Section: Pathology

Case Report

SQUAMOUS CELL CARCINOMA IN RARE ANATOMICAL LOCATIONS: A COMPREHENSIVE ANALYSIS OF URINARY BLADDER SCC, GALLBLADDER SCC, AND BREAST SCC

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ABSTRACT

Background: Squamous cell carcinoma (SCC) is a rare histological variant in anatomical sites with little or no squamous epithelium. Bladder SCC accounts for 2–5% of bladder cancers in non-endemic regions and is frequently associated with chronic irritation from vesical calculi. Gallbladder SCC constitutes 1–3% of biliary cancers and is characterised by aggressive behaviour and poor prognosis. Primary breast SCC constitutes less than 0.1% of breast carcinomas and typically exhibits a triple-negative phenotype with chemotherapy resistance.

Case Presentation: Five cases are presented: a 50-year-old male with bladder SCC and calculi; a second bladder SCC associated with chronic irritation; a 46-year-old female with gallbladder SCC; and a 63-year-old and a 57-year-old woman with primary breast SCC showing squamous differentiation.

Conclusion: When achievable, radical surgical resection provides the best prognosis, although five-year survival rates remain much lower than for conventional carcinomas at similar sites. Early histopathological diagnosis with immunohistochemical confirmation is essential. Multimodal strategies involving surgery, advanced pathology, and innovative therapies are required to improve overall patient outcomes.

Keywords: Squamous cell carcinoma, rare malignancy, histopathology, immunohistochemistry, chronic inflammation.

INTRODUCTION

Squamous cell carcinoma arising in organs where squamous epithelium is normally absent represents an intriguing clinical phenomenon that challenges our understanding of carcinogenesis.[1,2,3]

These malignancies arise through sequential transformation of native glandular epithelium into stratified squamous epithelium that undergoes dysplastic changes over time, evolving into invasive carcinoma.[1,2,3]

This transformation occurs as a consequence of chronic tissue injury leading to persistent inflammatory responses, which ultimately drive a metaplastic state, genomic instability, and progression to malignancy.[4,5,6]

Bladder involvement is most commonly reported, accounting for an estimated 2–5% of bladder malignancies in regions without endemic schistosomiasis.[2,3,7]

Vesical calculi are an independent risk factor of substantial importance, with reported epidemiological data suggesting an estimated 3.4-fold higher cancer risk in patients with bladder stones, particularly when stones exceed 4 cm in diameter.[9,10]

The ongoing mechanical damage caused by large calculi maintains continuous epithelial destruction, promoting the secretion of inflammatory cytokines and oxidative stress within the bladder microenvironment.[8,11]

Gallbladder squamous cell carcinoma is an uncommon occurrence, constituting only 1–4% of all biliary malignancies and showing very aggressive behaviour, with median survival often under nine months.[3,12,15]

Chronic gallbladder inflammation triggers squamous metaplasia, followed by dysplasia and carcinoma arising through cytokine-driven dysregulation of growth factor signalling.[1,3,14] These tumours characteristically present at advanced stages with transmural hepatic invasion attributable to the absence of a serosal barrier.[2,3,13]

Even with R0 resection, the prognosis is poorer, in line with the fundamentally aggressive squamous tumour biology.[12,16]

Primary breast squamous cell carcinoma accounts for less than 0.1% of invasive breast cancer and has a rapid growth rate, large tumour size at presentation, and a triple-negative immunophenotype that confers intrinsic chemotherapeutic resistance.[2,17,18]

Identification of these rare variants is crucial for accurate diagnosis and successful management.

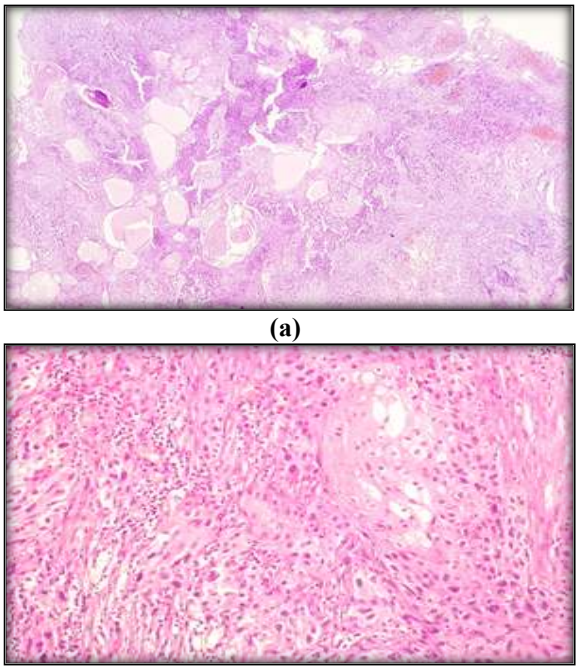
CASE REPORT

Case 1: Bladder SCC with Vesical Calculi: A 50-year-old man presented with intermittent lower abdominal pain during micturition interspersed with episodes of painless gross haematuria for several months. Imaging studies demonstrated a bladder mass overlying a considerable calculus of approximately 6 cm. The neoplasm was resected by transurethral resection of bladder tumour, with pathological examination showing multiple pale tan chips totalling 4 cubic centimetres. Microscopic study revealed metaplastic squamous epithelium with malignant transformation manifesting keratin pearl formation, dyskeratotic cells, and an infiltrative growth pattern into the lamina propria. [Figure 1]

