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CASE REPORT

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Verrucous carcinoma of the renal pelvis: case presentation and review of the literature

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Abstract Squamous cell carcinoma (SCC) of the renal pelvis is an uncommon tumour that has occasionally been associated with horseshoe kidney. The verrucous form of well-differentiated SCC has not been described previously at this site. We describe such a tumour in a 41-year-old man, who presented with gross haematuria and recurrent pyelonephritis caused by staghorn calculi within a horseshoe kidney. Histology showed extensive keratinising squamous metaplasia of the pelvic urothelium with an area of verrucous acanthosis and underlying invasion of the pelvic smooth muscle by broad tongues of squamous epithelium without atypia. Local lymph nodes were not involved by tumour. Immunohistochemistry and polymerase chain reaction revealed no evidence of human papillomavirus infection. The literature regarding verrucous carcinoma of the urothelial tract is reviewed.

Key words Verrucous carcinoma · Horseshoe kidney · Renal pelvis · Human papillomavirus · Polymerase chain reaction

Introduction

Verrucous carcinoma is an uncommon variant of well-differentiated squamous cell carcinoma and was originally described by Ackerman in 1948 [1]. It occurs at various sites, including the upper aerodigestive tract, skin bladder [6, 7] and genitalia. The tumour is characterised by a hyperplastic, papillomatous, wart-like architecture and shows infiltration of the underlying stroma by broad tongues of invasive neoplastic epithelium showing minimal degrees of atypia. Although searches for human papillomavirus (HPV) infection in these neoplasms have had contrasting results, virus had been identified in some of the tumours [19], and it is possible that incorporation of viral DNA may have an aetiological role in tumour formation in some instances. In tumours of the bladder, however, virus has not been found [7].

Although classical squamous cell carcinomas have been described in the renal pelvis in association with calculi, irradiation [21] and horseshoe kidney [13, 17], to the best of our knowledge the verrucous variant has not previously been reported in the kidney. We describe a case of such a tumour arising within a horseshoe kidney in association with a staghorn calculus. We searched for the presence of HPV by immunohistochemistry and polymerase chain reaction. The literature on verrucous carcinoma of the urinary tract is reviewed.

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Clinical history

A 41-year-old gentleman presented with right loin pain and fever. Examination and investigations revealed a horseshoe kidney containing calculi. No useful function of the right moiety was found on isotope studies. He underwent a partial nephrectomy at which the right hemihorseshoe and calculi were removed.

The specimen weighed 2.2 kg and measured 16×8×6 cm. Slicing revealed little remaining renal parenchyma, but what did remain was adherent to the perinephric fat. A large fragmented calculus was present within the pelvis. The epithelial lining of the pelvis was thickened and had the macroscopic appearance of hairless skin. Several haemorrhagic blisters were noted along the epithelium. Blocks were taken and sections 5 μm thick were prepared and stained with haematoxylin and eosin. Microscopy confirmed that the pelvis and ureter were lined with keratinising squamous epithelium. There was marked underlying mixed acute and chronic pyelonephritis with atrophy of the renal parenchyma. The squamous epithelium extended to the urothelial resection margin. A small focus approximately 1.5 cm across was identified microscopically as having a more papillomatous architecture (Fig. 1). In this area there was superficial invasion of the pelvic smooth muscle by broad rete pegs (Fig. 1). The latter were composed of well-differentiated squamous epithelium characteristic of verrucous

