CASE REPORT

Mycoplasma bovis-induced Aneurysm after Intravesical Bacillus Calmette-Guérin Therapy: A Case Study and Literature Review

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Abstract:
Mycoplasma bovis infection after intravesical Bacillus Calmette-Guérin (BCG) therapy is rare. A 65-year-old Japanese man with history of bladder cancer and intravesical BCG therapy, presented with low-grade fever. An aneurysm with perianeurysmal fluid was suspected and endovascular aortic repair was performed. After 160 days, he developed blood-streaked sputum and computed tomography images revealed that the perianeurysmal fluid area was increasing in size. A multiplex polymerase chain reaction using sputum identified M. bovis. Treatment with anti-tuberculosis drugs reduced the size of the perianeurysmal fluid area. After intravesical BCG therapy, the possibility of M. bovis infection should be considered, thus further investigations are required.

Key words: Mycobacterium bovis, aortic aneurysm, Bacillus Calmette-Guérin therapy, multiplex polymerase chain reaction

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Introduction

Bacillus Calmette-Guérin (BCG) intravesical therapy is widely used for the treatment of superficial bladder cancer. The exact mechanisms underlying the antitumor effects of BCG are unknown. The intravesical instillation of BCG triggers a variety of local immune responses that may persist for a number of months and which appear to be correlated with antitumor activity (1, 2). Its efficacy as an immunotherapy drug has been demonstrated in the treatment of bladder cancer and as prophylaxis against local recurrence (3). In 2006, it was estimated that there were 16,510 cases of bladder cancer in Japan; approximately 70% of untreated cases of bladder cancer involved non-muscular invasive bladder cancer, for which BCG therapy might have been appropriate (4). Intravesical BCG instillation is generally considered safe. Lamm et al., reported that the most common complications of intravesical BCG instillation are high fever (2.9%), hematuria (1%), and infectious granulomatous complications, such as hepatitis (0.5%) and pneumonia (0.5%) (5). However, some cases of life threatening BCG sepsis have been reported (5). Mycobacterium bovis infection of an aortic aneurysm after intravesical BCG therapy is an extremely rare complication. In this report, we document the case of a 65-year-old man who developed a ruptured aortic aneurysm due to M. bovis infection after intravesical BCG therapy.

Case Report

A 65-year-old Japanese man was admitted to a different institution with low-grade fever, which had persisted for 31
days, 13 days before his admission to our hospital. He did not have any other symptoms, and chest radiography and abdominal computed tomography (CT) images were not suggestive of any abnormal findings. However, chest CT images revealed a thoracic saccular aneurysm with perianeurysmal fluid. No evidence of the aneurysm was found on CT images taken 11 months earlier. Since the possibility of an infected aneurysm could not be denied based on the CT findings or the patient’s symptoms, ampicillin/sulbactam (ABPC/SBT) was administered at a conventional dose of 3 grams every 6 hours [10 days before admission, ABPC/SBT was replaced by meropenem (1 gram every 6 hours)]. Two sets of blood cultures were obtained before antibiotic treatment was initiated; both returned negative results. Twelve days after the initiation of antibiotics, the patient complained of sudden back pain and progressed to hypovolemic shock. Repeat CT images revealed a ruptured thoracic aortic aneurysm, measuring 2.5×1.9 cm, with pleural effusion that indicated hemothorax (Fig. 1). He was therefore transferred to our hospital.

Upon admission, a physical examination revealed the following: body temperature, 36.2°C; blood pressure, 74/52 mmHg; heart rate, 78 beats/min; regular respiratory rate, 24 breaths/min. Respiratory tract sounds were not audible in the left lung. He had no peripheral lymphadenopathy, skin lesions, or neurological deficits, and cardiovascular and the abdominal examinations were unremarkable. His laboratory findings were as follows: white blood cells, 4,930/µL; hemoglobin, 5.9 g/dL; platelets, 5.5×10⁴/µL; C-reactive protein, 1.45 mg/dL; serum total protein, 5.3 g/dL; albumin, 3.5 g/dL; lactate dehydrogenase, 138 IU/L; aspartate aminotransferase, 123 IU/L; alanine aminotransferease, 33 IU/L; gamma-glutamyltransferase, 18 IU/L; blood urea nitrogen, 14 mg/dL; and creatinine, 0.65 mg/dL. An interferon-gamma release assay (T-SPOT.TB™) yielded a negative result.

