terminology, immunohistochemical profile, and clinical outcomes in a series of 50 cases from a single institution in India. Ann Diagn Pathol. 2013 Feb;17(1):1-9.
36. Lee L, Lee K, Nam J, et al. Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: result of a multi-center retrospective Korean study. Ann Oncol. 2008;19:321-6.
37. O'Hanlan K, Goldberg G, Jones J, et al. Adjuvant Therapy for Neuroendocrine Small Cell Carcinoma of the Cervix: Review of Literature. Gynecol Oncol. 1991;43:167-72.
38. Gardner J, Lagunes DR, Gehrig P. Neuroendocrine tumors of the gynecologic tract: A Society of Gynecologic Oncology clinical document. Gynecol Oncol. 2011;122:190-8.
39. Yoseph B, Chi M, Truskinovsky A, Dudek A. Large-cell neuroendocrine carcinoma of the cervix. Rare Tumors. 2012;4(e18):58-60.