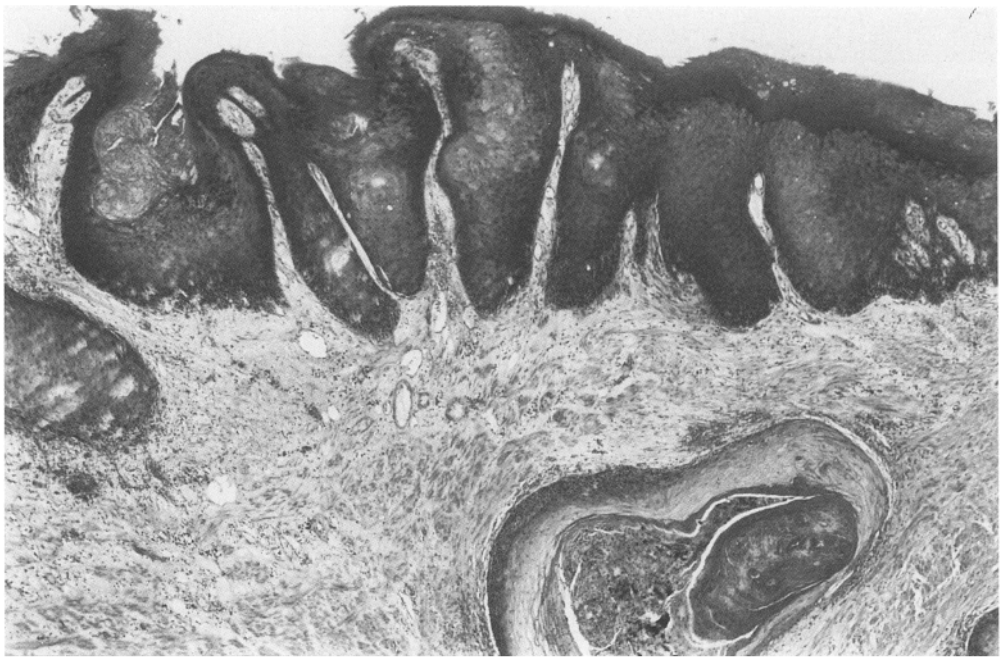

Fig. 1 Acanthotic, papillomatous architecture of verrucous carcinoma. (H&E)

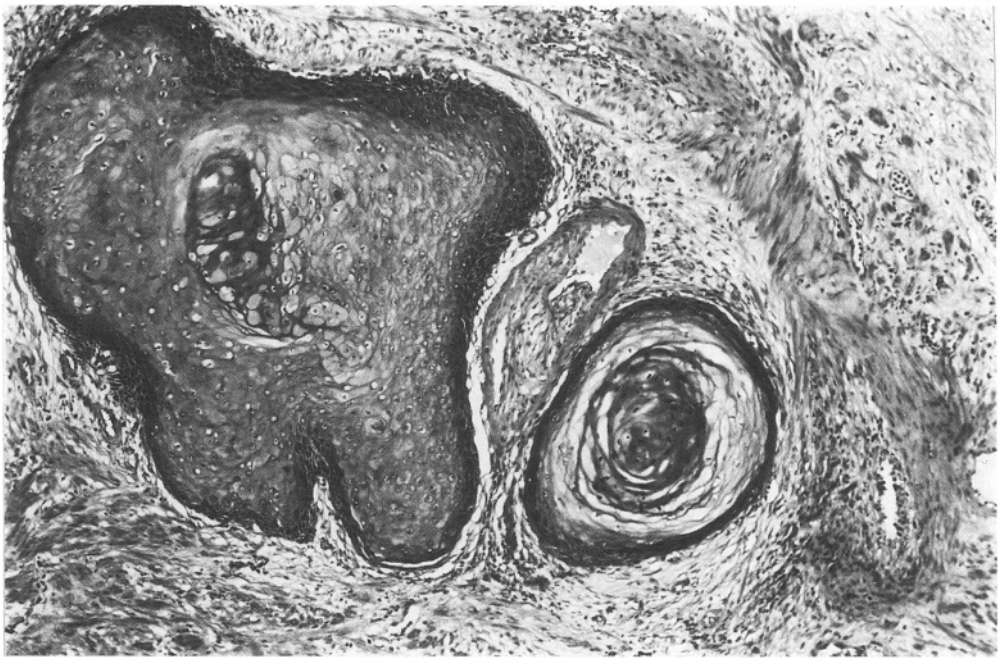

Fig. 2 Smooth muscle invasion by broad rete pegs. (H&E)