We revisited the patient’s history of bladder cancer. He had received six courses of intravesical BCG therapy [BCG Tokyo 172; BCG (80 mg) was injected through a catheter into the patient’s bladder every week for 6 weeks] 12 months previously. He had fever immediately after his sixth course of BCG. Based on his medical history, we performed culturing and polymerase chain reactions (PCRs) using blood, urine, pleural effusion, and bone marrow aspiration specimens, in order to test for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex; however, these tests yielded negative results. Blood was cultured for *M. tuberculosis* complex with a method using 2,3-diphenyl-5-thienyl-(2)-tetrazolium chloride (STC).

In view of his medical problems, open surgery was considered too risky. He was therefore treated with thoracic endovascular aortic repair and gauze packing in the left intrathoracic space. If his condition worsened, anti-tuberculosis treatment would have been administered. However, his condition improved following the initiation of treatment, and the antibiotics that were administered by the previous institution, were discontinued at 10 days after admission because...
the patient’s blood and pleural effusion bacterial cultures were negative. Sixty-one days after admission, gauze removal surgery was performed, and the patient was discharged on the 83rd day after admission. During admission, he developed thrombocytopenia and was diagnosed with idiopathic thrombocytopenic purpura. Oral prednisone was initiated at a total daily dose of 60 mg and his overall condition appeared to stabilize over the 5 months that followed, leading to the discontinuation of the medication.

One hundred sixty days after admission, he developed blood-streaked sputum. His sputum was tested for *M. tuberculosis* using acid-fast staining and a PCR; both tests were positive. The isolate identified as *M. bovis* or *Mycobacterium caprae* by a multiplex polymerase chain reaction of *cpf*32 and region of difference 9 and 12. (B) The isolates identified as BCG by a polymerase chain reaction of region of difference 1 (region of difference 1: BCG: 200 bp, other *M. tuberculosis* complex: 150 bp). (C) The isolates were identified as BCG Tokyo 172 by region of difference 16 (the size of region of difference 16 in BCG Tokyo 172 is unique).

**Discussion**

Infected aortic aneurysms are a rare form of aneurysm (0.9-1.3%) but result in serious clinical conditions and high mortality (7, 8). The most common causative pathogen is *Staphylococcus aureus*, followed by *Streptococcus* spp., *Salmonella*, and *Escherichia coli* (9). *M. bovis* includes several mycobacteria of the *M. tuberculosis* complex, which are closely related and pathogenic. It has a wide range of wild and domestic animal hosts; in the United States during 2006-2013, it caused 1.3-1.6% of culture-confirmed cases of tuberculosis in humans (10). BCG was recommended as a vaccine for tuberculosis and bladder cancer, following the evaluation of its efficacy and safety in clinical trials conducted in France in 1921. However, BCG-related infectious complications may occur following vaccination and intravesical BCG therapy. To our knowledge, in addition to our patient, the literature contains reports on a total of 29 patients with aneurysms infected by *M. bovis* after intravesical BCG therapy (11-36) (Table). According to these reports, all of the cases occurred in adults [mean age ± standard deviation (SD): 71.1 ± 5.46 years], and 28 of the 29 patients were males. The median time interval (±SD) between the last instillation and the onset of infection was 17 months (±15.9). Among the 21 patients who were reported to have complications when BCG was administered, fever was observed in 14 (66.6%); this frequency was higher than that reported in a review of 2,602 (2.9%) patients who were
treated with intravesical BCG (5). Among the 29 patients with *M. bovis*-infected aneurysms, 22 (75.9%) exhibited underlying disease, 6 (27.3%) had at least one risk factor for arterial sclerosis [hypertension (n=5), diabetes mellitus (n=2), and dyslipidemia (n=2)]]; 12 (54.5%) had a history of coronary artery disease or aneurysm, and 6 (27.3%) had a history of smoking. All patients exhibited at least one symptom; fever was observed in 14 (48.3%) patients while pain was observed in 23 (79.3%) patients. Lee et al., reported that the imaging features of infected aneurysms included lobulated vascular masses, indistinct, irregular arterial walls, perianeurysmal edema, and perianeurysmal soft-tissue masses (37). However, it was difficult to distinguish atherosclerotic aneurysms in some patients.

