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【 CASE REPORT 】

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

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Abstract:

Mycobacterium 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

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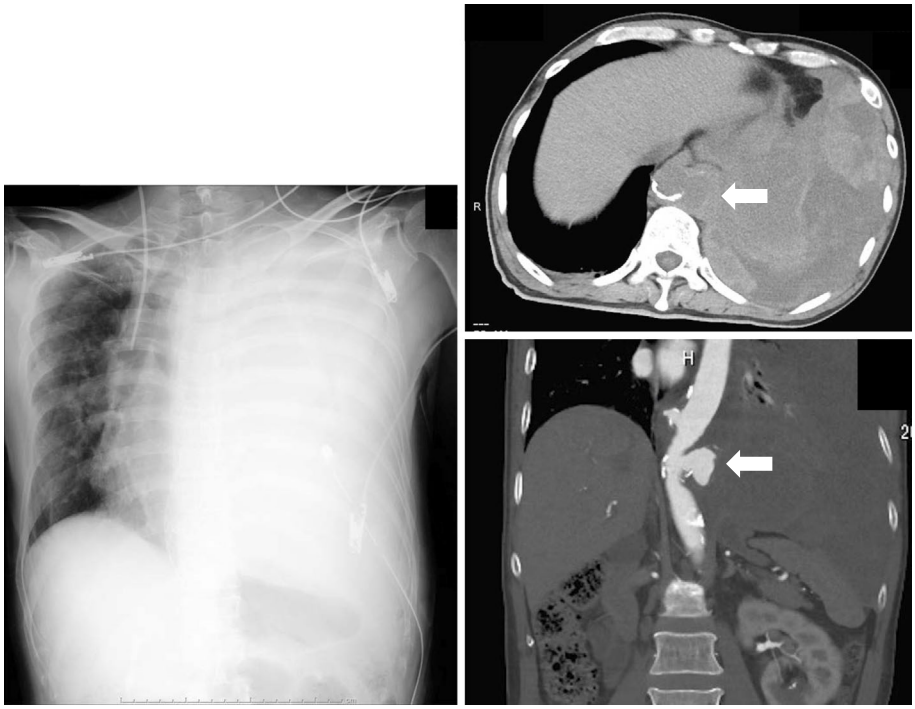

Figure 1. Chest radiography and computed tomography images obtained on the day of admission to our hospital. (A) Chest radiography shows left pleural effusion. (B) Chest computed tomography images reveal a ruptured thoracic aortic aneurysm (white arrow), measuring 2.5×1.9 cm, with pleural effusion that suggested hemothorax.

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℃; 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, 5.5×10^4/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 aminotransferase, 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

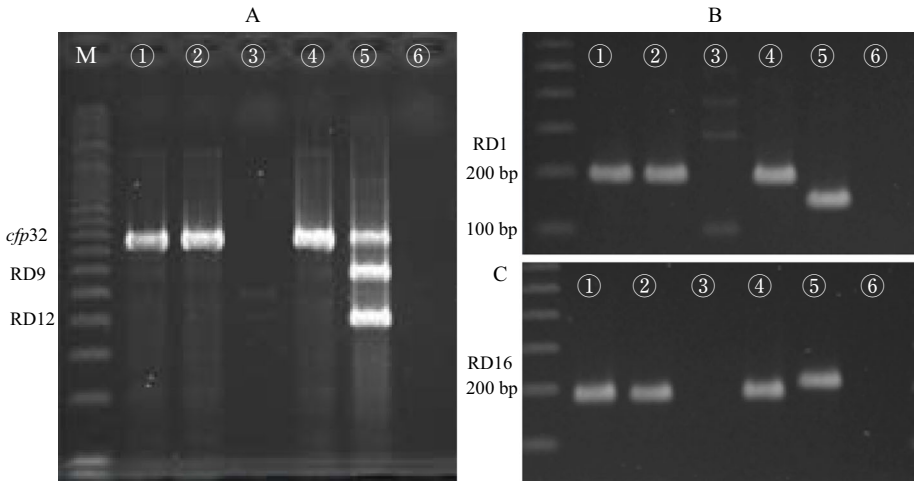

Figure 2. **The multiplex polymerase chain reaction to test for *Mycobacterium bovis* (*M. bovis*) (M: marker, ①, ②: the patient sample isolated from sputum, ③: Non-tuberculosis mycobacterium, ④: Bacillus Calmette-Guérin (BCG) Tokyo 172, ⑤: *Mycobacterium tuberculosis* (*M. tuberculosis*), ⑥: Negative control). (A) The isolates identified as *M. bovis* or *Mycobacterium caprae* by a multiplex polymerase chain reaction of *cfp32* 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).**

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. tuberculosis* complex was examined using a multiplex PCR analysis of the *cfp*32 gene and regions of difference 1, 9, 12, and 16. The methods employed by Chikamatsu et al. were used and in doing so the investigators identified BCG Tokyo172 (6) (Fig. 2). Conclusively, the acid-fast bacilli culture of the sputum grew *M. bovis*. The minimum inhibitory concentrations (MICs) of the anti-microbial agents against *M. bovis* was determined using BrothMIC MTB-I (Kyokuto Pharmaceutical Industrial, Tokyo, Japan) and the KYOKUTO PZA test, was as follows: rifampicin, ≤0.031 mg/L; isoniazid, 0.125 mg/L; etambutol, 1.0 mg/L; levofloxacin, 0.5 mg/L. However, the *M. bovis* was resistant to pyrazinamide. Chest radiography and CT images revealed neither infiltrative changes nor nodules; however, the low attenuation area surrounding the aortic graft was increasing in size and there adhesion to the left lower lobe of the lung was suspected (Fig. 3). Anti-tuberculosis treatment with rifampicin (600 mg, once daily), isoniazid (300 mg, once daily) and etambutol (750 mg, once daily) resulted in the resolution of the patient's symptoms and follow-up chest CT performed 6 months after the development of blood-streaked sputum showed a decrease in the size of the low attenuation mass surrounding the aortic graft.

