Pathol. Oncol. Res. (2011) 17:149–153
DOI 10.1007/s12253-010-9280-8

# Squamotransitional Cell Carcinoma of the Vagina: Diagnosis and Clinical Management

## A Literature Review Starting from a Rare Case Report

**Tito Silvio Patrelli · Enrico Maria Silini · Roberto Berretta · Elena Thai · Salvatore Gizzo · Alberto Bacchi Modena · Giovanni Battista Nardelli**

Received: 23 March 2010 / Accepted: 18 May 2010 / Published online: 30 May 2010


**Abstract** Primary squamotransitional cell carcinoma (STCC) is rare squamous cell tumor variant resembling transitional cell carcinoma (TCC) of the urinary tract. STCC occurs rarely in the vagina and its clinical and pathological correlates are poorly known. We report a unique case of a 66-year-old Italian woman with STCC of the vagina. A biopsy of the tumor was performed. The tumor qualified as a STCC. Following biopsy, the patient underwent radical hysterectomy (Piver's III-type) with bilateral salpingo-oophorectomy, upper colpectomy, appendicectomy, peritoneal cytology, and lymphadenectomy. The patient is now healthy without evidence of recurrence at 30 months after surgery. Pathologically, cytoarchitectural characteristics distinguish this histotype (STCC) from conventional squamous cell carcinoma of the genital tract. The cytokeratin staining pattern (CK7 positive and CK20 negative), the p63 expression and the positivity for p16ink4a and high-risk HPV are the main elements of differential diagnosis. We suggest that STCC of the vagina should be treated by radical surgery, possibly followed by adjuvant therapy based on staging results and should receive a long-term follow-up.

T. S. Patrelli · R. Berretta · S. Gizzo · A. Bacchi Modena · G. B. Nardelli
Ob/Gyn Clinic, University of Parma,
Parma, Italy

E. M. Silini · E. Thai
Institute of Pathology, University of Parma,
Parma, Italy

T. S. Patrelli (✉)
Dipartimento di Scienze Ginecologiche, Ostetriche e di Neonatologia, U.O. di Ginecologia e Ostetricia,
Via Gramsci, 14,
43100 Parma, Italy
e-mail: titosilvio.patrelli@gmail.com

**Keywords** Squamotransitional cell carcinoma · Transitonal cell carcinoma · HPV-DNA · Immunohistochemistry · Vagina · Cervix · Endometrium · Urogenital tract · Urothelial carcinoma · Squamous carcinoma

## Introduction

It is estimated that in 2009, in the United States alone, 2,160 women will develop squamous cell cancer of the vagina and 770 of them will die from the disease [1]. In 30% of cases, women with vaginal cancer report a previous tumor of the uterine cervix treated surgically no earlier than 5 years before [2–4]. The close correlation between human papillomavirus (HPV) infection and vaginal cancer has been know for several years now [5].

Primary squamotransitional cell carcinoma (STCC) is rare squamous cell tumor variant resembling transitional cell carcinoma (TCC) of the urinary tract. STCC occurs rarely in the vagina and its clinical and pathological correlates are poorly known... It was first described by Rose in 1998 and only five cases have been reported ever since [5–7, 19]. Here we report an additional case and a review of the literature that aims to identify recurrent features and to compare vaginal tumors with the more common cervical variants [7] (Table 1).

## Case History

V.A, a 66-year-old Italian woman (gravida 3, para 2) with natural menopause at age 52, underwent periodic cytologic screening for cervicovaginal cancer prevention. Her Pap smear tests from the years 1998, 2000, 2002 and 2003 were

negative for squamous intrahepithelial lesions (SIL) upon review. About 10 days before coming to our observation, she noticed vaginal bleeding. The gynecologic speculum examination taken upon admission showed a small bleeding mass, about 3 cm in maximum diameter, in the posterior vaginal fornix. The uterine cervix was normal, while the uterine body was slightly enlarged. The parametria and paracolpia were supple. Transvaginal sonography showed an inhomogeneously echoic retroverted/retroflexed uterus with several myomatous nodules, a thickened (6.4 mm) endometrial rim, adnexa with senile involutive ovaries, and no free fluid. The colposcopic and colpocytologic examinations were both negative. Cystoscopy revealed a normal bladder, with view of both ureteral orifices. Proctoscopy showed that the rectal mucosa was macroscopically free from infiltration. A chest X-ray was negative. A computerized tomography (CT) scan and a magnetic resonance imaging (MRI) scan showed no spread of the disease. A biopsy of the tumor was performed. Following biopsy, the patient underwent radical hysterectomy (Piver's III-type) with bilateral salpingo-oophorectomy, upper colpectomy, appendicectomy, peritoneal cytology, and lymphadenectomy. No residual disease was detected on pathological examination. No associated SILs were observed in the cervical or vaginal epithelium. The post-surgical oncology consultation did not indicate the need for adjuvant therapy, but advised close patient follow-up. The patient is now healthy without evidence of recurrence at 30 months after surgery.