carcinoma (Fig. 2). Preliminary observation revealed viral features in the surface epithelium with koilocytosis (Fig. 3). Two other separate microscopic foci of more classical early invasive squamous cell carcinoma were also identified at a distance from this lesion. A lymph node was found, which was tumour free. Another interesting feature was the appearance of the subepithelial bullae (Fig. 4). These contained red blood cells and inflammatory cells including prominent eosinophils, resembling pemphigoid. Immunohistochemistry was performed using a polyclonal HPV antibody (DAKO); this was negative. Antibodies to p53 and Ki67 antigens were also applied to the sections. No alteration in p53 was detected. Increased numbers of peribasal cells labelled with the proliferation marker when compared with flat metaplastic epithelium away from the tumour. However, a similar staining pattern was noted in adjacent hyperplastic, non-invasive areas.

In addition, polymerase chain reaction (PCR) was performed on the paraffin-embedded tissue in an attempt to identify the presence of any HBV DNA. Briefly, three consecutive 10-μm sections were dewaxed in 1 ml xylene and then 1 ml 100% ethanol, twice. The pellet was lyophylised and resuspended in 100 μl digestion mixture containing 50 mM TRIS-HCl (pH 8.5), EDTA 0.5% Tween 20 and 400 ng/μl proteinase K. Digestion was carried out overnight at 55° C. PCR was performed on a final volume of 50 μl containing 10 mM TIRS-HCl (pH 8.3), 50 mM KCl, 2.5 mM MgCl2 and 200 μM of each dNTP. For each set of primers the concentration and annealing temperature were specifically standardised. Primers used were HPV L1, HPV 6, HPV 11, HPV 16 and HPV 18. For template, 5 μl of the digested sample was added to the reaction mixture, which was overlaid with a drop of mineral oil. After hot start at 92° C for 2 min, 1.25 U *Taq* polymerase was

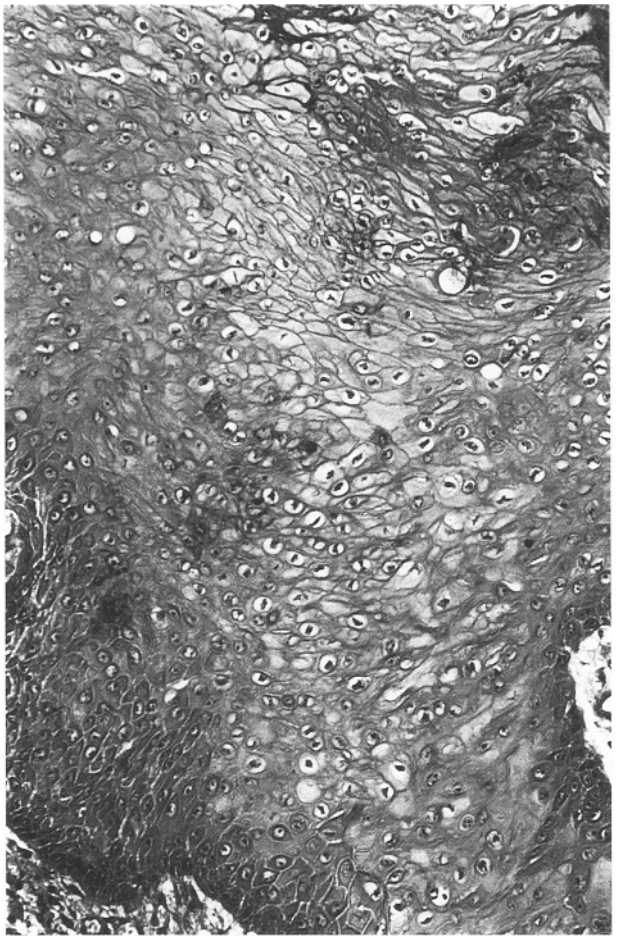

Fig. 3 Superficial keratinocyte cytoplasmic clearing suggestive of koilocytes. (H&E)