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

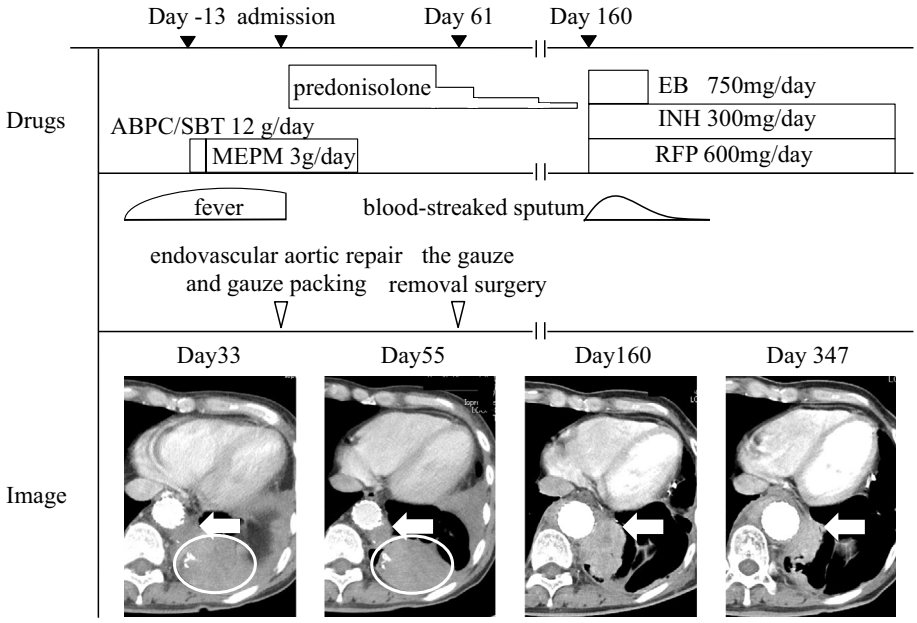

Figure 3. The clinical course. These images revealed that the low attenuation mass surrounding the aortic graft was increasing (white arrows) with time. The gauze in the intrathoracic space is represented by a white circle. ABPC/SBT: ampicillin/sulbactam, EB: etambutol, INH: isoniazid, RFP: rifampicin

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 in one of three ways: 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	Infrarenal 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	Infrarenal 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	Infrarenal aorta	77	Back and leg pain, and weight loss	Needle biopsy sampling culture of vertebral disk	Died	16
8	M	71	Myocardial infarction and atrial fibrillation	Dysuria	Infrarenal aorta	7	Abdominal pain and fever	Bacteriological analysis of aneurysm	Recovered	17
9	M	75	Coronary artery disease	Unknown	Infrarenal aorta	8	Back pain	Needle biopsy sampling culture of the iliopsoas 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	Infrarenal aorta	48	Fever	Culture of aneurysm specimen	Recovered	19
13	M	74	Coronary artery disease, hypertension, and diverticulosis	Confusion, chills, fever, pancytopenia, and transaminitis	Infrarenal 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	Suprarenal aorta	16	Abdominal pain, nausea and weight loss	Culture of autopsy specimen	Died	22
16	M	75	Unknown	Fever	Infratenal 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	Infrarenal aorta	48	Back pain and paresis	Culture of surgical bone sampling	Recovered	25
19	M	80	Hypertension and chronic obstructive pulmonary disease	Malaise	Infrarenal aorta	24	Fever, malaise, weight loss and back pain	Culture of aneurysm specimen	Recovered	26
20	M	79	Coronary artery disease	Unknown	Infrarenal aorta	11	Fever, fatigue and nigh sweat	Culture of aneurysm specimen	Recovered	27
21	M	75	Hypertension, diabetes, and dyslipidemia	Urosepsis	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	75	Hypertension, lymphoma, dyslipidemia, and chronic kidney disease	Fever, lethargy, and headaches	Suprarenal aorta	15	Fever, dyspnea, weight loss	Clinical diagnosis	Died	30
24	M	69	Coronary artery disease, hypertension, and atrial fibrillation	Unknown	Infrarenal aorta	10	Fever and back pain	Pathology of aneurysm specimen	Recovered	31
25	M	64	Coronary artery disease and diabetes	Fever	Infrarenal aorta and iliac artery	9	Fever and abdominal pain	Culture of pelvic retroperitoneal collection	Recovered	32
26	M	68	Gastric cancer	Fever	Infrarenal aorta	7	Back pain	Culture of aneurysm specimen	Recovered	33
27	M	73	None	Fever	Thoracic and abdominar aorta	10	Abdominal pain	Culture of aneurysm specimen and abscess of psoas muscle	Recovered	34
28	M	70	Unknown	Unknown	Abdominal aorta, iliac artery	1	Fever and back pain	Culture of aneurysm specimen	Recovered	35
29	M	65	None	Fever	Thoracic aorta	10	Fever and back pain	Culture of sputum	Recovered	Present case

BCG: Bacillus Calmette-Guérin

*The interval: the time interval between the last instillation and the onset of infection

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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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