BCG-related renal granulomas managed conservatively: A case series

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Abstract

Introduction: The aim of this case series is to present two cases of renal granulomas discovered incidentally post-intravesical Bacillus Calmette-Guerin (BCG) installations and were managed conservatively.

Case reports: The first case is a 68-year-old man with bladder and right ureteral orifice carcinoma in situ. After transurethral resection of the right ureteral orifice and bladder tumours, he received 6 + 3 weekly intravesical installations of BCG and then 6 + 3 weekly intravesical installations of BCG with interferon alpha (IFN) in the presence of an indwelling ureteral stent since he had refused cystoprostatectomy. At the 18-month follow-up, his computed tomography scan showed two right renal masses. Biopsy demonstrated non-necrotizing granulomatosis. Serial follow-up with imaging studies showed complete resolution of these masses without anti-tuberculous medications. The second case is a 74-year old man with left renal high-grade papillary urothelial carcinoma. After ureteral meatotomy and insertion of indwelling ureteral stents, he received 6 weekly intravesical installations of BCG followed by 3 weekly installations of BCG and IFN prior to the definitive management with laparoscopic left nephroureterectomy. Final pathology showed pT1 urothelial carcinoma and an incidental finding of BCG-related renal granulamotosis. The patient has been asymptomatic and did not require anti-tuberculous medications.

Conclusions: While these two cases demonstrate the ability of intravesical BCG to reach the renal pelvis, patients with a history of intravesical BCG with incidental renal masses may benefit from renal biopsy. These renal granulomas may resolve without anti-tuberculous medications.

Introduction

Intravesical Bacillus Calmette-Guerin (BCG) was first described for the treatment of superficial bladder cancer in 1976.[1] Currently, intravesical BCG installation is the standard of care for patients with high-risk non-muscle invasive bladder cancer.[2] Although 95% of patients receiving intravesical BCG do not experience any serious side effects, serious systemic infections, including fatal BCGosis, have been rarely reported.[3] A small number of granulomatous renal masses following intravesical BCG have been previously reported.[3-12] The incidence of such renal granulomas has been reported at a rate of 0.1% (2 cases out of 2602).[3] However, previous cases were managed with nephroureterectomy, anti-tuberculous medications or both. The aim of this case series is to present two cases of renal granulomas discovered incidentally post-intravesical BCG installations and were managed conservatively without any anti-tuberculous medications.

Case 1

A 68-year-old man, with a history of metabolic syndrome and deep venous thrombosis, presented with gross hematuria. He is a social cigar smoker. Cystoscopy revealed a large invasive-looking right lateral wall bladder mass next to the right ureteral orifice. Urine cytology was positive for high grade urothelial carcinoma. A triphasic computed tomography (CT) urogram did not demonstrate any evidence of upper tract lesions. Transurethral resection of the bladder tumour (TURBT) showed extensive urothelial carcinoma in situ (CIS) widely colonizing von Brunn nests. There was no invasive urothelial carcinoma. The patient was started on BCG (OncoTICE, Merck Canada Inc, Kirkland, QC) induction therapy with 50 mg weekly for 6 weeks. A repeat TURBT 3 months later did not reveal any residual urothelial carcinoma. Therefore, the patient was started on the BCG maintenance protocol and received the 3 weekly intravesical BCG installations.

At the 6-month follow-up, cytology remained positive and bladder biopsies, in addition to the resection of the right ureteral orifice, showed persistence of CIS at the bladder dome and right ureteral orifice. The patient refused cystectomy. Therefore, he was started on a second induction course of