added. Amplification was performed using a Perkin-Elmer thermal cycler under the following conditions: denaturation 94° C, 1 min; specific annealing temperature, 1 min; extension 72° C, 1 min for 39 cycles, followed by a final cycle with a prolonged extension step of 10 min at 72° C. Finally, 18 µl of the amplified product were electrophoresed and visualized on an ethidium bromide-stained 2% NuSieve/Agarose gel (3:1).

Discussion

This unique case of verrucous squamous cell carcinoma of the renal pelvis was an incidental finding on the occasion of a partial nephrectomy for severe renal impairment resulting from calculi in a horseshoe kidney. Squamous cell carcinomas of the renal pelvis have been described in association with calculi, as a late complication of hepatic irradiation [21] and, occasionally, in horseshoe kidneys [3]. In one case both stones and horseshoe kidney were present [17], as in our patient. None of these carcinomas was of the verrucous type. Verrucous carcinoma is well described in the bladder, with the largest series coming from Egypt [6]. El Bolkainy et al. found that 33 out of 1095 tumours associated with schistosomiasis were verrucous carcinomas. In 32 of these cases, schistosome eggs were identified in the surgical specimen. Only eight cases of in situ or invasive verrucous carcinoma unassociated with schistosomiasis have been reported (see Table 1). Other cases described as giant condylomata may have been similar verrucous neoplasms [22]. Giant condylomata are important in the differential diagnosis of verrucous carcinoma.

Ordinary condyloma accuminata present as warty exophytic lesions with characteristic histological appearances. No invasion is present, however, and a viral aetiology is usually evident microscopically. The de-

Fig. 4 Subepithelial bulla which contained red blood cells and conspicuous eosinophils. (H&E)

Table 1 Verrucous carcinoma of the urothelial tract unassociated with schistosomal cystitis (*HPV* human papillomavirus, *UTI* urinary tract infection, *TURBT* transurethral resection of bladder tumour, *ISH* in situ hybridisation, *PCR* polymerase chain reaction)

Reference	Clinical summary	Site	Pathological findings	Treatment	HPV detected
Wyatt and Craig [22][a]	Male, 73; right hydronephrosis with 15-year history of UTIs	Right lateral bladder wall	Single non-invasive verrucous carcinoma	TURBT ×2, followed by cystectomy	–
Holck and Jorgenson [9]	Male, 75; gross haematuria, dysuria, sterile pyuria, diverticulum	Right lateral bladder wall	Verrucous carcinoma infiltrating lamina propria	Suprapubic cystotomy ×2	–
Walther et al. [20]	Female, 43; hesitancy, dysuria, genital condylomata	Right lateral bladder wall	Verrucous carcinoma	TURBT followed by cystectomy	–
Boileau et al. [3]	Male, 83; urgency, incontinence, previous prostatectomy	Left posterior wall with infiltration of surrounding soft tissue	Verrucous carcinoma	Palliative radiotherapy	–
Batta et al. [2]	Female, 43; scleroderma, UTIs, obstructive uropathy, condylomata	Diffuse bladder involvement	Verrucous carcinoma with extensive condylomata	Anterior exenteration, chemotherapy	–
Horner et al. [10]	Female, 68; frequency, bilateral hydronephrosis, acute renal failure	Extensive bladder involvement	Verrucous carcinoma confined to bladder	Cystectomy	ISH negative for HPV 6, 11, 16, 18; PCR negative
Ellsworth et al. [7]	Female, 48; UTIs, haemorrhagic cystitis	Anterior bladder wall and dome	Verrucous carcinoma involving abdominal subcutaneous fat	Radical cystectomy	Negative for HPV immunohistochemistry
Pierangeli et al. [15]	Female, 48; dysuria, microscopic haematuria, keratinuria, right hydronephrosis	Right ureteric orifice	Verrucous carcinoma in situ	Right nephrectomy and partial cystectomy (recurred)	–
This case	Male, 41; horseshoe kidney, staghorn calculus	Right renal pelvis	Verrucous carcinoma with extensive squamous metaplasia	Right partial nephrectomy	No HPV by immunohistochemistry or PCR

