

Two Unusual Primary Carcinomas of the Glans Penis: Mucoepidermoid Carcinoma and Adenosquamous Carcinoma

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Abstract : Two cases of rare histologic subtypes of carcinomas involving glans penis are reported. Both contained two distinct cellular differentiation, squamous cells and mucin-producing cells. The first case was a 34-year-old Thai male with chronic ulcer at penis, showing predominant squamous cell carcinoma with interspersed small sheets of mucin-producing cells without discrete glandular structure, thus designated as "muco-epidermoid carcinoma". The involved inguinal lymph node revealed both squamous and mucin-producing cells.

Another case is a 39-year-old Thai male with penile ulcer, histologically proved to be carcinoma mainly constituted by malignant squamous part and focal glandular differentiation. The glands lined by columnar cells contained intraluminal and intracellular mucin. The bilateral sentinel lymph nodes were negative for malignancy.

The immunoperoxidase staining for carcinoembryonic antigen was positively marked with mucin-producing cells in both cases. In addition, transmission electron microscopic study of mucoepidermoid carcinoma identified three populations of cells, namely squamous cells with tonofilament, mucin-producing cells with microvilli, and lastly intermediate cells bearing dual differentiation.

These unusual carcinomas of glans penis are extremely rare conditions of unknown origin with a poorly defined prognosis. Discussion and review literature on the histologic definition and origin of these tumors are included.

เรื่องย่อ : มะเร็งที่ glans penis ชนิด mucoepidermoid carcinoma และชนิด adenosquamous carcinoma รายงานผู้ป่วย 2 ราย

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รายงานผู้ป่วยมะเร็งที่ glans penis จำนวน 2 ราย ชนิด mucoepidermoid carcinoma ในผู้ป่วยชายอายุ 34 ปี และชนิด adenosquamous carcinoma ในผู้ป่วยชายอายุ 39 ปี ซึ่งผู้ป่วยทั้งสอง มาพบแพทย์ด้วยแผลเรื้อรังที่ปลายอวัยวะเพศ

การตรวจชิ้นเนื้อของผู้ป่วยทั้งสองพบว่าเซลล์มะเร็ง มีการเปลี่ยนแปลงชนิดสแควมัส (squamous differentiation) ร่วมกับการสร้างสารคัดหลั่งชนิดมูก (mucin production) การพบลักษณะการเรียงตัว และการสร้างสารคัดหลั่งชนิดมูกในปริมาณที่ต่างกัน, การติดสีย้อม mucicarmine ในเซลล์มะเร็ง และผลการตรวจทางอิมมูโนวิทยาของเซลล์มะเร็งชนิด carcino-embryonic antigen ในเชิงบวก สนับสนุนการวินิจฉัยโรคดังกล่าว และการตรวจทางกล้องจุลทรรศน์อิเล็กตรอนชนิดทรานสมิชชันได้ยืนยันลักษณะ squamous differentiation และ mucin production

มะเร็งที่ปลายอวัยวะเพศชายส่วนใหญ่เป็นชนิด squamous cell ในขณะที่การรายงานมะเร็งชนิด mucoepidermoid carcinoma มีเพียง 1 ราย และ adenosquamous carcinoma มีเพียง 6 ราย (ไม่รวมผู้ป่วย 2 รายนี้) รายงานฉบับนี้จึงได้รวบรวมข้อมูลจากรายงานผู้ป่วยฉบับอื่นเพื่อการวินิจฉัย และอภิปรายต้นกำเนิดของมะเร็งดังกล่าว

BACKGROUND

The incidence of malignant neoplasms of the penis is approximately 1 in 100,000 or less than 0.5% of all male neoplasms in Western countries.¹ In Thailand, where circumcision is not widely exercised, the penile carcinomas represent between 0.9% and 2.3% of male neoplasms.² AFIP had proposed classification for primary penile carcinomas in 1998, categorizing malignant epithelial carcinoma of the penis into several categories: squamous cell carcinoma, adenosquamous carcinoma, mixed carcinoma, basal cell carcinoma, Paget's disease and other rare pure primary carcinomas.³ Penile carcinomas are almost always of squamous cell carcinoma variety. The most commonly involved site is the glans penis.