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BCG 16.6 mg with interferon alpha 2b (IFN, 50 million units), while the indwelling ureteral stent was left in place to keep the ureteral orifice open. Three months later, cytology remained positive. Right ureteroscopy (URS) with random biopsies of the bladder and the right collecting system showed persistent CIS at the right ureteral orifice. He refused cystectomy again and was placed on maintenance protocol of intravesical BCG and IFN. Three months later, urine cytology was still positive. Repeat URS and random biopsies were negative, but bladder biopsies showed persistence of CIS at the right ureteral orifice. Follow-up CT imaging 3 months later demonstrated no evidence of upper tract tumours, but there was fullness of the right renal pelvis. In addition, it showed the appearance of two solid lower pole enhancing lesions on the right kidney measuring 3.8 × 3.5 cm and 1.2 × 1.6 cm suspicious for renal cell carcinoma or urothelial (Fig. 1). At this time, urine cytology from the bladder was finally negative, while urine cytology from the right collecting system was positive. To differentiate between renal cell carcinoma and urothelial carcinoma, biopsy of the larger renal mass was performed and demonstrated non-necrotizing granulomatosis (Fig. 2, part A). Repeat bladder biopsies and cytologies were also negative. Follow-up CT scan 3 months later demonstrated reduction in the size of the renal lesions, and a CT scan 1 year later showed complete resolution with scarring without any treatment with anti-tuberculous medications (Fig. 1). The patient has been followed closely with upper tract imaging every 6 months and urine cytologies and cystoscopies every 3 months. He is still on maintenance BCG with the IFN protocol and has not had recurrences of his renal lesions for the last 2 years.

Case 2

A 74 year-old man presented with microscopic hematuria and upon investigation had positive urine cytology for high-grade urothelial carcinoma. He had never smoked. On cystoscopy, there were no bladder tumours. A triphasic CT scan did not reveal any upper tract collecting system filling defects. Random bladder biopsies were negative and selective urine cytology from the left collecting system was positive for high-grade urothelial carcinoma. Left URS revealed a tiny left upper pole papillary lesion which was biopsied (pTa high grade) and fulgurated with Holmium:YAG laser. Left ureteral meatotomy was also performed. He refused nephroureterectomy. Therefore, he received an induction course of 6 weekly intravesical installations of BCG (50 mg each) (OncoTICE, Merck Canada Inc, Kirkland, QC), while he had the indwelling ureteral stent. Surveillance URS 2.5 months from the initial URS showed that there were more extensive carpet-like lesions extending from the renal pelvis to the upper pole. Repeat biopsy revealed CIS. The patient was again offered a left nephroureterectomy. While the patient was deciding on the definitive management, he received the 3 weekly intravesical installations of BCG (16.6 mg) with IFN (50 million units) with the presence of his left ureteral stent. A repeat CT scan of the chest, abdomen, and pelvis failed to reveal any evidence of extra-renal extension or metastasis. The patient finally accepted a left laparoscopic radical nephroureterectomy, which was performed 2 weeks from his last BCG and IFN installation.

The final pathology showed high-grade urothelial carcinoma invading the lamina propria (pT1, pN0) with CIS in

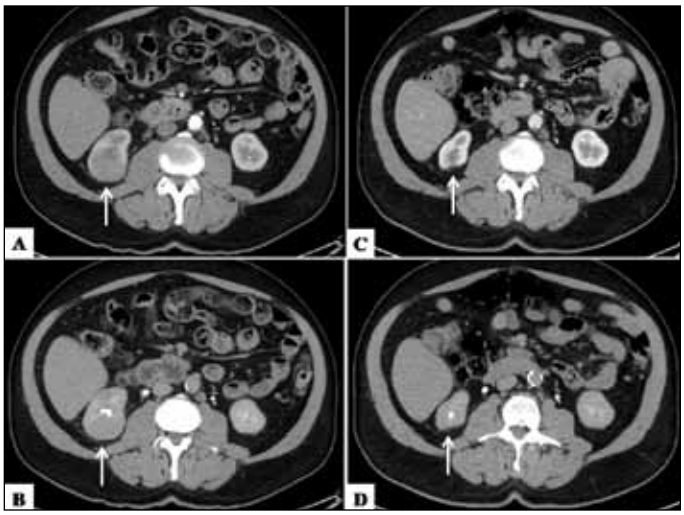

Fig. 1. Case 1: Axial CT images through the lower poles of the kidneys. **(A)** Arterial phase images demonstrating the right lower pole enhancing lesion (arrow). **(B)** Delayed phase images demonstrating the "central unaffected calyx sign" (arrow). **(C)** Arterial phase images one year later showing resolution of the right renal mass with scarring (arrow). **(D)** Delayed phase images one year later showing that the lower pole calyx is unaffected (arrow).

