Surgical Neurology International

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Case Report

Mycobacterium bovis spondylodiscitis after intravesical Bacillus Calmette-Guérin therapy

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Received: 26 August 11 Accepted: 23 September 11 Published: 14 November 11

This article may be cited as:
Obaid S, Weil AG, Rahme R, Gendron C, Shedid D. *Mycobacterium bovis* spondylodiscitis after intravesical Bacillus Calmette-Guérin therapy. Surg Neurol Int 2011;2:162.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2011/2/1/162/89879

Abstract

Background: Intravesical instillations of live-attenuated Bacillus Calmette-Guérin (BCG) are a well-known and effective method for prevention and treatment of bladder carcinoma and carcinoma *in situ*. Although considered a safe procedure with rare side effects, local and systemic complications may occur. While long bone ostemolyelitis has been well described, very few reports of BCG spondylodiscitis exist in the literature.

Case Description: A 67-year-old man developed low back pain, anorexia, and weight loss 11 months after a 6-week course of intravesical BCG instillations for the treatment of bladder carcinoma *in situ*. Imaging studies revealed L1-L2 spondylodiscitis with epidural and bilateral psoas abscesses. Tissue cultures obtained by percutaneous computed tomography-guided aspiration were positive for *Mycobacterium bovis*. Despite triple antituberculous therapy (isoniazid, rifampin, and ethambutol), clinical and radiological progression occurred. Therefore, L1 and L2 corpectomies with extensive debridement were performed, followed by 360° anterior-posterior instrumented fusion. After 20 months of follow-up, the patient remains asymptomatic and recurrence-free.

Conclusion: *Mycobacterium bovis* spondylodiscitis is a rare complication of intravesical BCG therapy. Although medical therapy with antituberculous agents is the first-line treatment, surgical decompression, debridement, and stabilization may be necessary in refractory cases.

Key Words: Bacillus Calmette-Guérin, osteomyelitis, spondylodiscitis, tuberculosis

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.89879

Quick Response Code:

INTRODUCTION

Intravesical instillations of live-attenuated Bacillus Calmette-Guérin (BCG) are a well-known and effective method for prevention and treatment of bladder carcinoma and carcinoma *in situ* (CIS).[1,2,4,7,14,15,17-19] Although considered a safe procedure with rare side effects, local and systemic complications may occur.[16,29] While long bone ostemolyelitis has been well described, very few reports of BCG spondylodiscitis exist in the literature.[1,2,4,7,14,15,17-19,21,24,27] We report a rare case of lumbar *Mycobacterium bovis* osteomyelitis following

intravesical BCG immunotherapy, which progressed under triple antituberculous therapy and warranted surgical decompression, debridement, and stabilization.

CASE REPORT

A 67-year-old man presented with a 5-month history of incapacitating low back pain (LBP), anorexia, and a 5-kg weight loss. Eleven months earlier, he had undergone a 6-week course of intravesical BCG instillation for superficial transitional cell CIS of the bladder. Physical examination revealed tenderness to palpation of the upper lumbar spine, but neurological examination was unremarkable. A complete blood workup was normal, including normal white blood cell count and normal erythrocyte sedimentation rate. Blood cultures and a tuberculin skin test were also negative. Computed Tomography (CT) and magnetic resonance imaging (MRI) of the lumbosacral spine revealed L1-L2 spondylodiscitis with a small, noncompressive anterior epidural collection and bilateral psoas muscle abscesses [Figure 1]. Percutaneous CT-guided drainage of the psoas abscesses was performed and aspirate cultures revealed *M. bovis*. The patient was treated conservatively using a thoracolumbar corset and triple antituberculous therapy (isoniazid, rifampin, and ethambutol).

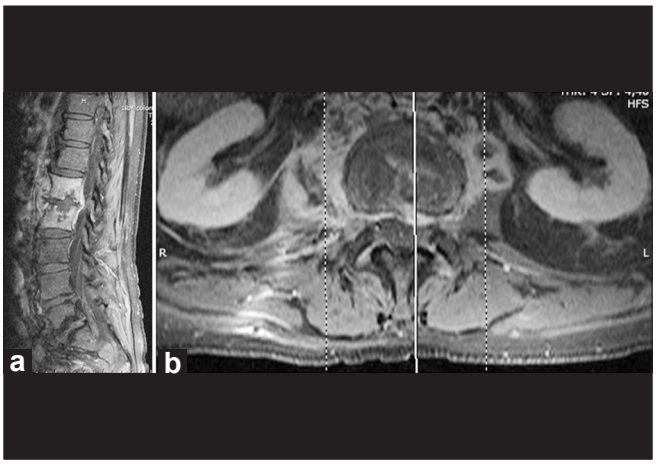

Figure 1: (a) Sagittal and (b) axial MRI of the lumbosacral spine revealed L1-L2 spondylodiscitis/osteomyelitis with a small, noncompressive anterior epidural collection and bilateral psoas muscle abscesses