To date, there have been 6 cases of adenosquamous carcinoma reported, 3 by Cubilla et al⁴, 1 by van Savage and Carson⁵, 1 by Masera et al⁶ and the last by Jamieson⁷. A single case of mucoepidermoid carcinoma reported in 2000 by Layfield and Liu⁸ was claimed to deserve separate entity according to different histologic features and more aggressive behavior by early regional lymph node metastasis.

MATERIALS AND METHODS

Primary carcinomas of the penis, limited to penectomy specimens, on file in the Department of Pathology of Siriraj Hospital during the period between 1998 and 2003 were histologically reviewed. Of the 46 cases, two were selected for the presence of mucin-producing cells with malignant features. Further studies were carried out using the formalin-fixed paraffin blocks. Recut slides were stained with mucicarmine and immunohistochemical staining using the avidin-biotin-peroxidase complex (ABC) method. Positive staining with mucicarmine and monoclonal anti-CEA antibody favored glandular differentiation. In addition, the tissue from Case 1 was submitted for transmission electron microscopic examination. Clinical information, including follow-up, were obtained from medical records.

Case 1

A 31-year-old Thai male with congenital phimosis presented with a year long chronic ulcer of the glans penis. Circumcision was done 6 months before presentation. The pathologic findings of prepuce reported hyperkeratosis and chronic inflammation. The ulcerative growth doubled in size in one

month. Physical examination revealed 2.5 cm ulcerative growth on the glans penis with palpable bilateral inguinal lymph nodes.

The partial penectomy specimen with right inguinal node excision was performed 2 months after presentation. A 4 cm-long distal part of penis displayed a 3.2x3 cm diameter, 0.6 cm deep, dry, gray, ulcerative lesion involving the entire surface of the glans penis, including the periurethral area. The lymph nodes submitted measured 2 cm at their greatest dimension.

The tumor mainly comprised moderately differentiated squamous cell carcinoma. About 25% of the remaining neoplastic cells were found to be arranged in sheets or singly intermingled in squamous islands (Figure 1), exhibiting abundant eosinophilic, clear to basophilic granular cytoplasm with a sharp cytoplasmic border (Figure 2). There was no evidence of discrete glandular structure. The eosinophilic cells contained large vesicular nuclei with prominent nucleolus, while the clear to basophilic cells displayed eccentric nucleus with fine hyperchromatin. The mitotic count was 15/10 hpf. These granular cytoplasmic cells were positively stained with mucicarmine and marked with CEA (Figure 3). The mucin-producing cells were commonly found in the infiltrative strands and at the tip of the glans near the external urethral meatus. The urethral mucosa, submucosal gland, corpus cavernosus spongiosus and resection margin were free of tumors. No vascular invasion was observed, however, an inguinal lymph node was involved by malignant cells with those squamous and mucin-producing cells.

Transmission electron microscopic study identified three populations of cells, namely squamous cells with tonofilament (Figure 4), mucin-producing cells with microvilli (Figure 5), and intermediate cells bearing dual differentiation (Figure 6). The intermediate cells contained both tonofilament and microvilli.

The patient appeared well during his three months post-operative check up. The chest X-ray was unremarkable. A whole abdomen CT scan revealed no evidence of distance metastasis and no intraabdominal lymphadenopathy.

Case 2

A 39-year-old Thai male complained of one month rapidly growing verrucous mass with bleeding and exudate on the glans penis. The bilateral inguinal lymph nodes were not palpable. Two years prior to this presentation, he underwent circumcision due to phimosis and balanitis. The balanitis remained as a few erosive, crusted, erythematous patches. Skin biopsy of the glans penis was reported as Zoon's balanitis.