[a] Wyatt and Craig also suggested that four cases previously reported as condyloma acuminatum of the bladder may in fact be verrucous carcinomas

bate as to whether giant condyloma of Bushke-Loewenstein actually represents verrucous carcinoma (or is a well-differentiated squamous cell carcinoma arising in coexistent condyloma acuminata) is beyond the scope of this report. Verrucous squamous hyperplasia is another mimic of verrucous carcinoma, but once again definitive observation of underlying invasion should point to the correct diagnosis. When invasion is not seen a diagnosis of in situ verrucous carcinoma may be appropriate [15]. In fact, as Pierangeli et al. [15] point out, verrucous carcinoma in situ may appear in foci of verrucous hyperplasia and evolve into an invasive squamous carcinoma.

Despite the association between HPV (especially types 6 and 11) and verrucous carcinoma [4, 10] in some, but not all [5, 8, 11, 12], tumours of the anogenital region, no viral material was identified in our tumour. In fact, virus seems to be consistently absent from verrucous tumours of the bladder [7], and it is likely that our tumour arose on a background of chronic inflammation caused by the presence of calculi, and perhaps it is not surprising that virus was not detected at this site. Virus may only be present in those invasive carcinomas that develop in giant condylomata acuminata (if indeed these are different tumours; see above).

The results of immunohistochemical staining for Ki67 antigen show that in verrucous neoplasms a larger proportion of cells is within the replicating pool. The adjacent areas of hyperplasia also contained more Ki67-positive cells than the metaplastic epithelium, so that the significance of the former is uncertain. Ploidy studies (nor performed on this tumour) have shown diploid DNA content in penile verrucous carcinomas [8, 11].

Although p53 detection has been associated with all levels of dysplasia and invasion in oral squamous cell carcinomas [18], p53 was not detected in a verrucous carcinoma at this site despite p53 detection in the preceding dysplastic phase. Pilotti et al. [16] found no alteration in expression and/or mutation of p53 in five cases of verrucous carcinoma of the lower genital tract by immunohistochemical and molecular techniques (it is worth noting that p53 was altered in two cases of invasive squamous carcinoma associated with giant condyloma). p53 Immunohistochemistry was not altered in our tumour.

Although p53 mutations are found in a wide range of human malignancies, it may be that the development of verrucous carcinoma does not involve alteration of this tumour suppressor gene.

The term verrucous carcinoma is used for a specific histological appearance of a well-differentiated squamous cell carcinoma, which is said to infiltrate locally and have little tendency to metastasise to regional lymph nodes or distant sites. This is certainly the case with our tumour. However, it has been suggested that verrucous carcinomas behave more aggressively following irradiation, and some even report this behaviour in the absence of radiation [14]. This may in fact be due to areas of more typical squamous cell carcinoma in an otherwise characteristic verrucous carcinoma [14]. It may be that we should reserve the term verrucous carcinoma for well-differentiated squamous cell carcinomas with only the verrucous component, unassociated with classical foci within the same tumour.

The patient remains well 6 months after surgery, and it is likely that there will be no direct sequelae as these tumours usually infiltrate locally and rarely metastasise. We feel therefore that our case may be treated clinically as a completely resected incidental tumour. However, owing to the extensive keratinising squamous metaplasia and the multifocal nature of this tumour with coexistent classical early invasive squamous cell carcinoma, the patient will require closely monitored long-term follow up of the residual urinary tract tissue, especially the left renal pelvis, to check that no tumour remains in the non-resected kidney.

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