Long et al. reported that tubercle bacilli may reach the aortic wall through the direct bacterial invasion of the arterial wall with degeneration due to atherosclerosis; the invasion of the adventitia or media by the vasa vasorum; or direct extension from a contiguous focus such as a lymph node or paraspinal abscess (38). Among the patients that are listed in Table, the methods that were used to diagnose *M. bovis*-induced aneurysms included the culture of the aneurysm (n=16), the culture of the tissue surrounding the aneurysm (n=7), a clinical diagnosis (n=5), [the culture of another tissue type (n=1), the pathological examination of the aneurysm (n=2), and other (n=2)]. In the present case, open surgery was considered to be associated with a high degree of risk. For this reason, histopathological and microbiological examinations were not performed to confirm the diagnosis. Thus, the *M. bovis*-induced aneurysm was clinically diagnosed using the following evidence: the rapid formation of a thoracic saccular aneurysm with perianeurysmal fluid in only 11 months; the increased size of the low attenuation area surrounding the aortic grafts within 160 days; the decrease in the area of the perianeurysmal fluid after treatment with anti-tuberculosis drugs. *M. bovis* isolated from sputum was possibly derived from the area of low attenuation surrounding the aortic graft, since the CT images revealed that only the perianeurysmal fluid area adhered to the left lower lobe of the lung and that neither infiltrative changes nor nodules were observed. In addition, oral prednisone might have contributed to the deterioration of the infected aneurysm, thus masking fever. Moreover, the gauze removal surgery might have worsened the perianeurysmal infection. The blood-streaked sputum eventually resolved and the low attenuation mass surrounding the aortic graft decreased in size after treatment with anti-tuberculosis drugs.

The treatment of aortic aneurysms due to *M. bovis* include antimicrobial therapy with or without surgery. *M. bovis* is usually susceptible to anti-tuberculosis drugs, including rifampicin, isoniazid, and etambutol. It is resistant to pyrazinamide (39). However, the optimal duration of therapy for aortic aneurysms is unknown. Thirteen of the cases of aortic aneurysms that we reviewed included data on the duration of antimicrobial therapy after the diagnosis; 12 cases received antibiotic treatment for ≥9 weeks and 9 cases received antibiotic treatment for ≥12 weeks. Moreover, in some cases, medical therapy alone was inadequate (15, 21). The surgical managements included debridement of the vessel with extra-anatomic bypass and in situ repair with a prosthetic graft; both methods have yielded good results. In the present case, open surgery was considered to be too risky; thus, he was treated using thoracic endovascular aortic repair. Ting et al. reported that a patient with multiple Sal-
### Table. Twenty Nine Reported Cases of Infected Aneurysm by Mycobacterium Bovis.

