Central European Journal of Urology

CASE REPORT

UROLOGICAL ONCOLOGY

Guillain-Barré Syndrome following intravesical Bacillus Calmette-Guérin therapy for bladder cancer: a rare and intriguing case report

Vincent Khor[1,2], Omar Fahmy[1,2,3], Christopher Kheng Siang Lee[1,2,3], Mohd Ghani Khairul-Asri[1,2,3]

[1]Department of Urology, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, Malaysia
[2]Department of Urology, Hospital Serdang, Selangor, Malaysia
[3]Department of Urology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, Malaysia

Citation: Khor V, Fahmy O, Lee CKS, Khairul-Asri MG. Guillain-Barré Syndrome Following Intravesical Bacillus Calmette-Guérin Therapy for Bladder Cancer: A Rare and Intriguing Case Report. Cent European J Urol. 2023; 76: 311-314.

Article history
Submitted: April 24, 2023
Accepted: Oct. 25, 2023
Published online: Nov. 20, 2023

Corresponding author
Khairul Asri Mohd Ghani
Hospital Sultan Abdul Aziz Shah UPM
Faculty of Medicine and Health Sciences
Department of Urology
Universiti Putra Malaysia
Darul Ehsan 43400,
Malaysia
khairulasri@upm.edu.my

Intravesical Bacillus Calmette-Guérin (BCG) therapy is a standard treatment for non-muscle invasive bladder cancer, but some patients experience side effects that lead to treatment discontinuation. Local side effects are typically mild, while systemic side effects can be severe and life-threatening. BCG therapy has immunotherapy effects on bladder cancer, but the mechanism is not fully understood. Due to its effect on the immune system, patients may also develop rare autoimmune complications, such as neuropathy. This case report suggests a potential association between BCG therapy and Guillain-Barré Syndrome (GBS), as a patient developed GBS after receiving intravesical BCG therapy for invasive bladder cancer.

Key Words: Guillain-Barré Syndrome ‹› autoimmune neuropathy ‹› intravesical Bacillus Calmette–Guérin ‹› BCG ‹› invasive bladder cancer

CASE PRESENTATION

A 52-year-old Chinese lady presented with painless gross haematuria for one month. She has underlying hypertension and a history of transabdominal hysterectomy and bilateral salphingo-oophorectomy (TAHBSO) for uterine fibroid many years ago, for which she was started on hormonal replacement therapy. She is a non-smoker with no occupational hazard or family history of genitourinary cancer. Physical examination was unremarkable. Electrocardiogram showed sinus rhythm with a regular pulse rate ranging from 70–80 beats per minute (bpm).

Computed tomography (CT) showed a 4.6 x 4.7 cm Bosniak 4 complex renal cyst at the upper pole of right kidney. Flexible cystoscopy revealed multiple papillary bladder tumours, with the largest measuring 3 cm. She underwent transurethral resection of bladder tumour (TURBT), and the histopathological examination showed high-grade invasive urothelial carcinoma with no muscularis propria invasion (pT1HG). She was given a single course of intravesical mitomycin post-operatively. No tumour was found during the second relook TURBT. She subsequently underwent laparoscopic right radical nephrectomy. Histopathological examination showed pT1b

WHO/ISUP Grade 2 clear cell RCC with negative surgical margins. She recovered well and had a normal heart rate (70–80 bpm).

One month later, she was started on intravesical Bacillus Calmette–Guérin (BCG) induction therapy using Immunobladder® (Japan BCG Laboratory). One vial of 80mg BCG was diluted into 50cc and given as intravesical therapy through a urethral catheter. She tolerated the treatment well with no complications. After the third treatment cycle, she complained of peripheral numbness and tingling sensation over bilateral limbs. Subsequently, she had right upper limb and lower limb weakness, which progressed bilaterally. The sensorimotor symptoms started distally and progressed in ascending direction upwards. Muscle power bilaterally was 4/5 with absent knee reflex bilaterally. She was also found to have unexplained sinus tachycardia with no significant cause. We excluded infections and venous thromboembolism, which could cause tachycardia.

CT brain showed no significant intracranial abnormality. Whole spine magnetic resonance imaging showed no evidence of spinal canal stenosis or abnormal signal to suggest myelopathy or spinal metastasis. Lumbar puncture was performed, and CSF analysis showed albumin-cytological dissociation. The CSF protein was elevated (1702 mg/L), while cytology, microscopic examination (cell count: 0) and cultures of CSF were clear and negative. A nerve conduction study (NCS) demonstrated electrophysiological evidence of diffuse sensorimotor (predominantly demyelinating) polyneuropathy. Her serum immunological workup suggested autoimmune aetiology (Table 1).