Immunohistochemistry showed positivity for p63 and CK7 with loss of CK20 expression, indicating a diagnosis of primary bladder SCC. The concurrent massive calculus showed surface concretions indicative of chronic stone disease.

Case 2: Gallbladder SCC

A 46-year-old woman presented with progressively increasing right upper quadrant discomfort accompanied by constitutional symptoms (anorexia and unintentional weight loss). Radiological examination revealed generalised thickening of the gallbladder wall with an intraluminal polypoid mass (3 × 2 cm) raising suspicion for malignancy. Surgical resection revealed infiltrative growth along the gallbladder wall, with a polypoid segment 3 × 2 cm in depth reaching the hepatic parenchyma.



(a)

(b)

Figure 1: Bladder SCC with vesical calculi (Case 1). (a) Low power (H&E, ×4); (b) high power (H&E, ×40).

Histopathological examination showed islands and clusters of atypical squamous cells with marked dyskeratosis and classic keratin pearl formation [Figure 2], arranged in infiltrative nests across the muscularis propria with extension into perivesicular adipose tissue. Immunohistochemistry displayed strong nuclear p63 and cytoplasmic CK5/6 positivity, confirming the diagnosis of primary gallbladder SCC. Adjuvant chemotherapy was started after surgical resection.

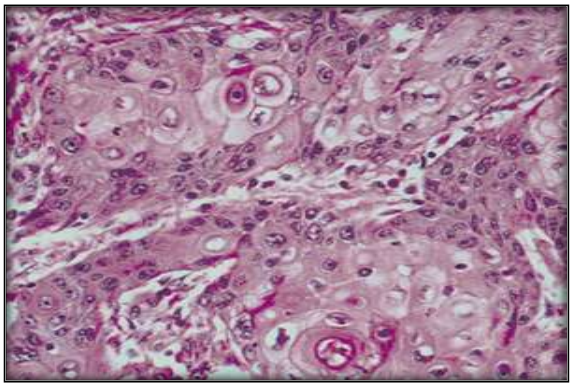
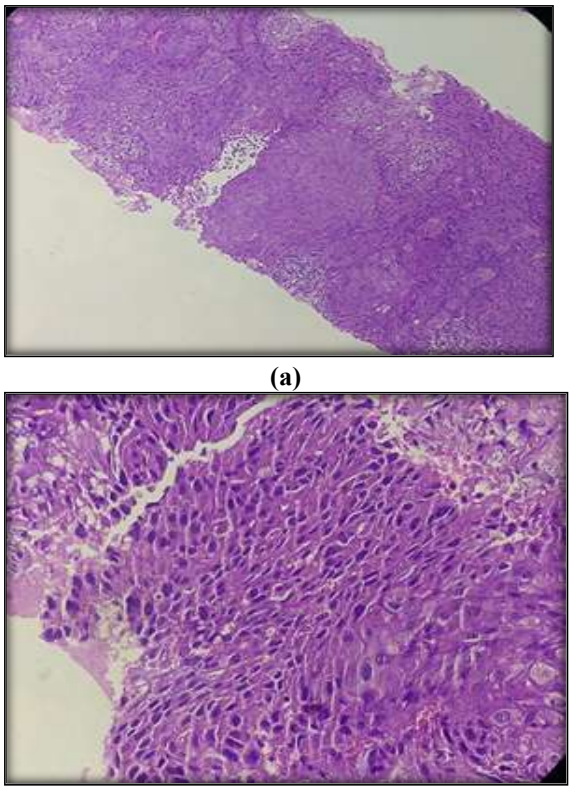


Figure 2: Gallbladder SCC (Case 2) showing keratin pearl formation (H&E, ×40).

Case 3: Primary Breast SCC

A 63-year-old woman presented with a 4-month history of progressive painless enlargement of the right breast (upper inner quadrant) without skin changes or nipple discharge. Clinical examination and imaging showed a 3.5 × 3 cm irregular, suspicious mass. Core needle biopsy confirmed

metaplastic carcinoma with squamous differentiation. Surgical resection showed a well-circumscribed grey-white lesion; microscopically, central keratinous debris was surrounded by atypical squamous cells with marked nuclear pleomorphism infiltrating the surrounding mammary stroma. [Figure 3] Extensive investigations excluded metastatic lesions from extra-mammary primary sites such as the lung, cervix, and head and neck. Immunohistochemistry revealed a triple-negative (ER−, PR−, HER2−) status with high p63 and CK5/6 expression, consistent with a primary breast origin.