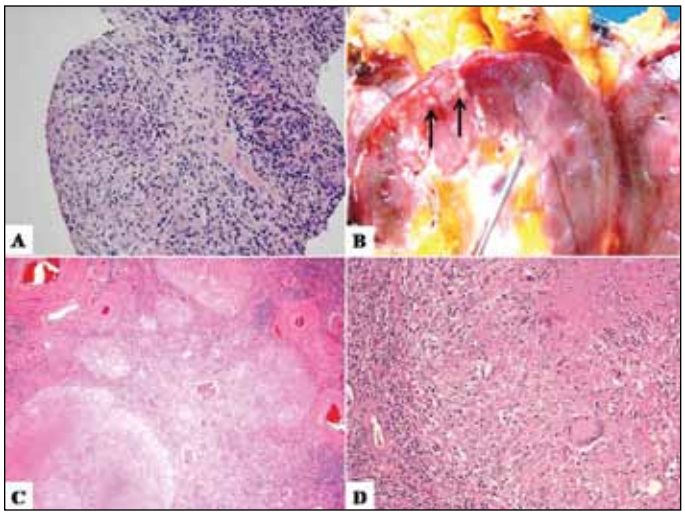

Fig. 2. **(A) Case 1:** Core biopsy of the right lower pole renal mass showing granulomatous reaction secondary to BCG. **(B) Case 2:** Macroscopic appearance of the affected kidney showing multiple round small whitish cortical lesions (arrows). **(C) Case 2:** Microscopic low-power view showing well-defined confluent areas of necrosis. **(D) Case 2:** Higher magnification showing necrotizing granulomatous inflammation with multinucleated giant cells.

the renal pelvis. In addition, the upper pole showed grossly granular appearance (Fig. 2). On microscopic examination, it showed severe BCG-related granulomatous inflammation and chronic interstitial inflammation (Fig. 2). He did not have any constitutional symptoms and was not treated with anti-tuberculous medications. He has been followed with serial cystoscopies every 3 months, and with CT scans every 6 months and BCG/IFN intravesical maintenance without any signs of local recurrence or metastasis for the last 2 years.

Discussion

Although renal granulomas post-intravesical BCG has been reported at a rate of 0.1%, previous cases were managed with nephroureterectomy, anti-tuberculous medications or both.[3] We report two cases of renal granulomas discovered incidentally post-intravesical BCG installations and were managed conservatively without any anti-tuberculous medications. There are several interesting aspects of these two cases.

First, both patients had intravesical installations of BCG after ureteral meatotomy and in the presence of indwelling ureteral stents. Vesicoureteral reflux has been shown in up to 77% of patients post-TURBT when the resection is close to the ureteral orifice.[13,14] Although we did not have an objective test for evidence of reflux with the presence of ureteral stents, the mechanism of BCG granuloma in these two cases is likely to be related to reflux of the intravesical BCG rather than hematogenous spread since there were no systemic side effects, such as fever. In addition, previous cases of hematogenous spread of BCG have been related to untreated cystitis or traumatic insertion of catheter at time of BCG administration, which were not present in these two cases.[3] Furthermore, intravesical installations started at least 2 weeks after TURBT and URS.[2] Although both antegrade intra-renal and intravesical installations of BCG have been described for the management of upper tract urothelial carcinoma, we have favoured the intravesical approach over percutaneous antegrade approach to minimize the risk of life-threatening BCGosis and risk of tumour seeding of the nephrostomy tract.[15-18] It is interesting to note that renal granulomas post-intra-renal installation of BCG has been reported at a much higher rate of 25% when compared with intravesical installation (0.1%).[3,19] The fact that both of these patients developed renal granulomas may support the use of intravesical BCG for management of upper tract urothelial carcinoma.