A partial penectomy specimen contained a 3x3 cm diameter, 0.8 cm deep, light brown infiltrative growth involving the entire surface of the glans penis. The penile urethra and resected margins were free of tumors.

Microscopic evaluation identified a focal glandular differentiation (an area of one or two layers of cuboidal cells aligned with the lumen or arranged in cribriform pattern) (Figure 7). The remaining 95% of the tumor mass was composed of well differentiated squamous cell carcinoma (Figure 8). The glandular cells had homogeneous eosinophilic to clear cytoplasm with round to oval basally located nuclei. These cells contained vesicular chromatin and prominent nucleoli. The mitotic index was 6/10 hpf. The glandular formation was located on the surface of the glans, away from meatus. The tumor was confined to the epidermis and lamina propria. The histochemical staining for mucicarmine of the glandular epithelium was positive both intracellularly and intraluminally (Figure 9A). The immunoperoxidase staining for CEA positively marked these cells (Figure 9B). Bilateral sentinel lymph nodes measuring up to 1.5 cm in diameter were all negative for malignancy. The patient remained free of tumors after 12 months of follow-up.

DISCUSSION

Two cases of unusual penile carcinoma exhibited both squamous part and mucin-producing part. They differ in cellular arrangement and lymph node involvement, and thus deserve separate designations.

Case 1 displayed malignant squamous cells admixed with the mucin-producing cells without glandular formation. The early regional lymph node

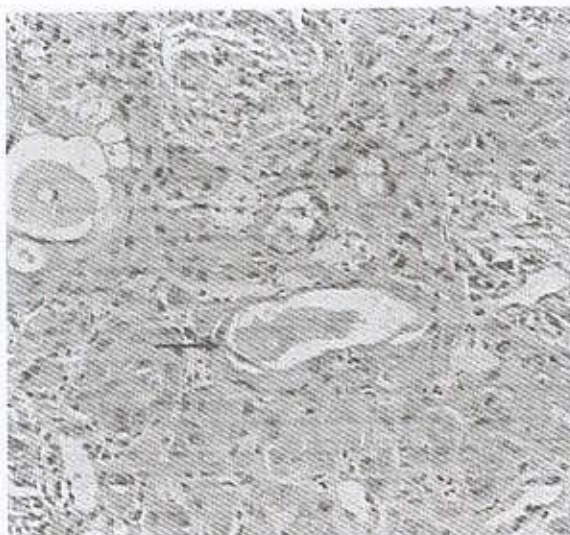


Figure 1. Light microscopic picture from case 1 demonstrating the sheet of squamous cells intermixed with the mucin-producing cells.

Islands of moderately differentiated squamous cell carcinoma (arrow) gradually merge with groups of malignant mucin producing cells (arrow head). H&E x200

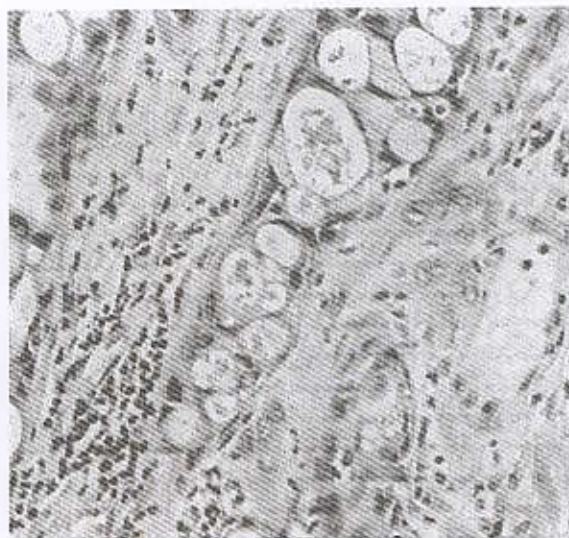


Figure 2. Demonstrating the mucin producing cells. The clear to basophilic mucin producing cells display eccentric nuclei with fine hyperchromatin. The cytoplasm is clear to basophilic with sharply defined border. There is no definite gland formation. H&E x400

