



ESETISMERTETÉS

CASE REPORT

Guillain-Barré syndrome caused by intravesical instillation of Bacillus Calmette-Guérin

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Introduction – Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy. In the vast majority of patients, 1–4 weeks before the onset of GBS-related symptoms, an event such as upper respiratory tract or gastrointestinal tract infection, surgical intervention or vaccination is present. To the best of our knowledge, this is the first case of GBS that occurred after intravesical Bacillus Calmette-Guérin (BCG) therapy in the absence of tuberculosis or any other infection in the English literature.

Case report – A 65-year-old male patient, who had no systemic disorders except hypertension and coronary artery disease, underwent transurethral resection of a bladder tumour further to imaging studies investigating macroscopic haematuria. A pathologic examination revealed a non-muscle-invasive high-grade (pT1HG) transitional cell carcinoma. Immediately after the fourth cycle of intravesical BCG, which was administered 2 months after surgery, the patient experienced numbness and weakness in his lower and upper extremities, respectively. There were no signs or symptoms related to an acute cranial pathology or infectious disease. Nerve conduction studies, which were carried out on the 7th day after the onset of the neurologic symptoms, revealed a demyelinating sensorimotor polyneuropathy with mild secondary axonal damage in upper and lower limbs with a sural sparing pattern.

Conclusion – Without tuberculosis infection, GBS can occur secondary to increased immune response and antibodies triggered by intravesical BCG therapy. However, considering the worldwide use of BCG vaccination and thousands of intravesical BCG therapies, this is a very rare adverse effect.

Keywords: BCG; bacille Calmette-Guérin; Guillain-Barré syndrome; intra-vesical

Bacillus Calmette-Guérin intravesicalis instillációja által okozott Guillain-Barré-szindróma

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Bevezetés – A Guillain-Barré-szindróma (GBS) egy akut gyulladásos demyelinációs polyneuropathia. A betegek túlnyomó többségénél a GBS-hez kapcsolódó tünetek megjelenése előtt 1–4 héttel valamilyen esemény, például felső légúti vagy gastrointestinalis traktus fertőzés, műtéti beavatkozás vagy védőoltás jelentkezik. Legjobb tudomásunk szerint ez az első olyan GBS-eset, amely intravesicalis bacillus Calmette-Guérin (BCG-) terápia után fordult elő tuberculosis vagy bármilyen más fertőzés hiányában az angol szakirodalomban.

Esetismertetés – Egy 65 éves férfi beteg, akinek magas vérnyomás és koszorúér-betegség kivételével nem volt szisztémás betegsége, makroszkópos haematuria okát kereső képalkotó vizsgálatok után hólyagdaganat transzurethralis reszekcióján esett át. A patológiai vizsgálat nem izominvazív, előrehaladott (pT1HG) átmeneti sejtes carcinomát mutatott ki. Közvetlenül a műtét után két hónappal beadott negyedik intravesicalis BCG-ciklust követően a beteg zsibbadást és gyengeséget tapasztalt az alsó, illetve a felső végtagjaiban. Nem volt akut cranialis patológiára vagy fertőző betegségre utaló jel vagy tünet. A neurológiai tünetek megjelenését követő 7. napon elvégzett idegvezetési vizsgálatok demielinizáló szenzomotoros polyneuropathiát mutattak ki, enyhe másodlagos axonalis károsodással a felső és alsó végtagokban, megkímélt suralis mintázattal.

Következtetés – Az intravesicalis BCG-terápia által kiváltott fokozott immunválasz és antitesttermelés következtében tuberculosis-fertőzés nélkül is előfordulhat GBS. Tekintettel azonban a BCG-vakcináció világméretű használatára és az intravesicalis BCG-terápiák ezreire, ez nagyon ritka mellékhatás.

Kulcsszavak: BCG, bacillus Calmette-Guérin, Guillain-Barré-szindróma, intravesicalis kezelés

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy characterized by symmetrical weakness and areflexia¹. In the vast majority of patients, 1-4 weeks before the onset of GBS-related symptoms, an event such as upper respiratory tract or gastrointestinal tract infection, surgical intervention, or vaccination is present². Its association with tuberculosis has been shown, despite being rare^{3,4}. A patient with GBS secondary to miliary tuberculosis, which is attributed to intravesical Bacillus Calmette-Guérin (BCG) therapy, is reported in the literature⁵. However, to the best of our knowledge, ours is the first case of GBS that occurred after intravesical BCG therapy in the absence of tuberculosis or any other infection in the English literature.