## Histopatological Findings

Several whitish fragments were submitted for histology and entirely processed. At microscopy, an exophytic

**Table 1** Clinical features of STCC of the vagina. Our case vs the others previously reported

| | Rose et al. | Vesoulis and Erhardt | Tardio and Salas | | Gao et al. | Present case |
|---|---|---|---|---|---|---|
| | | | 1st case | 2nd case | | |
| Age | 82 | | 78 | 67 | 68 | 66 |
| Clinical features: | | | | | | |
| - Pap smear test | ? | Positive | ? | ? | Positive | Negative |
| - Vaginal bleeding | Yes | No | Yes | Yes | No | Yes |
| Reported history of transitional cell carcinoma of the urinary tract | No | No | No | No | No | No |
| Diameter | 40 mm | Not reported | 8 mm | 10 mm (1st)<br>6 mm (2nd) | 70 mm (approx.) | 30 mm |
| Location | Anterior | Anterior<br>Posterior | Left | Introitus (1st)<br>Right (2nd) | Posterior | Posterior |
| Cystoscopy | Urethral involvement | Not reported | Negative | Negative | Negative | Negative |
| Proctoscopy | Not performed | Not reported | Not performed | Not performed | Negative | Negative |
| CT scan | Negative | Not reported | Negative | Negative | Negative | Negative |
| X-ray | Negative | Not reported | Negative | Negative | Negative | Negative |
| Previous hysterectomy + salpingo-oophorectomy | Yes<br>Cervical dysplasia | Yes<br>Microinvasive cervicovaginal squamous cell carcinoma | Yes<br>Invasive cervical carcinoma | Yes<br>(Cause not known) | Yes<br>Uterine leiomyoma | No |
| Radiation therapy | | Not reported | | | | |
| - external | Yes | | Yes | No | Yes | No |
| - intracavitary | Yes | | No | No | No | No |
| Chemotherapy (5-fluorouracil) | No | Not reported | No | Yes | No | No |
| Surgical treatment | No | Yes | No | Yes[a] | No | Yes[b] |
| Follow-up | 13 months: disease free | Not reported | 18 months: disease free | 18 months: disease free | Not reported | 24 months: disease free |

[a] Total vaginectomy

[b] Radical hysterectomy (Piver's III-type) with bilateral salpingo-oophorectomy, upper colpectomy, appendectomy, peritoneal cytology, and lymphadenectomy

multilayered epithelial proliferation of polygonal cells with transitional features was observed. The lesion showed a solid and inverted papillary growth pattern with prominent fibrovascular cores. The cells were monomorphic, with a high nuclear/cytoplasmatic ratio, oval nuclei with grooves, hyperchromasia, and frequent mitotic figures (Fig. 1a, b). In limited areas, the tumor showed abortive squamous differentiation (Fig. 1c). At the base of the lesion, confluent growth in interlacing strands was observed associated to a desmoplastic stromal reaction that was consistent with invasion. Immunohistochemistry was performed on formalin-fixed paraffin-embedded sections of the lesion, showing strong labeling for high- and low-molecular-weight cytokeratins, cytokeratin 7 (CK7) and p63. Staining for cytokeratin 20 (CK20) was negative. The tumor also showed strong and diffuse expression of p16ink4a (mouse monoclonal E6H4®, MTM Laboratories AG, Heidelberg, Germany) (Fig. 1d).

HPV detection and typing were performed on DNA extracted from formalin-fixed paraffin-embedded tissue using the INNO-LiPA HPV genotyping assay, version V2 (Innogenetics N.V., Ghent, Belgium) according to the manufacturer's instructions [8]. The current version of the assay allows the simultaneous and separate detection of 15 high-risk and 10 low-risk HPV types. The tumor was positive for HPV 35.

The tumor qualified as a papillary squamotransitional cell carcinoma with predominant transitional features [9].