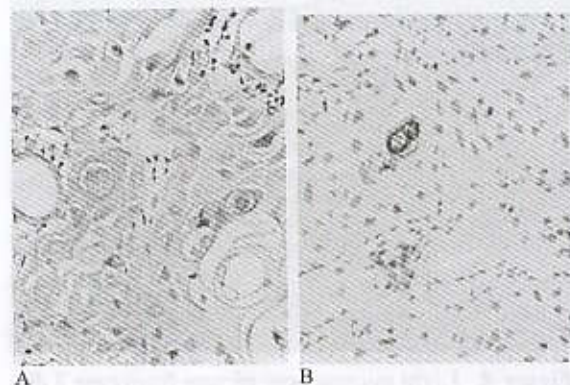


Figure 3. A: The intracytoplasmic mucin is demonstrated by Mucicarmine. B: These cells also mark with Anti-Carcinoembryonic Antigen Antibody. x 400



Figure 4. Showing a malignant squamous cell containing numerous tonofilaments (T) and desmosome (rectangled). x7,700

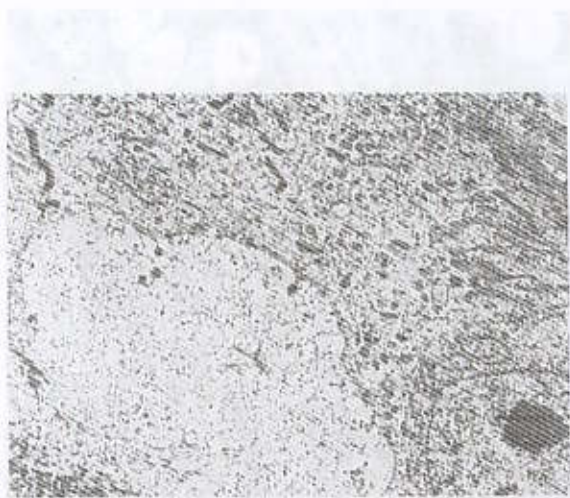


Figure 5. The mucin producing cell displaying microvilli (rectangled). x9,240

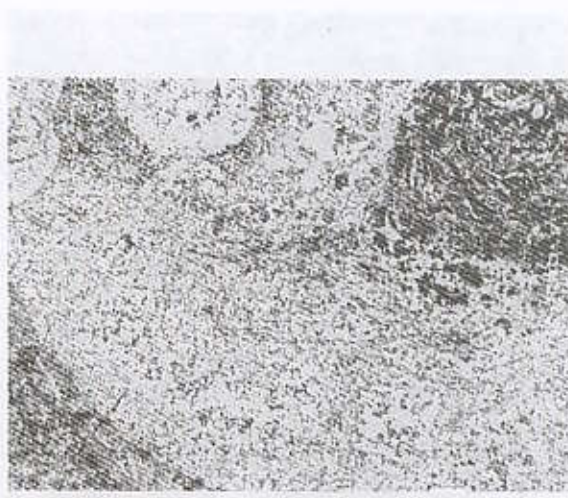


Figure 6. Transmission electron microscope picture showing an intermediate cell which contains both tonofilament (T) and microvilli (rectangled). x6,160

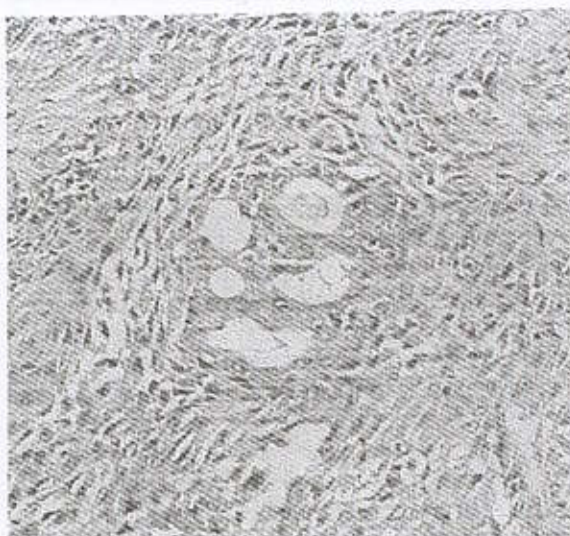


Figure 7. Discrete glands lined by tall columnar cells with definite lumen formation. H&E x200