Table 1. *Serological Workup*

Positive	Anti-Nuclear Antibody (ANA), P-Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA), Sulfatide IgM, Sulfatide IgG
Negative	Anti-dsDNA, C-ANCA, Anti-Myeloperoxidase (MPO), Anti-Proteinase 3 (PR3), Extracable Nuclear Antigens Panel [SS-A(Ro), SS-B (La), RNP, Sm, Scl-70, Jo1), IgM and Ig G for (GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b), Anti-Amphiphysin, Anti-CV2 Antigen, Anti-Paraneoplastic Antigen Ma2 (PNMa2Ab), Anti-Ri (RiAb), Anti-Yo (YoAb), Anti-Hu (HuAb), Anti-Recoverin (RecovAb), Anti-SOX1 (SOX1Ab), Anti-Titin (TitinAb)

She was started on intravenous immunoglobulin (IVIg) therapy. Her symptoms improved significantly with the resolution of tachycardia (Figure 1). The patient's neurological and motor function also improved with rehabilitation. NCS performed two months after IVIg showed significant improvement in sensorimotor polyneuropathy (Figure 2). She refused further NCS as she had recovered to her normal baseline. Further maintenance intravesical BCG therapy was withheld.

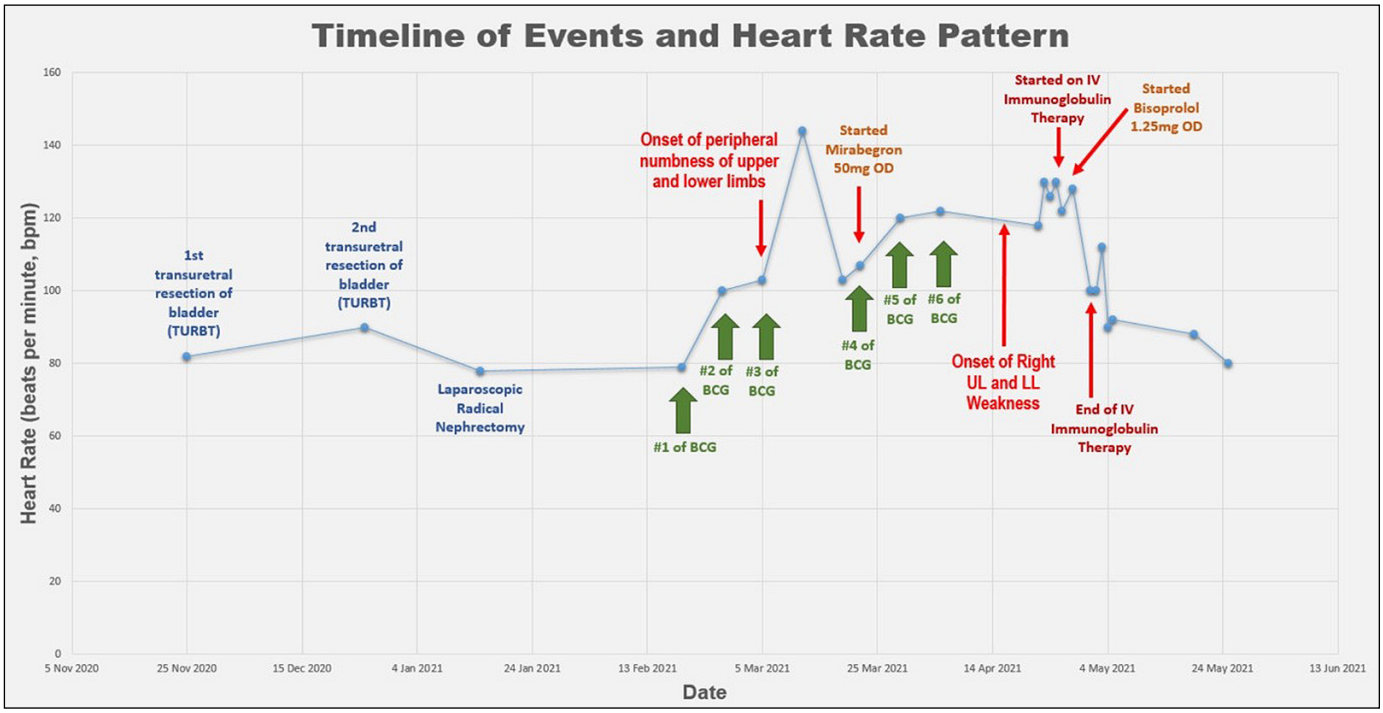

Figure 1. *Heart rate (HR) pattern – Patient had resting HR around 70 – 80 bpm. After starting intravesical BCG therapy, she developed sinus tachycardia and no cause was found despite extensive investigations. The HR returned to baseline after completion of intravenous immunoglobulin (IVIg) therapy and improvement of neurological symptoms.*

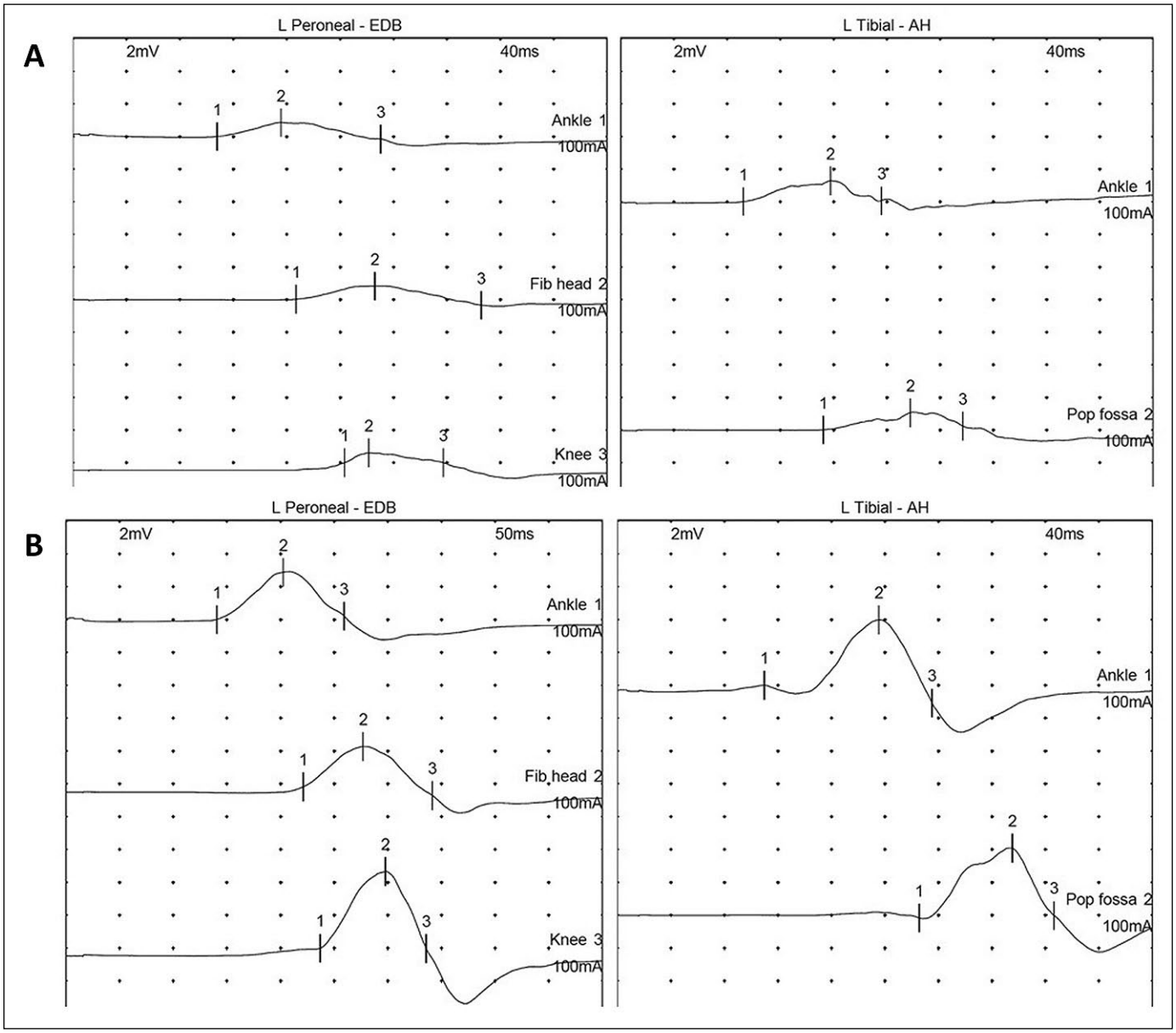

Figure 2. *Nerve Conduction Studies (NCS) – **(A)** Pre-IVIg NCS showing that the Compound Muscle Action Potential (CMAP) were reduced and temporally dispersed on bilateral upper and lower limbs, with prolonged F wave of bilateral tibial nerves. **(B)** Post-IVIg NCS showing improvement of CMAP amplitude while F wave of the bilateral tibial and peroneal were within normal limits.*