## Discussion

Squamotransitional cell carcinomas (STCC) of the uterine cervix and endometrium were described as early as 1986 by Randall et al. and later by Alboress-Savedra and Young [12] and Koenig et al. [9]. These tumors differen-

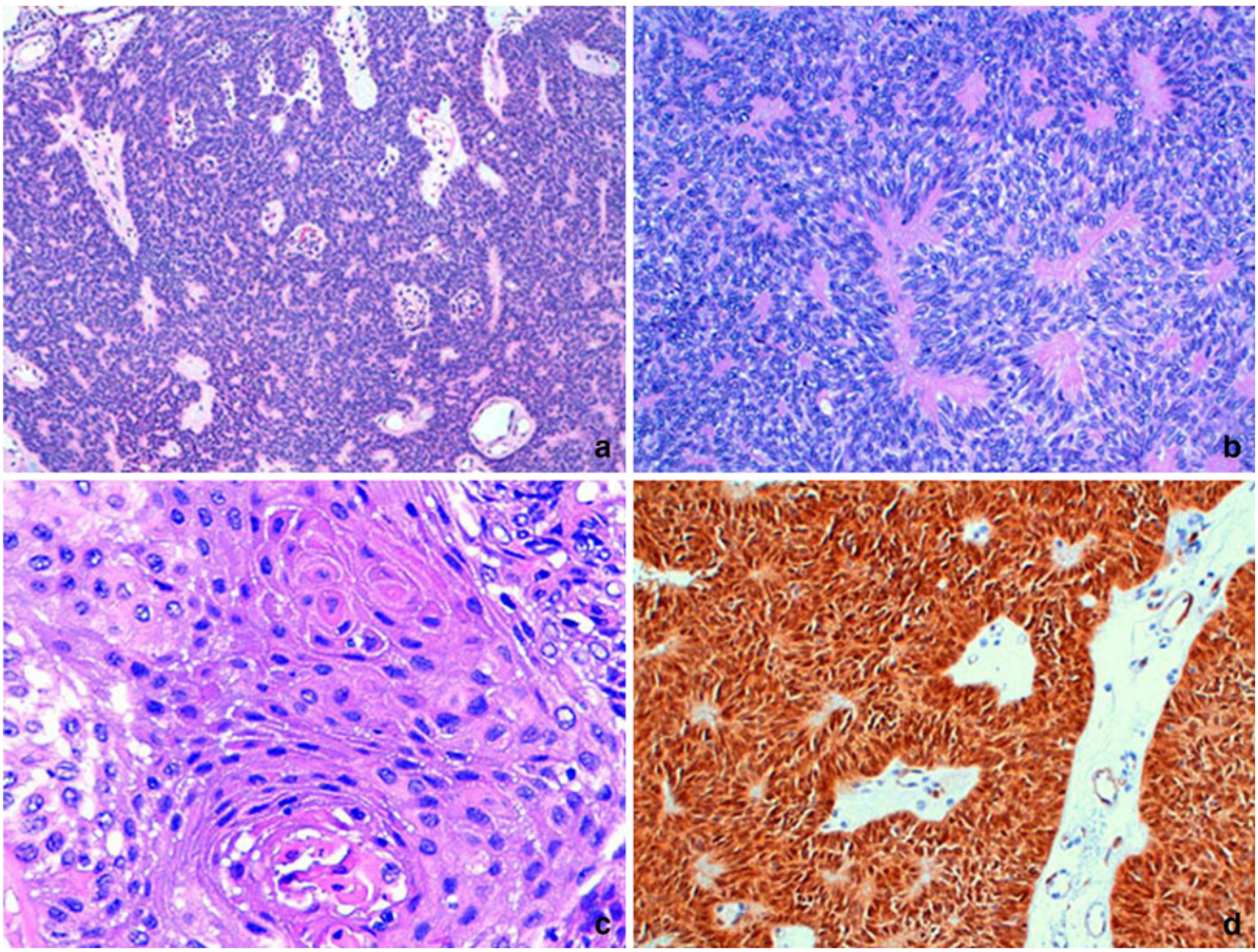


**Fig. 1** **a** Inverted papillary architecture with prominent fibrovascular cores (H&E, ×10); **b** transitional cell component characterized by uniform oval nuclei with longitudinal grooves and basal palizading (H&E, ×20); **c** squamous cell component featuring larger eosinophilic cytoplasms and abortive squamous pearls (H&E, ×40); **d** p16ink4a immunostaining showing strong and diffuse nuclear and cytoplasmic labelling (3,3′diaminobenzidine, ×20)