| Case | Sex | Age | Main underlying diseases excluding bladder cancer | The complication caused by BCG injection | Location | Interval* (month) | Main symptoms | The method of diagnosis (infection by BCG) | Outcome | References |
|------|-----|-----|--------------------------------------------------|----------------------------------------|---------|------------------|--------------|------------------------------------------|---------|------------|
| 1    | W   | 62  | Malignant melanoma                               | Bacteremia                             | Infraenal aorta                      | 17      | Back pain       | Culture of aneurysm specimen             | Recovered | 10         |
| 2    | M   | 74  | Unknown                                          | Fever and pain localized at the bladder | Femoral artery                       | 21      | Lumbar pain     | Culture of pelvic collection and thrombus | Recovered | 11         |
| 3    | M   | 67  | None                                             | Fever, hypotension and anuria          | Abdominal aorta, iliac artery        | 14      | Fever, dysuria, and dull | Pathology of autopsy specimen             | Died     | 12         |
| 4    | M   | 69  | Aneurysm                                         | Mild urgency and frequency of urination| Aortic arch                          | 36      | Confusion, weight loss, and fatigue | Culture of autopsy specimen               | Died     | 13         |
| 5    | M   | 80  | Unknown                                          | Fever and rigors                       | Infraenal aorta                      | 24      | Back pain       | Culture of fluid surrounding aortic graft | Recovered | 14         |
| 6    | M   | 71  | Aneurysm                                         | Malaise                               | Abdominal aorta                      | 26      | Fever and malaise | Culture of aneurysm specimen             | Recovered | 15         |
| 7    | M   | 76  | Myocardial infarction                            | Unknown                               | Infraenal aorta                      | 77      | Back and leg pain, and weight loss | Needle biopsy sampling culture of vertebral disk | Died     | 16         |
| 8    | M   | 71  | Myocardial infarction and aortic fibrillation    | Dysuria                               | Infraenal aorta                      | 7       | Abdominal pain and fever     | Bacteriological analysis of aneurysm       | Recovered | 17         |
| 9    | M   | 75  | Coronary artery disease                          | Unknown                               | Infraenal aorta                      | 8       | Back pain        | Needle biopsy sampling culture of the iliopectine muscle | Recovered | 18         |
| 10   | M   | 72  | Deep venous thrombosis                           | Sweating and flu-like symptoms         | Femoral artery                       | 12      | Fever and inguinal pain | Culture of sputum and tissue of aneurysm | Recovered | 19         |
| 11   | M   | 58  | Unknown                                          | Unknown                               | Abdominal aorta                      | 36      | Fever, back pain and weight loss | Culture of aneurysm specimen              | Recovered | 19         |
| 12   | M   | 71  | Aneurysm                                         | Malaise                               | Infraenal aorta                      | 48      | Fever            | Culture of aneurysm specimen              | Recovered | 19         |
| 13   | M   | 74  | Coronary artery disease, hypertension, and diverticulosis | Confusion, chills, fever, pancytopenia, and transaminists | Infraenal aorta | 12 | Weakness, diaphoresis and dyspnea | Culture of aneurysm specimen              | Recovered | 20         |
| 14   | M   | 68  | Unknown                                          | Fever and malaise                      | Carotid artery                       | 24      | Neck swelling    | Needle biopsy sampling culture of lymph node | Recovered | 21         |
| 15   | M   | 65  | Aneurysm                                         | None                                  | Suprrenal aorta                      | 16      | Abdominal pain, nausea and weight loss | Culture of autopsy specimen               | Died     | 22         |
| 16   | M   | 75  | Hypertension, diabetes, and dyslipidemia         | Fever                                 | Infraenal aorta and femoral artery   | 32      | Pain in the hip joint | Culture of aneurysm specimen           | Recovered | 23         |
| 17   | M   | 67  | Unknown                                          | Fever and malaise                      | Popliteal artery                     | 23      | Fever and pain in the knee | Clinical diagnosis                        | Recovered | 24         |
| 18   | M   | 69  | Appendicitis, colon cancer, and aneurysm         | Unknown                               | Infraenal aorta                      | 48      | Back pain and paresis       | Culture of surgical bone sampling         | Recovered | 25         |
| 19   | M   | 80  | Hypertension and chronic obstructive pulmonary disease | Malaise                               | Infraenal aorta                      | 24      | Fever, malaise, weight loss and back pain | Culture of aneurysm specimen             | Recovered | 26         |
| 20   | M   | 79  | Coronary artery disease                          | Unknown                               | Infraenal aorta                      | 11      | Fever, fatigue and high sweat | Culture of aneurysm specimen             | Recovered | 27         |
| 21   | M   | 75  | Hypertension, diabetes, and dyslipidemia         | Urosepsias                            | Abdominal aorta and femoral artery   | 24      | Abdominal and back pain | Culture of blood and tissue of aneurysm   | Recovered | 28         |
| 22   | M   | 79  | None                                             | Unknown                               | Carotid artery etc                   | 18      | Neck pain, fatigue and weight loss | Culture of abscess surrounding aneurysm   | Died     | 29         |
| 23   | M   | 71  | Hypertension, lymphoma, dyslipidemia, and chronic kidney disease | Fever, lethargy, and headaches         | Suprrenal aorta                      | 15      | Fever, dyspnea, weight loss | Clinical diagnosis                        | Died     | 30         |
| 24   | M   | 69  | Coronary artery disease, hypertension, and aortic fibrillation | Unknown                               | Infraenal aorta                      | 10      | Fever and back pain   | Pathology of aneurysm specimen            | Recovered | 31         |
| 25   | M   | 64  | Coronary artery disease and diabetes             | Fever                                 | Infraenal aorta and iliac artery     | 9       | Fever and abdominal pain    | Culture of pelvic retroperitoneal collection | Recovered | 32         |
| 26   | M   | 68  | Gastric cancer                                  | Fever                                 | Infraenal aorta                      | 7       | Back pain            | Culture of aneurysm specimen             | Recovered | 33         |
| 27   | M   | 73  | None                                             | Fever                                 | Thoracic and abdominair aorta        | 10      | Abdominal pain        | Culture of aneurysm specimen             | Recovered | 34         |
| 28   | M   | 70  | Unknown                                          | Abdominal aorta, iliac artery         | 1       | Fever and back pain   | Culture of aneurysm specimen             | Recovered | 35         |
| 29   | M   | 65  | Fever                                            | Thoracic aorta                        | 10      | Fever and back pain   | Culture of aneurysm specimen             | Recovered | Present case |

BCG: Bacillus Calmette-Guérin

*The interval: the time interval between the last institution and the onset of infection
monella infected thoracic aortic aneurysms, was successfully treated by endovascular repair (40). However, in the presence of infection, this technique should therefore be considered on an individual basis.

In conclusion, we described a case of a ruptured aortic aneurysm caused by M. bovis, which was challenging to diagnose. In some cases after intravesical BCG therapy, we should consider the possibility of aneurysm caused by M. bovis and it may be important to conduct further evaluations, including surgical and microbiological evaluations.

The authors state that they have no Conflict of Interest (COI).

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