Three months later, the patient exhibited worsening of his LBP with new-onset pain and mild weakness (4/5) in the right L2 distribution. Repeat CT and MRI [Figure 2] revealed progression of the spondylodiscitis with marked expansion of the anterior epidural abscess and compression of the cauda equina. Given the latter findings, surgical decompression, debridement, and stabilization were indicated. Through an anterior thoracoabdominal approach, L1 and L2 corpectomies with extensive debridement were performed, followed by T12-L3 instrumented fusion using a cadaveric femoral strut allograft [Figure 3a]. Following this first stage, a minimally invasive posterior T11-L4 instrumentation using percutaneously placed pedicle screws was performed to supplement the ventral construct [Figure 3b].

Postoperatively, the patient had an uneventful recovery with a complete resolution of his LBP and motor deficit. Antituberculous therapy was continued for a total of 9 months. After 20 months of follow-up, he

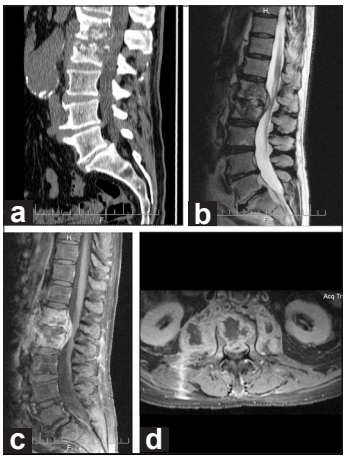

Figure 2: (a) Sagittal CT reconstructions of the lumbosacral spine demonstrate an extensive lytic process involving the L1 and L2 vertebral bodies.There is a significant involvement and narrowing of the L1-L2 disc space with endplate erosion. (b)-(d) MRI of the lumbar spine confirms CT findings and suggests L1-L2 spondylodiscitis. In addition, there is a progression of a large enhancing anterior epidural collection, which is compressing the thecal sac at L1-L2 and bilateral psoas muscle abscesses are demonstrated.

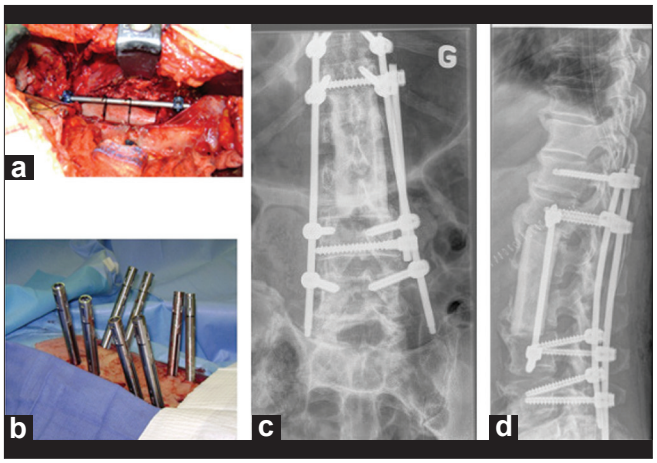

Figure 3: (a, b) Intraoperative photographs demonstrate the two-stage surgical procedure: L1 and L2 corpectomies with femoral strut grafting and T12-L3 instrumented fusion through a left thoracoabdominal approach (a), followed by minimally invasive T11-L4 posterior instrumentation using percutaneously placed pedicle screws (b). (c,d) Postoperative radiographs of the lumbosacral spine

remains asymptomatic with no evidence of infection or tumor recurrence. Radiographic imaging demonstrated satisfactory alignment [Figures 3c and 3d].

DISCUSSION

The BCG vaccine was initially used in 1921 to prevent infection from tuberculosis.[19] It is a live-attenuated strain of *M. bovis*, a component of the *Mycobacterium tuberculosis* complex.[1] Since its introduction in 1976, intravesical BCG immunotherapy has been shown to be an effective therapy for preventing and treating superficial transitional cell bladder carcinoma and CIS.[1,19] It eradicates bladder cancer through its inherent antineoplastic properties and local immune response.[22] Although generally safe, serious side effects may occur in less than 5% of patients.[15] Most serious adverse effects result from a systemic granulomatous infection with the BCG strain. Osteitis is rare following BCG immunization, occurring in less than 37 per 100,000 cases,[29] and its occurrence following intravesical BCG is exceptional. Only 13 cases of vertebral osteomyelitis resulting from intravesical BCG instillations have been previously reported in the literature[1,2,4,7,14,15,17-19,21,24,27] [Table 1]. In half of these cases, the infection showed good response to antituberculous therapy. Our case highlights that the infectious process may progress despite a three-drug regimen including isoniazid, rifampin, and ethambutol.