**Table 2** Pathological features of STCC of the vagina.Our case vs the others previously reported

| | Rose et al. [5] | Vesoulis and Erhardt [6] | Tardio and Salas [19] | | Gao et al. [7] | Present case |
|---|---|---|---|---|---|---|
| | | | 1st case | 2nd case | | |
| Histology | STC differentiation (predominance of the former) | STC differentiation | STC differentiation | STC differentiation | STC differentiation (predominance of the latter) | STC differentiation (predominance of the latter) |
| CK7 | Positive | Negative | Positive | Positive | Positive | Positive |
| CK20 | Negative | Negative | Negative | Negative | Negative | Negative |
| p63 | Not tested | Not tested | Not tested | Not tested | Positive | Positive |
| HPV DNA (16) | Positive | Positive | Not tested | Not tested | Not tested | Positive |
| p16inkaa immunostaining | Not tested | Not tested | Not tested | Not tested | Not tested | Positive |

tiate from benign papillary squamous tumors and from verrucous carcinoma for their papillary architecture and their resemblance to urinary tract tumors [5, 9, 12]. The urothelial differentiation of STCCs has been correlated by some authors to the common embryonic origin of the urogenital tract [22].

STCC of the uterine cervix is an established tumor variant and "subtypes" have been tentatively categorized by researchers in a number of studies [9–12]. In 1997, Koenig et al. [9] reported a series of 32 STCCs of the cervix and proposed a classification based on morphology into three groups: squamous cell carcinoma (SCC), mixed squamous and transitional (squamotransitional) cell carcinoma (STCC), and transitional cell carcinoma (TCC) [9] (Tables 2 and 3). This subdivision in tumor subtyes was aimed to differentiate into prognostic groups and the authors reported different treatments in their series (radical surgery vs non-radical surgery vs medical therapy). However, there is lack of consensus on the principles informing this classification as all tumor subtypes have a potential for late recurrence and metastasis.

Papillary carcinomas of the vagina have also been reported—albeit in a very limited number of cases—that were histologically characterized by the presence of transitional cells, either alone or with squamous differentiation, according to Koenig's classification into TCC [15–18] and STCC [5–7, 19], respectively. Primary STCC of the vagina has been characterized so far only in five cases. This histologic variant should be suspected in all cases of papillary tumors of the vagina, not only in women with a cytologic diagnosis of high-grade SIL and cervical HPV DNA positivity, but also—as in our case—in women with negative cervical screening.

Cytoarchitectural characteristics distinguish this histotype from conventional squamous cell carcinoma of the genital tract [5, 7, 9, 10]. The cytokeratin staining pattern (CK7 positive and CK20 negative) [7], the p63 expression [13] and the positivity for p16ink4a and high-risk HPV [9, 14] are the main elements of differential diagnosis with a metastasis of a urinary TCC [20, 21]. The latter is made up exclusively of transitional cells with no squamous differentiation, that express both CK7 and CK20 and usually

**Table 3** Features of transitional vs squamotransitional cell carcinoma of the vagina [23]

| | TCC of the vagina | STCC of the vagina |
|---|---|---|
| Reported cases in the literature | 6 | 5 + present case |
| Immunohistochemistry | CK7+ [22] | CK7+[a] |
| | CK20+ [22] | CK20−[a] |
| Cytology | Pure transitional cell morphology | Polygonal cells with transitional features and limited areas with cells showing abortive squamous differentiation |
| Association with transitional cell carcinoma of the urinary tract | Yes (Multicentric papillary transitional cell carcinoma of the urogenital tract [5]) | No |
| High risk HPV-DNA | Negative | Positive |
| p16inkaa immunostaining | Negative | Positive |
| Prognosis | Favorable<br>Non-invasive, non-metastatic | Suspected to be unfavorable |

[a] Only one case: CK7- and CK20- [6]

associates with a past medical history of multicentric TCC of the urinary tract, and a favorable prognosis [23].

In three cases of vaginal STCCs—including the present case—the HPV DNA status was known and in all it was positive for high-risk genital types. This is a major pathogenetic difference from urothelial tumors that also represents a useful element in differential diagnosis. Integrated HPV 16 was also observed by in situ hydridization in some STCC of the cervix [9, 24]. Finally, p16ink4a immunostaining is an useful surrogate marker for the presence of oncogenic proteins of high-risk HPVs. Overall, these arguments support the notion that vaginal tumors are indeed variants of STCC, rather than primary or secondary forms of urothelial carcinoma [5, 9, 16, 17].

Based on the virological and pathological findings, we believe that therapeutic counseling for STCC of the vagina is comparable to that for the cervical forms already described by Koenig [9]. Considering the potential for late recurrence and metastasis and the lack of clinical experience, we suggest that STCC of the vagina should be treated by radical surgery, possibly followed by adjuvant therapy based on staging results and should receive a long-term follow-up.