The second important point is to perform a renal biopsy in patients with a history of intravesical BCG presenting with renal masses. In fact, several cases of nephroureterectomy have been reported since these masses were mistaken for renal cell carcinoma or urothelial carcinoma.[10,12,16] When analyzing available published case reports on renal granulomas, we found that most cases reported multifocality of renal granulomas with multiple renal masses on imaging studies,[4,8,11-12,16] while others reported solitary renal foci.[5,7,9,10] Both patients in the present series had multiple renal granulomas. Another sign is the "central unaffected calyx sign" on delayed phase CT images that has been previously described in patient with a renal BCG granuloma.[11] In contrast to a malignant tumour that would destroy neighbouring calyces, the authors discovered that renal BCG granuloma did not affect the calyx within the mass.[11] Although, not specific, this sign was present on the delayed phase CT images for the first patient (Fig. 1). Inevitably the role of a renal biopsy in this scenario was indispensable and allowed us to avoid nephroureterectomy for the first case.

Finally, both patients were managed conservatively without any anti-tuberculous medications since they did not have any systemic symptoms. In fact, the renal masses in the first case resolved spontaneously after 1 year without withdrawal of intravesical BCG or instituting anti-tuberculous treatment. Therefore, this raises questions regarding the need for anti-tuberculous medications for patients with renal granulomas without systemic symptoms. Except for the case report by Mody and colleagues, in which the patient underwent nephroureterectomy, all of previous case reports of renal granulomas were treated with 6 to 12 months of anti-tuberculous medications.[3-12,16,20] Therefore, here we present two cases of asymptomatic renal granulomas that were managed without anti-tuberculous medications. However, the reason we were able to manage these patients without anti-tuberculous medications was related to the absence of fever and systemic symptoms. Except for two case reports by Rocha and Wada, all of the reported cases of renal granulomas presented with systemic constitutional symptoms of fever.[3-12,16,20] Perhaps the absence of fever in the two cases presented here could be related to the dose and strain of BCG used. Whereas in these two cases, 50 mg of BCG Tice strain was used, previous reports of febrile renal granulomas were reported with BCG Connaught strain[5,11,16] or BCG Tice strain at higher dose of 120 mg per installation.[9] A recent randomized clinical trial has shown that superior immunogenicity and efficacy of BCG Connaught strain when compared with BCG Tice strain.[21] In addition, anti-tuberculous medications may have reduced the efficacy of the immunotherapy with intravesical BCG especially in the first patient with persistent CIS who had refused cystoprostatectomy. Therefore, in patients with renal granulomas without systemic symptoms, renal granulomas may resolve spontaneously without the need for anti-tuberculous medications.

Conclusion

While these two cases demonstrate the ability of intravesical BCG to reach the renal pelvis, patients with history of intravesical BCG who present with incidental renal masses