All previous cases of spinal BCG osteomyelitis secondary to intravesical BCG therapy have occurred at the thoracolumbar spine in elderly men (mean 79 years, range 66–90 years). Vertebral osteomyelitis in these patients is thought to result from hematogenous dissemination of BCG infection.[10,11,15,17,25] Although an immunity-mediated hypersensitivity reaction could theoretically underlie the granulomatous inflammatory response in the spine, identification of *M. bovis* in all cases (including our case) strongly suggests an actual dissemination of the bacillus from the bladder to the spine. Vascular dissemination and large-vessel mycotic vasculitis have been described following intravesical BCG immunotherapy, lending further support to hematogenous spread as a pathogenetic mechanism.[25] Injury to the bladder endothelium probably constitutes the first step for this hematogenous spread, which can occur as a result of several factors, including traumatic bladder catheterization, bladder injury during instillation, concurrent severe cystitis, bladder outlet obstruction, pelvic radiation, transurethral tumor resection, and prostate biopsy.[16,20,26,30,32] The BCG infection likely spreads through Batson's plexus, a network of valveless veins that connect the deep pelvic veins to the internal vertebral venous plexuses, which may explain its predilection for the thoracolumbar spine.[9]

Table 1: A summary of reported cases of vertebral osteomyelitis/discitis following intravesical Bacillus Calmette-Guérin instillations

Reference	Age/ Sex	Time to onset	Clinical presentation	Level and type of spinal infection	Antimicrobial therapy	Surgery	Outcome
Katz *et al.*[15]	67/M	16 months	LBP, buttock/ thigh pain, right L5 and S1 radiculopathies, anorexia	L4--L5 spondylodiscitis	INH + RIF + EMB	L4--S1 laminotomies and L4--L5 discectomy, anterior spinal decompression and L3--L5 fusion using fibular bone graft	No long-term follow-up
Fishman *et al.*[7]	90/M	4 weeks	LBP	T11--T12 osteomyelitis	INH + RIF + EMB	Open surgical biopsy	Not specified
Civen *et al.*[4]	81/M	7 months	LBP, weight loss	T12--L1 spondylodiscitis, epidural abscess	INH + RIFx 12 months	Open surgical biopsy, Harrington rods for spinal stabilization	Asymptomatic at 1 year
Sugita *et al.*[27]	71/M	2 months	LBP	T7 spondylitis	INH + RIF + SM	Anterior spinal fusion	Not specified
Morgan and Iseman[9]	77/M	2 weeks	LBP, weight loss, kyphotic deformity	T11--L1 osteomyelitis, epidural soft tissue mass	INH + RIF + EMB × 9 months, then INH + RIF × 6 months	Surgical decompression, anterior and posterior spinal fusion	"Functional" at 1 year
Rozenblit *et al*[24]	76/M	6 years	LBP, right leg pain, weight loss	L4 osteomyelitis	INH + RIF + EMB + ciprofloxacin	Percutaneous aspiration of prevertebral collection	Asymptomatic at 8 months, died 15 months later from myocardial infarction

Table 1: Contd...