Case report

A 65-year-old male patient with a history of hypertension, coronary artery disease, and smoking for 40 years was admitted to our clinic with macroscopic haematuria. Ultrasonography and computed tomography urography revealed tumoral lesions 20 mm and 10 mm in size on the left lateral wall (**Figure 1**). After transurethral resection of the bladder tumour (TUR-B), a pathologic examination showed a non-muscle-invasive high-grade (pT1HG) transitional cell carcinoma.

After 4 weeks, a re-TUR-B was performed. Three weeks after the re-TUR-B, intravesical BCG induction therapy was administered. Preceding each BCG instillation, complete urinalysis was conducted and urinary tract infection and haematuria were eliminated. No traumatic catheterization was encountered and the first four cycles of intra-vesical BCG therapy were uneventful (SII-Onco-BCG 40 mg/mL x 2 vial®). There was a one-week interval between each cycle. Before the fifth cycle of the induction therapy, the patient presented in a wheelchair. After reporting that he had felt numbness and weakness in his legs and arms 4 and 2 days before, respectively, he was referred to the emergency department.

He had no symptoms of fever, chill, cough, expectoration, or shortness of breath. A physical examination of the thorax was negative and oxygen saturation on room air was 98%. Chest X-ray and computed tomography of the thorax were unremarkable. A neurologic examination was negative for nuchal rigidity and facial asymmetry, and extraocular eye movements were intact. Upper and lower extremity Medical Research Council (MRC) scale scores were

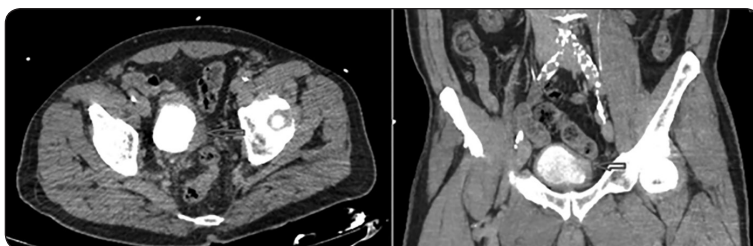


Figure 1. Images of bladder cancer in computed tomography urography

3+/5 bilaterally and symmetrically distal and then proximal in the follow-up. Glove-and-stocking hypoesthesia was present. Deep tendon reflexes were decreased in the upper extremities and absent in the lower extremities. Cranial and cervical magnetic resonance imaging was normal. No remote metastasis of the bladder cancer was present in fluorodeoxyglucose positron emission tomography. The patient was hospitalized with a pre-diagnosis of GBS.

Levels of C-reactive protein, alkaline phosphatase, thyroid stimulating hormone, vitamin B12, and folate were normal, as well as complete blood count analysis. Urine culture and serologic tests for human immunodeficiency virus, syphilis, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus were negative. No serum paraproteins were present. Antinuclear antibodies, dsDNA, cANCA, and anti-citrullinated protein antibody tests were all negative. Lumbar puncture (LP) was not performed due to the patient's refusal. Nerve conduction studies performed on the 7th day after the onset of neurologic symptoms showed a demyelinating sensorimotor polyneuropathy with sural sparing pattern and with mild secondary axonal damage in the upper and lower limbs. F responses were lost in all examined motor nerves and multiple A-waves were recorded from the left tibial nerve (**Table 1, Figure 2**). The patient developed severe neuropathic pain in his legs, which was relieved by amitriptyline. After partial improvement with intravenous immunoglobulin of 0.4 g/kg for 5 days, the patient

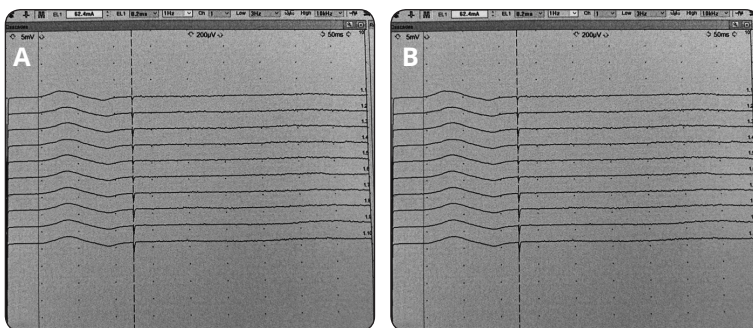


Figure 2. Absence of F wave in the left ulnar motor nerve (A) and left median motor nerve (B)

was referred to a physical medicine and rehabilitation clinic; therefore, we could not perform a follow-up EMG although we planned it in the 3rd week.

