Aorto-enteric fistula development secondary to mycotic abdominal aortic aneurysm following intravesical bacillus Calmette–Guerin (BCG) treatment for transitional cell carcinoma of the bladder

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INTRODUCTION: Intravesical BCG–instillation for bladder cancer is considered safe but is not without risk. While most side-effects are localised and self-limiting, the development of secondary vascular pathology is a rare but significant complication.

PRESENTATION OF CASE: A 77-year-old male presented with a mycotic abdominal aortic aneurysm and associated aorto-enteric fistula 18 months after receiving intravesical BCG-instillations for early stage transitional cell carcinoma.

DISCUSSION: Response rates to intravesical BCG for early stage transitional cell carcinoma are high. The procedure produces a localised inflammatory response in the bladder but the exact mechanism of action is unclear. The treatment is generally well tolerated but BCG-sepsis and secondary vascular complications have been documented.

Mycotic abdominal aneurysm with associated aorto-enteric fistula secondary to BCG is very rare. Few examples have been documented internationally and the extent of corresponding research and associated management proposals is limited.

Surgical options include in situ repair with prosthetic graft, debridement with extra-anatomical bypass and, occasionally, endovascular stent grafting. Recommended medical therapy for systemic BCG infection is Isoniazid, Rifampicin and Ethambutol.

CONCLUSION: Current screening methods must be updated with clarification regarding duration of anti-tuberculous therapy and impact of concomitant anti-tuberculous medication on the therapeutic action of intravesical BCG. Long-term outcomes for patients post graft repair for mycotic aneurysm are unknown and more research is required regarding the susceptibility of vascular grafts to mycobacterial infection. Recognition of the risks associated with BCG-instillations, even in immunocompetent subjects, is paramount and must be considered even several months or years after receiving the therapy.

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chronic left upper limb pain secondary to compression neuropathy, treated with Pregabalin 150 mg BD.

On initial examination he was haemodynamically stable with equal blood pressures of 157/84 mmHg in both arms and a Glasgow Coma Scale (GCS) of 15. He was tender on light palpation of the epigastric and umbilical areas but a pulsatile lesion could not be palpated due to a degree of abdominal distension and body habitus. There was no mucus, fresh blood or melaena on rectal examination. Erect chest X-ray did not show any evidence of perforated visera; however, ultrasound found an infra-renal abdominal aortic aneurysm with no identifiable free fluid in the peritoneum.

Thoraco-abdominal computed tomography (CT) confirmed the presence of a 6 cm × 5.5 cm aortic aneurysm. A contained leak and associated haematoma proximal to the right psoas muscle was also identified (Fig. 1i); as was a suspected migration of blood into the duodenum (Fig. 1ii). The iliac arteries were noted to be patent but narrowed bilaterally and atheromatous. Consequently, the patient was deemed unsuitable for endovascular aneurysm repair (EVAR) and prepared for open surgical management.

During transfer to theatre, the patient developed haematemesis and melaena, but as blood loss was minimal and haemodynamic stability maintained during anaesthetic induction, operative repair proceeded.

Intra-operatively the aneurysm seemed mycotic in nature due to its saccular and lobulated appearance (Fig. 2). An aorto-duodenal fistula was also noted and aneurysmal specimens were collected for assessment. Surgical repair was performed using a 14 mm Gelsoft graft pre-soaked in Rifampycin with insertion of a gastroduodenoscopy drain and feeding jejunostomy.

Frank haematemesis on extubation necessitated a post-operative tracheostomy. Ionotropes were commenced due to a significant drop in systolic blood pressure, the development of a compensatory tachycardia and increased oxygen requirement.

While the harvested tissue did not demonstrate acid-fast bacilli, extensive caesating necrosis, palisaded epitheloid granuloma and the presence of multinucleated giant cells were highly suggestive of tuberculosis.

The patient underwent respiratory review 7 days post-procedure and was commenced on enteric anti-tuberculous preparations per jejunostomy. The following day, left abdominal wall cellulitis and worsening abdominal distension was observed with a significant amount of draining faeculant fluid and associated leukocytosis (21.7 × 10⁹/L).

Repeat abdominal CT showed a moderate amount of free fluid in the peritoneum and a disproportionately large amount of free gas for the respective post-operative date; both findings suggestive of perforation or anastomotic leak. The patient consequently underwent laparotomy and insertion of a proximal loop jejunostomy. Free gas and over 3 l of faeculant fluid were found in the peritoneal cavity and a leak at the feeding jejunostomy site was located. Peritoneal saline lavage was performed with insertion of pelvic-, left- and right upper quadrant drains.

On return to the high dependency unit, the patient developed acute renal failure and was commenced on haemofiltration. Oxygen requirement again increased to 50% via tracheostomy and chest X-ray showed bibasal consolidation. Ionotrope requirements increased and renal function deteriorated further despite intervention. Thirteen days post-operatively, the patient passed away.

