

中文題目：因巨大膀胱結石引發之膀胱鱗狀上皮細胞癌

英文題目：Squamous Cell Carcinoma of the Bladder Induced by A Huge Bladder Stone

作者：莊哲明<sup>1</sup>，蕭惠樺<sup>1</sup>

服務單位：<sup>1</sup>高雄醫學大學附設醫院血液腫瘤科

**Introduction:** Squamous cell carcinoma (SCC) accounts for 3 to 5 % of bladder cancers in North America and Europe and up to 75 percent of bladder cancers in areas where *Schistosoma haematobium* infection is endemic.<sup>1</sup> Reported risk factors associated with the development of squamous cell carcinoma include chronic or recurrent urinary tract infections, bladder calculi, pelvic radiation therapy, antecedent intravesical Bacillus Calmette-Guerin (BCG) treatment, and prolonged exposure to cyclophosphamide, particularly when complicated by hemorrhagic cystitis.<sup>2</sup> Thus, We report a case of a 69-year-old male patient presenting with muscle invasive bladder SCC with a history of large bladder calculus and recurrent stone formation.

**Case presentation:** A 69-year-old man with type 2 diabetes mellitus a history of open vesicolithotomy for a bladder stone 15 years ago, presented to our Urology clinic in January 2021 due to progressive dysuria and hematuria for 3 months. The general physical examination was unremarkable, and abdominal examination did not reveal any tenderness or a palpable bladder. His urine analysis showed > 100 white blood cells and > 100 red blood cells per high power field. Urine culture yielded no significant growth. X-ray KUB (Kidney, ureters and bladder) showed a 9.6 x 8.0 cm bladder stone (Fig. 1A).

Initially, the patient was treated with open vesicolithotomy for stone removal in January 2021. However, after removing the stone, a large solid exophytic tumor involving the right lateral wall of the bladder and the trigone was revealed. Incisional biopsy was done and histopathology showed well-differentiated squamous cell carcinoma. Further abdominal contrast-enhanced computed tomography (CT) suggested extravesical tumor invades pelvic wall without lymph nodes involvement, cT4bN0M0 (Fig. 1B). Therefore, patient underwent radical cystectomy and pelvic lymph nodes dissection in February 2021 with total 16 lymph nodes obtained. Final pathologic staging revealed perivesical fat involvement but neither regional nor pelvic lymph nodes were involved, pT3aN0M0. The surgical margins were free, with 6.5 cm distant from surgical margin of urethra. Adjuvant chemotherapy with gemcitabine and cisplatin (GC) was applied for 3 months but follow-up CT in May 2021 showed metastatic lesions at the anterior lower abdominal wall and left pubic ramus. Due to recurrent disease status, induction systemic chemotherapy is indicated but patient seek supportive care only and we transferred him to hospice department.

**Discussion:** Bladder SCC can be subclassified as bilharzial and nonbilharzial depending on the etiology due to *Schistosomiasis haematobium*. Nonbilharzial SCC is associated with conditions causing chronic bladder irritation which are bladder stones, recurrent urinary tract infections, chronic bladder outlet obstruction, indwelling catheters, cyclophosphamide exposure and even intravesical BCG which result in subsequent metaplasia and malignant transformation.<sup>2</sup>

Few studies have evaluated the association of bladder stones in relation to bladder cancer. A case-control study has shown that a twofold increase in bladder cancer risk was observed with a history of bladder stones, irrespective of a history of urinary tract infections.<sup>3</sup> In another prospective cohort study of kidney or ureteral stones, the standardized incidence ratio for bladder cancer was

1.4 (95% CI (confidence interval) 1.3–1.6, n = 319).<sup>4</sup> However, there are no large-scale studies that have looked at the percentage of SCC diagnosed with a concomitant bladder calculus.

There are little trails regarding treatment of bladder SCC due to small case numbers and different histologic expressions. These patients were often excluded from large prospective trails, which made SCC of the bladder difficult to treat owing to lack of good evidenced guidelines. Nevertheless, several retrospective studies have evaluated various treatment strategies for these patients.

First-line management for non-metastatic, muscle-invasive SCC is cystectomy, which gains its support from observational and retrospective data. Analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 2003 showed that cystectomy reduced 2- year mortality from 73% to 57% in SCC compared with 56% to 44% in UC with adjusted bladder cancer-specific mortality difference of 0.16 (95% CI, 0.09-0.23; P < 0.001).<sup>5</sup> Unlike patients with urothelial carcinoma (UC), which has much evidence that cisplatin-based neoadjuvant or adjuvant chemotherapy improves overall survival, studies of SCC of the bladder have not demonstrated benefit for patients receiving neoadjuvant or adjuvant chemotherapy.<sup>6</sup>

For patients with locally advanced, unresectable SCC of the bladder, radiation with concomitant chemotherapy represents a reasonable approach. However, there are little prospective data to guide management. the phase III BC2001 trial show efficacy for fluorouracil and mitomycin given concurrently with radiotherapy (RT) compared with RT alone in patients with high-grade muscle invasive bladder cancer, with improved local and locoregional control and a trend toward better survival.<sup>7</sup> However, only 2.7 % of patients were non-UC type and its efficacy among these patients cannot be well-defined due to small subgroup numbers. A very similar regimen is effective and well tolerated in patients with squamous cell cancer of the anus, so this treatment of SCC of the bladder may be reasonable, especially in patients who are poor candidates for platinum-containing regimens.

Unlike locally advanced SCC, there are no specific treatment suggestions for metastatic condition. In contrast to chemosensitive UC, SCC has low responsiveness to standard chemotherapy. In the only prospective studies exploring chemotherapy in SCC, Galsky et al treated eight patients with paclitaxel, ifosfamide, and cisplatin. two of eight patients achieved a complete response, and the median survival was 8.9 months.<sup>8</sup> Another study of schistosomiasis-associated bladder cancer in the Middle East, Southeast Asia, and South America found that neoadjuvant chemotherapy with gemcitabine and cisplatin induced high response rates with a moderate toxicity profile.<sup>9</sup> However, this result cannot directly apply to all patients of bladder SCC since most cases in developed countries are non-schistosomiasis associated SCC.

**Conclusion:** In conclusion, SCC is a rare bladder cancer type that often caused by chronic bladder irritation with poorer prognosis compared with UC. Conventional chemotherapies usually yield poor responses. Nevertheless, these patients may benefit from the innovative novel immune checkpoint inhibitors, and further studies are needed for solid evidences.