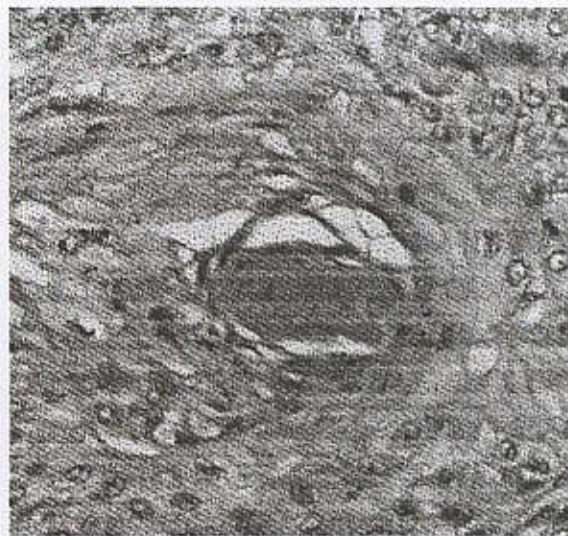


Figure 8. Light microscopic picture from case 2 displaying well differentiated squamous cell carcinoma. H&E x200

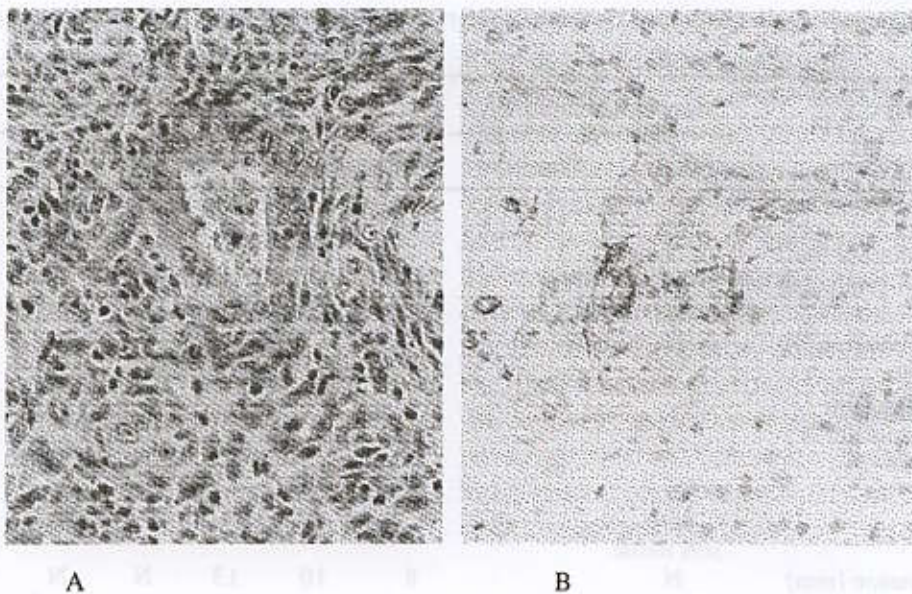


Figure 9. A: The glandular cells were positively stained with mucicarmine.
B: They marked with anti-Carcinoembryonic Antigen antibody (right). x200

involvement suggested aggressive behavior. Hence, it was diagnosed as mucoepidermoid carcinoma. Furthermore, the presence of three cellular components, namely squamous cells, mucin producing cells and intermediate cells confirmed by ultrastructural identification, fulfill the definition of this tumor type.