## References


1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59(4):225–249
2. Peters WA III, Kuman NB, Morley GW (1985) Carcinoma of the vagina. Cancer 55:892–897
3. Rubin SC, Young J, Mikuta JJ (1985) Squamous carcinoma of the vagina: treatment, complications, and long term follow-up. Gynecol Oncol 20:346–353
4. Benedet JL, Murphy KJ, Fairey RN, Boyes DA (1983) Primary invasive carcinoma of the vagina. Obstet Gynecol 62:715–719
5. Rose PG, Stoler MH, Abdul-Karim FW (1998) Papillary squamotransitional cell carcinoma of the vagina. Int J Gynecol Pathol 17:372–375
6. Vesoulis Z, Erhardt CA (2001) Cytologic diagnosis of vaginal papillary squamotransitional cell carcinoma. A case report. Acta Cytol 45:465–469
7. Gao Z, Bhuiya T, Falkowski O (2005) Papillary squamotransitional cell carcinoma of the vagina: a case report and review of literature. J Obstet Gynaecol 25:94–96
8. Kleter B, van Doorn LJ, Schrauwen L, Molijn A, Sastrowijoto S, ter Schegget J, Lindeman J, ter Harmsel B, Burger M, Quint W (1999) Development and clinical evaluation of a highly sensitive PCR-reverse hybridization line probe assay for detection and identification of anogenital human papillomavirus. J Clin Microbiol 37:2508–2517
9. Koenig C, Turnicky RP, Kankam CF, Tavassoli FA (1997) Papillary squamotransitional cell carcinoma of the cervix: a report of 32 cases. Am J Surg Pathol 21:915–921
10. Randall ME, Andersen WA, Mills SE, Kim JA (1986) Papillary squamous cell carcinoma of the uterine cervix: a clinicopathologic study of nine cases. Int J Gynecol Pathol 5:1–10
11. Urist MJ, Di Como CJ, Lu ML, Charytonowicz E, Verbel D, Crum CP, Ince TA, McKeon FD, Cordon-Cardo C (2002) Loss of p63 expression is associated with tumor progression in bladder cancer. Am J Pathol 161:1199–1206
12. Lininger RA, Wistuba I, Gazdar A, Koenig C, Tavassoli FA, Albores-Saavedra J (1998) Human papillomavirus type 16 is detected in transitional cell carcinomas and squamotransitional cell carcinomas of the cervix and endometrium. Cancer 83:521–527
13. Robert ME, Fu YS (1990) Papillary squamous cell carcinoma of the uterine cervix—a review with emphasis on prognostic factors and unusual variants. Semin Diagn Pathol 7:173–189
14. Qizilbash AH (1974) Papillary squamous tumors of the uterine cervix: a clinical and pathologic study of 21 cases. Am J Clin Pathol 61:508–520
15. Bass PS, Birch B, Smart C, Theaker JM, Wells M (1994) Low-grade transitional cell carcinoma of the vagina—an unusual cause of vaginal bleeding. Histopathology 24(6):581–583
16. Fetissof F, Haillot O, Lanson Y, Arbeille B, Lansac J (1990) Papillary tumour of the vagina resembling transitional cell carcinoma. Pathol Res Pract 186(3):358–364
17. Jendresen MB, Kvist E, Glenthøj A (1997) Papillary transitional cell tumour in the vagina. Scand J Urol Nephrol 31 (1):107–108
18. Singer G, Hohl MK, Hering F, Anabitarte M (1998) Transitional cell carcinoma of the vagina with pagetoid spread pattern. Hum Pathol 29(3):299–301
19. Tardío JC, Salas C (2001) Vaginal papillary carcinomas with transitional cell differentiation: a morphological variant of squamous cell carcinoma? Histopathology 39(4):436–438
20. Mondaini N, Giubilei G, Raspollini MR, Crisci A, Orlando V (2005) Recurrence of vaginal implantation of transitional cell carcinoma of the urinary tract. Gynecol Oncol 97 (2):669–670
21. Hermanova M, Vitezslav V, Husicka R, Neumanova R, Pacik D (2008) Multicentric transitional cell carcinoma of the vagina and the ureter. Ann Diagn Pathol 12(5):365–367
22. Labonte S, Tetu B, Boucher D, Larue H (2001) Transitional cell carcinoma of the endometrium associated with a benign ovarian Brenner tumor: a case report. Hum Pathol 32:230–232
23. Ordonez NG (2000) Transitional cell carcinomas of the ovary and bladder are immunophenotypically different. Histophatology 36:433–438
24. Ollayos CW, Lichy J, Duncan BW, Ali IS (1996) Papillary squamous carcinoma of the uterine cervix: report of case with HPV 16 DNA and brief review. Gynecol Oncol 63:388–391