may benefit from renal biopsy. These renal granulomas may resolve without anti-tuberculous medications.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumours. *J Urol* 1976;116:180-3.
2. Kassouf W, Kamat AM, Zlotta A, et al. Canadian guidelines for treatment of non-muscle invasive bladder cancer: a focus on intravesical therapy. *Can Urol Assoc J* 2010;4:168-73. http://dx.doi.org/10.5489/cuaj.10051
3. Lamm DL, van der Meijden AP, Morales A, et al. Incidence and treatment of complications of Bacillus Calmete-Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596-600.
4. Stanisic TH, Brewer ML, Graham AR. Intravesical Bacillus Calmette-Guerin therapy and associated renal masses. *J Urol* 1987;135:356-8.
5. De Biosgisson PH, Roussel F, Leclerc D, et al. Granulomatous renal mass during endovesical BCG therapy for bladder carcinoma. *Urology* 1991;37:557-60. http://dx.doi.org/10.1016/0090-4295(91)80324-Z
6. Gonzalez JA, Marcol BR, Wolf MC. Complications of intravesical Bacillus Calmette-Guerin: A case report. *J Urol* 1992;148:1892-3.
7. De Souza Rocha M, Campagnari JC. Granulomatous renal mass after treatment with intravesical Bacille Calmette-Guerin. *AJR Am J Roentgenol* 1994;163:996-7. http://dx.doi.org/10.2214/ajr.163.4.8092061
8. Goh PYT, Htoo MM, Yeong KY. Case report: Renal granuloma following intravesical Bacillus Calmette-Guerin. *Clin Radiol* 1996;51:69-71. http://dx.doi.org/10.1016/S0009-9260(96)80225-X
9. Siskron FT, Venable DD, Gonzalez E, et al. Granulomatous mass in a nonrefluxing renal unit after bacillus Calmette-Guerin therapy for bladder cancer. *J Urol* 1997;158(3 Pt 1):882-3. http://dx.doi.org/10.1097/00005392-199709000-00056
10. Wada Y, Sugiyama Y, Kikukawa H, et al. Isolated renal tuberculosis following intravesical Bacillus Calmette-Guérin therapy for bladder cancer. *Urol Int* 2004;72:257-60. http://dx.doi.org/10.1159/000077126
11. Senes AT, Badet I, Lyonnet D, et al. Granulomatous renal masses following intravesical bacillus Calmette-Guerin therapy: The central unaffected calyx sign. *Br J Radiol* 2007;80:e230-3. http://dx.doi.org/10.1259/bjr/42250860
12. Mody GN, Tran V, Landman J. BCGosis: Case report of intravesicular bacilli calmette-Guerin causing upper tract granulomas stimulating renal mass without evidence of ipsilateral vesicoureteral reflux. *Urology* 2009;73:444:e9-10.
13. Rees RW. The effect of transurethral resection of the intravesical ureter during the removal of bladder tumours. *Br J Urol* 1969;41:2-5. http://dx.doi.org/10.1111/j.1464-410X.1969.tb09900.x
14. De Torres Mateos JA, Banús Gassol JM, Palou Redorta J, et al. Vesicorenal reflux and upper urinary tract transitional cell carcinoma after transurethral resection of recurrent superficial bladder carcinoma. *J Urol* 1987;138:49-51.
15. Schnapp DS, Weiss GH, Smith AD. Fever following intracavitary Bacillus Calmette-Guerin therapy for upper tract transitional cell carcinoma. *J Urol* 1996;156(2 Pt 1):386-8.
16. Tavolini M, Gardiman M, Benedetto G, et al. Unmanageable fever and granulomatous renal mass after intracavitary upper tract Bacillus Calmette-Guerin therapy. *J Urol* 2002;167:244-5. http://dx.doi.org/10.1016/S0022-5347(05)65425-0
17. Rhee JJ, Jarrett TW. Percutaneous Management of Upper Urinary Tract Transitional Cell Carcinoma. *Smith's Textbook of Endourology*. 3rd edition. 2012;ch28. http://dx.doi.org/10.1002/9781444345148.ch28
18. Audenet F ,Traxer O, Bensalah K, et al. Upper urinary tract instillations in the treatment of urothelial carcinomas: A review of technical constraints and outcomes. *World J Urol* 2013;31:45-52. http://dx.doi.org/10.1007/s00345-012-0949-3
19. Bellman GC, Sweetser P, Smith AD. Complications of intracavitary Bacillus Calmette-Guerin after percutaneous resection of upper tract transitional cell carcinoma. *J Urol* 1994;151:13-5.
20. Squires FB, Coakley FV, Berg WJ, et al. Bilateral renal masses after local Bacillus Calmette-Guerin therapy for postcystectomy ureteral cancer. *Abdom Imaging* 1999;24:200-1. http://dx.doi.org/10.1007/s002619900477
21. Rentsch CA, Birkhäuser FD, Biot C, et al. Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. *Eur Urol* 2014;66:677-88. http://dx.doi.org/10.1016/j.eururo.2014.02.061

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