3. Discussion

BCG is a live attenuated strain of Mycobacterium bovis, rendered anti-virulent by culture on a beef bile medium. It was first used as an instillation for superficial bladder cancer in 1976 by Morales et al. Since then it has become the preferred treatment for in situ bladder carcinoma, immunoprophylaxis after resection of Ta/T1 disease, and for recurrent stage Ta disease, with response rates of 60–94% reported for early stage transitional cell carcinoma.

BCG-instillation produces a localised inflammatory response in the bladder but the exact mechanism of action is unclear. Recent literature suggests the role of a mononuclear cell infiltrate and the neutrophil-mediated release of tumour necrosis factor apoptosis related ligand (TRAIL: Apo-2L).

Intravesical BCG is a well-tolerated treatment. Adverse symptoms, including haematuria, bacterial cystitis, granulomatous prostatitis, orchitis and epididimitis, tend to be localised and self-limiting, although systemic reactions such as fever (2.9%), malaise, hepatitis and pneumonitis (0.7%) are recognized. BCG-sepsis as well as ocular and vascular complications such as abdominal aortic aneurysms are rare. Fifty percent of mycotic aneurysms secondary to BCG instillation have ruptured and necessitated emergency surgery.
There are few documented cases of BCG-instillations causing both mycotic aneurysms and primary aortoenteric fistulas. A 2009 literature review of cases since 1975 found only 21 patients with mycotic aneurysms attributable to BCG therapy. Aneurysms of the abdominal aorta are most common, but aneurysms of other arteries including femoral, popliteal and carotid arteries are also documented.

Furthermore, there are less than 20 documented cases of aortoenteric fistulas following BCG infection, developing concurrently or independently of mycotic aneurysms. Mortality rates over 50% have been documented for such fistula development.

Proposed mechanisms for the infection of vasculature by M. bovis include haematogenous dissemination causing direct intimal colonization (particularly after urological trauma at the time of instillation), lymphatic spread in the retroperitoneum, or direct extension from an infected psoas abscess. Positive lung biopsies and sputum samples, alongside the retrieval of non-caesating granulomas from bone marrow aspirates and liver biopsies in BCG patients, supports the idea of haematological spread. Moreover, a polysaccharide holotoxin consisting of glucose, heptose, glucosamine and galactosamine inside the cell membrane of M. bovis has been extracted and seen to increase vascular permeability and induce complement cascade activation.

The classic triad of pulsatile mass, abdominal pain and fever may be present in a patient with a mycotic aneurysm secondary to M. bovis, but this is not always the case. The difficulty of identifying BCG on tissue samples complicates diagnosis further. The gold standard mycobacterial culture requires a minimum incubation period of 6–8 weeks while acid-fast stains require a minimum of 10,000 organisms per gram of tissue to obtain a positive result. BCG may also be detected using PCR or inferred from the presence of typical caseating granulomas.

Management of complications resulting from BCG therapy can be divided into that of the specific complication and that of the BCG infection. With regard to mycotic aneurysms, surgical options include in situ repair with a prosthetic graft, debridement with extra-anatomical bypass and, occasionally, endovascular stent grafting. In our case, this was complicated by the aorto-enteric fistula.

Recommended medical therapy for systemic BCG infection is Isoniazid, Rifampicin and Ethambutol (Pyrazinamide is not recommended due to widespread resistance). Some advocate the addition of corticosteroids, particularly for granulomatous hepatitis. While the duration of anti-microbial therapy is a contentious issue, lifelong therapy with periodic clinical evaluation and imaging studies such as CT, is advised in cases of in situ aortic reconstruction.

4. Conclusion

This case highlights the risks posed by BCG-instillation and supports recommendations to safeguard against and monitor for potentially life-threatening complications. Clarification is required regarding duration of anti-tuberculous therapy and the impact of concomitant anti-tuberculous medication on the therapeutic action of instillations. Long-term outcomes for patients post graft repair for mycotic aneurysm are unknown and more research is required regarding the susceptibility of vascular grafts to mycobacterial infection.

Recognition of the risks associated with BCG-instillations, even in immunocompetent subjects, is paramount. The consideration of such effects in patients presenting to hospital even several months or years after receiving BCG therapy is equally significant.

5. Learning points

- Intravesical bacillus Calmette–Guerin (BCG) installation is a recognized adjunct therapy with high response rates for early bladder cancer.
- Although an effective and generally well-tolerated treatment, side-effects range from localised irritation to compromised vascular wall integrity. These should be considered even several months or years after receiving BCG therapy.
- The proposed mechanism of action of BCG incorporates TRAIL and the recruitment of various immune mediators.
- There is a need for review of current guidelines on anti-tuberculous therapy as well as definitive recommendations regarding long-term vascular surveillance for patients undergoing BCG therapy.

Conflict of interest statement

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Ethical approval

Consent obtained from patient’s next of kin.

Authors’ contributions

Dr Anthony Roylance, Mr John G Mosley, Mr Mohideen Jameel, Dr Virginie Walker and Dr Axel Sylvan have all contributed to the analysis and interpretation of data, drafting and revising of the article and have given final approval of the version to be submitted.

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