Surveillance cystoscopy and CT scans did not show any evidence of cancer recurrence.

DISCUSSION

Guillain-Barré Syndrome is an immune-mediated polyradiculoneuropathy characterised by the acute onset of neurological symptoms, including progressive weakness, symmetric flaccid paralysis or sensory abnormalities. This condition was first described a century ago by three French neurologists, Georges Guillain, Jean-Alexandre Barré, and Andre Storhl, in two patients with albumin-cytological dissociation in their cerebrospinal fluid (CSF) [1]. Through decades of research, we now learn that GBS can broadly be classified into acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute axonal motor neuropathy (AMAN), depending on the location of the target antigen. However, GBS is clinically heterogeneous, and patients can present with atypical symptoms, as evidenced by case reports in the medical literature. Prior respiratory tract or gastrointestinal infections, older vaccines such as the brain-derived Semple rabies vaccine, and the use of immune check-

point inhibitors in oncological patients have been associated with GBS [2]. Although rare, GBS has been linked to tuberculosis and has been reported in some cases following BCG vaccination [3]. Only one case report describes the possible association of GBS and intravesical BCG instillation The patient experienced BCG sepsis due to a traumatic catheterisation and later developed GBS after starting anti-tuberculosis treatment. The systemic BCG dissemination could have activated the body's immune cascade resulting in an autoimmune reaction and GBS [4].

To diagnose GBS, the patient should at least have symmetrical flaccid weakness and decreased reflexes without any alternative causes. Other criteria include a monophasic illness pattern, albumin-cytological dissociation of CSF and electrodiagnostic evidence of neuropathy. In our case, although the serological markers are not classical of GBS, the monophasic clinical symptoms, albumin-cytological dissociation in CSF, and the NCS were quite suggestive of GBS.

The immune response caused by BCG is mostly not specific. BCG has a direct cytotoxic effect on cancer cells by causing apoptosis, inducing cell necrosis, oxidative stress and others. After the absorption and internalisation of BCG, it activates the innate and acquired immune system, releasing various types of interleukins and cytokines. These activate the T-lymphocytes, macrophages, neutrophils, natural killer cells and others, which can continue to release cytokines, further promote the immune cascade reaction, and then kill the tumour cells [5]. We postulate that these immunological reactions produce autoimmune antibodies with a similar structure that can bind to the receptors on the myelin sheath, resulting in GBS. This might explain why we did not find the classical GBS antibodies during our serological examination. It is possible that the sinus tachycardia served as an initial warning sign of the inflammatory mediators' influence before GBS set in.

It is imperative to acknowledge that this is only the second documented occurrence of a correlation between GBS and intravesical BCG therapy. The rarity of GBS resulting from this treatment cannot be overstated, and it is crucial for healthcare professionals to be aware of its potential adverse events and consider GBS when confronted with neurological symptoms following intravesical BCG therapy. Further observation and investigation are necessary to fully comprehend the underlying causes and accurately ascertain the risk of GBS with BCG therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Jasti AK, Selmi C, Sarmiento-Monroy JC, Vega DA, Anaya JM, Gershwin ME. Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment. Expert Rev Clin Immunol. 2016; 12: 1175-1189.
2. Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. Lancet. 2021; 397: 1214-1228.
3. Wilmshurst JM, Macleod MJ, Hughes E, Hughes RA. Acute sensory neuropathy in an adolescent girl following BCG vaccination. Eur J Paediatr Neurol. 1999; 3: 277-279.
4. Webb K, Venkatesan P. Guillain Barré syndrome associated with bladder instillation of Bacille Calmette Guérin (BCG). JMM Case Rep. 2018; 5: e005164.
5. Han J, Gu X, Li Y, Wu Q. Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect. Biomed Pharmacother. 2020; 129: 110393.