(a)

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Figure 3: Primary breast SCC (Case 3). (a) Low power (H&E, ×4); (b) high power (H&E, ×40).

Case 4: Primary Bladder SCC (without calculus)

A 58-year-old woman presented with recurrent painless haematuria and irritative lower urinary tract symptoms for 5 months. Ultrasonography and contrast-enhanced imaging revealed an irregular polypoid mass arising from the posterior bladder wall without upper tract obstruction, and no bladder calculus was identified. Transurethral resection of bladder tumour yielded grey-white tissue fragments. Histopathological examination showed invasive nests of atypical squamous cells with keratin pearl formation, intercellular bridges, and stromal infiltration. Immunohistochemistry showed diffuse positivity for p63 and CK5/6, with focal p40 expression and negative urothelial markers, supporting the diagnosis of primary bladder SCC. Clinical and radiological evaluation did not reveal schistosomiasis, prior irradiation, or metastasis from another primary site.

Case 5: Primary Breast SCC

A 57-year-old woman presented with a 3-month history of a rapidly enlarging painless lump in the left breast. Examination showed a 4 × 3.5 cm firm, irregular mass in the upper outer quadrant, with no nipple discharge or skin ulceration. Mammography and ultrasonography suggested a suspicious solid lesion, and core biopsy showed malignant epithelial cells with squamous differentiation. Wide local excision demonstrated infiltrating sheets and nests of atypical squamous cells with keratinisation and marked nuclear pleomorphism. Immunohistochemistry showed ER−, PR−, and HER2-negative status with strong p63 and CK5/6 positivity, confirming primary breast SCC. Metastatic squamous carcinoma from other sites was excluded on clinical workup.

DISCUSSION

The present series (N = 5) represents an illustrative collection of squamous cell carcinoma at anatomical sites where native squamous epithelium is absent or minimal, comprising two bladder cases (one with a concurrent vesical calculus), one gallbladder case, and two primary breast cases. The bladder case with a concurrent massive calculus is clinically important because the coexistence of a massive calculus and invasive carcinoma underscores the chronic inflammation paradigm central to the squamous metaplasia–dysplasia–carcinoma sequence; this mechanistic pathway operates through sustained epithelial injury, inflammatory cytokine release, oxidative stress accumulation, and acquisition of genomic instability over prolonged intervals, as noted by Lu et al. (2025), Michaud (2007), Nesi et al. (2015), and Chow et al. (2013).[5,8,9,11] Bladder SCC accounts for approximately 2–5% of bladder malignancies in non-endemic regions,[2,3,7] with bladder calculus conferring an approximately 3.4-fold increased malignancy risk based on case–control analyses,[9] and massive stones exceeding 4 cm showing a particular association with transformation despite incomplete mechanistic understanding, as documented by Subba et al. (2022) and Fernando et al. (2017).[7,10]

Despite the anatomical diversity, the cases demonstrate unifying pathogenic mechanisms consistent with inflammation-driven squamous metaplasia preceding malignancy. The gallbladder case exhibited polypoid growth with hepatic invasion and strong p63/CK5/6 immunoreactivity, consistent with Dashti et al. (2024) and He et al. (2025), describing transmural extension facilitated by the absence of a serosal layer and median survival under nine months for pure squamous histology.[1,3] The breast cases confirmed a triple-negative immunophenotype (ER-negative, PR-negative, HER2-negative) with p63/CK5/6

positivity, concordant with Anne et al. (2019) and Seddik et al. (2015), who reported triple-negative status in approximately 90% of primary breast SCC and inherent chemotherapy resistance attributable to the lack of targetable receptors.[6,18] The additional bladder SCC case without a calculus supports the possibility that chronic irritation is not always clinically obvious, while the second breast SCC case reinforces the rarity but reproducibility of the same histological and immunophenotypic pattern across independent presentations.

CONCLUSION

Squamous cell carcinomas originating at anatomically unusual sites are aggressive neoplasms with a poor prognosis despite multimodal therapy. Radical surgical resection remains the cornerstone of management, achieving superior outcomes in early-stage disease. Most cases present at an advanced stage, reflecting the indolent clinical behaviour preceding diagnosis and the aggressive biological conduct following manifestation. Five-year survival rates substantially lag behind those of conventional carcinomas of equivalent stage at the same anatomical sites. Early recognition through meticulous histopathological evaluation remains essential for accurate diagnosis and appropriate therapeutic planning. Future research into the molecular underpinnings of these malignancies may yield targets for novel therapeutic intervention, potentially improving currently dismal survival statistics.

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