Discussion

To the best of our knowledge, our patient is the first case of GBS in the English literature that started after intravesical BCG therapy without any signs of tuberculosis. In the nerve conduction studies performed in the 1st week, the absence of conduction response in sensory nerve conduction examinations except for the sural sparing pattern, prolonged distal latencies in motor nerve conduction examinations, absence of F responses, and the presence of multiple A waves in the tibial nerve suggested the diagnosis of typical acute inflammatory demyelinating polyneuropathy, and we completed our examination with nerve conduction examination without performing needle EMG. We thought that the median and ulnar response amplitudes being slightly lower than normal, despite the demyelinating polyneuropathy in the foreground, might be compatible with a very mild and new-onset axonal involvement. The limitations were the lack of LP due to the patient's refusal and the lack of follow-up EMG in the 3rd week due to the patient's referral to a rehabilitation clinic.

Guillain-Barré syndrome is an autoimmune disease in which T-cell activation causes the production of antibodies against peripheral nerve antigens. This activation can be triggered by vaccination, surgical interventions and infectious agents such as Epstein-Barr virus, cytomegalovirus, *Mycobacterium pneumoniae*, and *Campylobacter jejuni*, although the initiator cannot be found in 40% of cases^{5,6}.

There are several GBS cases associated with *Mycobacterium tuberculosis* infection in the literature^{3,4}. However, in two cases, GBS was ascribed to BCG vaccines. One was a 13-year-old girl whose gait deteriorated with frequent falls until she was unable to stand 4 days after a BCG vaccination and who was diagnosed as having GBS⁷. The other patient was a 68-year-old man who developed GBS secondary to miliary tuberculosis caused by intra-vesical BCG therapy⁵. In our patient, GBS started after intravesical BCG therapy without any signs of tuberculosis. Apart from exposure to intravesical

Table 1. The report of electromyography – nerve conduction studies

Motor Nerve Conduction Studies			
Nerve	Lat	Amp	CV
	ms	mV	m/s
Medianus Motor Right			
Wrist – APB	6.21	4.4	
Elbow–Wrist	13.6	4.0	33.8
Peroneus Motor Left			
Ankle – EDB	5.94	1.75	
Fib. head – Ankle	13.3	1.10	42.1
Ab. fib. head – Fib. head	15.2	1.11	42.1
Peroneus Motor Right			
Ankle – EDB	5.99	2.4	
Fib. head – Ankle	12.6	1.21	51.4
Ab. fib. head – Fib. head	20.3	1.01	10.4
Tibialis Motor Left			
Ankle – Abd hal	4.75	5.0	
Knee – Ankle	13.1	4.0	45.5
Tibialis Motor Right			
Ankle – Abd hal	6.19	4.0	
Knee – Ankle	15.2	2.4	41.1
Ulnaris Motor Right			
Wrist – ADM	3.19	4.2	
Bl. elbow – Wrist	7.63	3.4	56.3
Ab. elbow – Bl. elbow	10.3	2.8	56.2
Sensory Nerve Conduction Studies			
Nerve	Peak Lat	Amp	CV
	ms	uV	m/s
Medianus Sensory Right			
Dig II – Wrist	–	–	
Suralis Sensory Left			
Mid. lower leg – Lat. Malleolus	3.69	4.4	41.1
Suralis Sensory Right			
Mid. lower leg – Lat. Malleolus	3.12	2.8	48.3
Ulnaris Sensory Right			
Dig V – Wrist	–	–	

BCG, we found no evidence of any other pathogen that might have been a trigger for GBS.

Intravesical BCG therapy causes a massive local immune response. Adhesion of BCG to the urothelium, which includes malignant cells, induces the secretion of cytokines and chemokines, resulting in the migration of

different immune cells to the bladder wall⁸. Cellular immunity is stimulated by phagocyte activation and the new cytokine environment, whereas humoral immunity is stimulated by the direct immune response of CD4+ T cells with differentiation to TH1 and/or TH2 cells⁹. Besides the local immunotherapeutic effects of intravesical BCG, systemic immunologic effects are also demonstrated¹⁰.

Conclusion

Guillain-Barré syndrome can develop secondary to increased immune response and antibody production due to intravesical BCG therapy in the absence of tuberculosis infection. However, considering the worldwide use of BCG vaccination and thousands of intravesical BCG therapies, this is a very rare adverse effect.

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Collected the data, and drafted and revised the manuscript. Both authors read and approved the final manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE – All procedures in this study were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from individual participants included in the study.

CONSENT FOR PUBLICATION – Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS – The authors declare that they have no conflict of interest.

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