Reference	Age/ Sex	Time to onset	Clinical presentation	Level and type of spinal infection	Antimicrobial therapy	Surgery	Outcome
Aljada *et al.*[2]	79/M	2.5 years	LBP, left hip pain, left lower extremity weakness	L3 osteomyelitis	INH + RIF × 12 months	Decompressive laminectomy	Persistent leg weakness at 1 year
Abu-Nader[1]	76/M	7 years	LBP, anorexia, weight loss, bilateral lower extremity weakness, paresthesias	T6--T7 spondylodiscitis	INH + RIF + EMB × 12 months	Percutaneous biopsy of disc space	Symptoms improved
NIkaido *et al.*[19]	86/M	2 years	LBP	T12--L1 spondylodiscitis	INH + RIF + EMB	Percutaneous biopsy of disc space	Remission of symptoms at 1 month, died later of heart disease
Mavrogenis *et al*[17]	72/M	11 years	LBP, leg pain, L2--L5 radiculopathies, anorexia, weight loss	L3--L4 spondylodiscitis, L3--L5 epidural soft tissue mass with anterior dural sac compression	INH + RIF + EMB × 12 months	Wide L3 and L4 decompressive laminectomies, L2--L5 posterior instrumented spinal fusion	Pain-free at 18 months
Patel *et al.*[21]	66/M	5 months	LBP	T10--T11 spondylodiscitis, T10--T11 epidural soft tissue mass with anterior cord compression	INH + RIF + EMB planned for 12 months	Percutaneous biopsy of the right T10 pedicle	Symptoms improved at 3-month follow-up
Josephson *et al*[14]	75/M	6 months	LBP, generalized weakness, depression	L1--L2 spondulodiscitis, L1--L3 epidural soft tissue mass	INH + RIF × 12 months	Percutaneous aspiration	No long-term follow-up
Colebatch *et al.*[5]	67/M	2 years	LBP	L4--L5 discitis	INH + RIF + EMB + PZA × 2 months, then INH + RIF × 5 months	Percutaneous disc space aspiration	Significant symptomatic improvement at 2 months, no long-term follow-up
Present case	67/M	4.5 months	LBP, anorexia, weight loss	L1--L2 osteomyelitis, anterior epidural abscess	INH + RIF + EMB × 9 months	Percutaneous drainage of psoas abscesses, L1 and L2 corpectomies with femoral strut grafting and T12--L3 instrumented fusion, minimally invasive T11--L4 posterior instrumentation	Asymptomatic and disease-free at 20 months

M: Male, LBP: Low back pain, INH: Isoniazid, RIF: Rifampin, EMB: Ethambutol, SM: Streptomycin, PZA: Pyrazinamide

An immunocompromised state may also contribute to the infection, thus accounting for its occurrence in the elderly population.[1]

Clinically, BCG spondylodiscitis typically presents with LBP and constitutional symptoms. Patients may also exhibit neurological deficits and spinal instability or deformity. The infection is commonly associated with psoas abscesses and occasionally with an epidural abcess.[14] The delay from intravesical BCG immunotherapy to symptom onset is highly variable, with patients developing symptoms anywhere between 2 weeks and 11 years (mean 31 months) following treatment.[6] The persistence of BCG bacilli in the urinary tract for prolonged periods

of time may account for the long latency period before spinal infection in some patients.[3,30]

M. bovis infection should be suspected whenever primary spondylodisctis occurs in a patient with a recent or remote history of BCG immunotherapy. The tuberculin skin test is not very useful in this setting because most patients are elderly and demonstrate anergy to the test.[1] Tissue must be obtained from the site of infection, and Ziehl-Neelsen staining should be performed to look for acid-fast bacilli. Cultures usually take several days before revealing *Mycobacterium*. Polymerase chain reaction and advanced molecular typing techniques will allow identification of *M. bovis*.[8,12,13,28,31]

Antimicrobial therapy has been shown to be effective in the treatment of systemic manifestations following intravesical BCG therapy.[23] Although there is no definitive consensus on the treatment regimen, most authors have used isoniazid and rifampin in combination as first-line agents, often with a second-line agent such as ethambutol.[1,2,4,7,14,15,17-19,21,24,27] Subsequent BCG instillations should also be withheld.[1] Using this treatment strategy, 6 of the 12 previous cases with sufficient treatment and follow-up details showed good response to medical therapy.[1,5,7,19,21,24] Three cases progressed after initial medical therapy, requiring surgical decompression and fusion.[17,18,27] In two other cases, surgical intervention was necessary at the time of diagnosis to decompress and/or stabilize the spine. One of these patients had a good outcome,[4] while the other one did not.[2] The last patient required a second surgical intervention for disease progression despite initial medical and surgical therapy.[15] We report another case of disease progression under antituberculous therapy, resulting in pain and neurological deficit. Following surgical decompression, debridement, and fusion, the patient eventually had a favorable outcome and remains infection-free after 20 months of follow-up.

CONCLUSION

M. bovis spondylodiscitis may occur from months to years following intravesical BCG immunotherapy. This diagnosis should be suspected whenever primary spondylodiscitis occurs in a patient with a recent or remote history of BCG immunotherapy, particularly when the patient is elderly and the thoracolumbar spine is affected. The infection may progress despite appropriate antituberculous therapy, which may result in pain, neurological deficit, and spinal instability or deformity. In such cases, surgical intervention is warranted to decompress and stabilize the spine and treat the infection.

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