Mucoepidermoid carcinoma, originally described as a separate entity by Steward et al in 1945, consists of a variable combination of mucus-secreting cells, squamous cells, and so-called intermediate cells. It is the most common carcinoma of the salivary gland⁹. Other primary locations include bronchial glands, larynx, breast, pancreas, hepatobiliary tract, thymus, thyroid, conjunctiva and cervix. The first mucoepidermoid carcinoma of the penis with appearance reminiscing the mucoepidermoid carcinoma of cervix, was reported by Layfield and Liu in 2000.⁸ It was claimed to have more aggressive behavior with early lymph node metastasis (Table 1).

Case 2 consisted of malignant squamous cells and malignant mucin-producing cells with discrete glandular formation. The regional lymph nodes were found negative for tumors and favored less aggressiveness. Thus diagnosis was adenosquamous carcinoma. According to the histologic description,

adenosquamous carcinoma of the penis was composed of dominant squamous part with focal glandular part, usually in discrete manner.⁴ Only 6 cases of adenosquamous carcinoma have been reported (Table 1). The squamous components usually show predominantly glandular part. Both components are discrete, with exceptionally rare admixtures present. Frequent glandular portion commonly presents just below the squamous epithelium at the perimeatus. The squamous may be warty and deeply invasive (usual type). The glands are lined by cuboidal or cylindrical epitheliums have intraluminal and intracellular mucin and are immunologically positive for carcinoembryonic antigen.

The origin of these mucin-producing cells is under debate. Histologically, the glans penis is covered by non-keratinizing stratified squamous epithelium in the circumcised man and keratinizing stratified squamous epithelium in the uncircumcised man. There is no adnexal or glandular structure in the glans penis.¹⁰ Therefore, the mucoepidermoid carcinoma and adenosquamous carcinoma are very unlikely to occur in the glans penis. The postulation concerning the origin of these carcinoma with secretory capacity were 1) the embryologically misplaced mucus-producing cells of the glans epithelium,

Table 1. Clinicopathologic features of two mucoepidermoid carcinomas and seven adenosquamous carcinomas.

	Mucoepidermoid CA		Adenosquamous CA						
	Lay	War	Cub1	Cub2	Cub3	Mas	Jam	Van	War
Age	55	31	74	72	37	30	50	54	39
Duration of disease (mo)	N	3	72	9	6	5	N	≅12	1
Site of mucin-producing cell	P	P	P	P	G	G	G	G	G
Size (cm)	N	3.2	6.5	6.5	10	1	N	3.4	3
Anatomical invasion	N								
Lamina propria		+	+	+	+	+	N	+	+
Corpus spongiosum		-	+	+	+	+	N	+	-
Corpus cavernosum		-	-	+	-	N	N	+	-
Buck's fascia		-	-	-	+	N	N	N	-
Dartos		-	-	-	+	N	N	N	-
Others	deep soft tissue								
Depth of invasion (mm)	N	6	8	10	13	N	N	N	8
Squamous grading	well to mod	mod	poor	warty	warty	poor	mod	mod	well
Mitosis (10 hpf)	N	15	40	24	14	N	N	N	6
Lymph node	+	+	NR	NR	+	+	-	+	-
Follow-up: NED (mo)	N	3	12	lost	102	died	5	12	12

N = not available; P = perimeatal; G = glans; NR = not removed

especially in the perimeatal region (as in Case 1), 2) elusive pluripotent stem or reserved cell like that in salivary gland, and 3) the aberrance of malignant squamous cells (as for Case 2, where malignant glandular cells were situated away from perimeatal area).³

The term mucoepidermoid carcinoma and adenosquamous carcinoma occasionally are used synonymously in organs such as the lung, the pancreas and the small intestine. Meanwhile, with the

limited number of cases and the short duration of follow-up for both adenosquamous and mucoepidermoid carcinoma of penis, we prefer to categorize them separately in order to signify the more aggressive behavior of the later entity. However, additional cases with qualitative and quantitative histologic parameters and long-term clinical outcome are required to better define both entities.

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