


Salmonella enteritis Spondylitis with *Brucella melitensis* Infection: A Rare Case of Mixed Infections of Spine

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Background: As a widespread back condition in orthopedics, spondylitis is rarely caused by *Salmonella*. Here, we report a rare case of spondylitis caused by *Salmonella enteritis* associated with *Brucella melitensis*.

Case Presentation: *Salmonella* septicemia was initially diagnosed in a 27-year-old woman with high fever and low back pain, but her symptoms did not improve after 3 days of antibiotic treatment. The patient was then referred to our hospital's Department of Infectious Diseases. This patient had mild anemia. There were no positive results for tuberculosis antibody and Rose Bengal plate agglutination (RBPT). When the patient's symptoms did not improve after diagnostic anti-tuberculosis treatment, he was transferred to our Orthopaedics department for lumbar posterior lesion removal, decompression, internal fixation, cage implantation, and bone grafting fusion under general anesthesia. Following the operation, a postoperative specimen culture and a real-time polymerase chain reaction (real-time-PCR) indicated *Salmonella enteritis* with *Brucella melitensis* (*B. melitensis*) infection. The symptoms improved and inflammatory markers returned to normal after 2 weeks of treatment with levofloxacin, rifampicin, and doxycycline.

Conclusion: Anaemic patients with immunocompromised conditions should be given special attention in the diagnosis of *Salmonella* spondylitis. Surgery should be considered if antibiotic therapy fails to identify the pathogen that is infecting the patient with infectious spondylitis.

Keywords: *Salmonella*, brucellosis, spondylitis, mixed infection

Background

Salmonella is a gram-negative intracellular bacterium. Enteritis is usually caused by *Salmonella enteritis*, which lives in the intestines of humans and animals. For patients with underlying diseases or factors suppressing their resistance to infection, it may occasionally affect extraintestinal organs, like the brain, thyroid, and musculoskeletal system.¹ *Salmonella*-related spondylitis accounts for 0.45% of osteomyelitis cases.² Immunocompromised patients, especially those with sickle cell disease, are prone to *Salmonella enteritis* osteomyelitis.³ Multiple organs can be affected by Brucellosis; osteoarticular involvement is the most common brucellosis complication, manifesting as spondylitis, arthritis, sacroiliitis, discitis, osteomyelitis, tenosynovitis, and bursitis, involvement of the lumbar and thoracic vertebrae can lead to symptoms such as lumbar and thoracic spondylitis and discitis.⁴⁻⁶ In this report, we describe the rarity of *Salmonella enteritis* spondylitis complicated by *B. melitensis* infection. No previous literature has described this co-infection.

Case Presentation

A 27-year-old female with a maximum body temperature of 40.4°C developed low back pain and percussive pain in the renal area about 3 weeks ago. Cotrimoxazole was sensitive to bovine *Salmonella enteritis* in blood cultures obtained at Beijing Wanging Hospital (Beijing, China). A combination of antibiotics etimicin sulfate (300mg po qd), cefoxitin (2g po q12h) and cotrimoxazole (4g po qd) was administered. In spite of 3 days of treatment, her symptoms did not improve, so she sought further treatment at our

hospital. Previously, the patient had been healthy and did not have any significant medical or surgical history. In addition to eating burgers from unknown vendors before fever, she had no history of epidemic areas, livestock, contact with cattle, sheep, or habit of consuming unpasteurized milk, tuberculosis, smoking, intravenous drug use, or any other HIV infection factors.

At admission, the body temperature was 38.4°C. During the physical examination, there were palpable pains in the spinous processes of the lumbar 4 and 5 vertebrae, lumbar forced positions, lumbar back pain, and limited lumbar flexion. Neither inguinal nor axillary lymph nodes were found, nor was there any evidence of hepatosplenomegaly. Laboratory tests were as follows: hemoglobin (Hb) 96 g/L, red blood cell count (RBC) $2.84 \times 10^{12}/L$, serum ferritin $12 \mu\text{g}/L$, mean corpuscular volume (MCV) was 74.6 fL, mean corpuscular hemoglobin content (MCH) was 23.8 pg, and mean corpuscular hemoglobin concentration (MCHC) was 302g/L, white blood cell (WBC) $8.05 \times 10^9/L$ accompanied by neutrophil elevation, platelet $344 \times 10^9/L$, erythrocyte sedimentation rate (ESR) 117mm/h, C-reactive protein (CRP) 75.7mg/L, albumin 34.3g/L, fasting blood glucose 5.6 mmol/L, HIV antibody negative, complement C3 1290mg/L, complement C4 330 mg/L, IgM 1.04 mg/L, IgG 9.66 mg/L, IgA 1.09 mg/L. In the absence of tuberculosis antibodies, the RBPT and acid-fast staining of the sputum smear were also negative, and the chest X-ray was normal. The blood culture was also free of bacteria and fungi after 5 days.

The L4/5 vertebral space was narrowed on the preoperative X-ray (Figure 1A and B). Preoperative CT showed the intervertebral disc of L4/5 and adjacent vertebral body were heavily damaged with dense pores (Figure 1C and D). Preoperative sagittal MRI showed vertebral body and intervertebral disc lesions with low signal on T1-weighted imaging (T1WI), high signal on T2-weighted imaging (T2WI), and high signal on fat-suppressed T2-weighted imaging (FS-T2WI), which was significantly enhanced after enhancement (Figure 1E–H). Coronal MRI showed vertebral body damage of L4 and L5 complicated by intervertebral disc damage of L4/5 (Figure 1I–L).

The patient's symptoms did not improve after diagnostic anti-tuberculosis treatment at the Department of Infectious Diseases of our hospital. As a result, he was transferred to Department of Orthopedics for surgical treatment. Preliminary diagnosis is suppurative spondylitis, although brucellosis spondylitis and spinal tuberculosis cannot be ruled out. Following general anesthesia, lumbar posterior lesion removal, decompression, internal fixation, cage implantation, and bone graft fusion were performed (Figure 2A–D). Real-time PCR of the nucleus pulposus samples showed that there was *B. melitensis* (Figure 3).

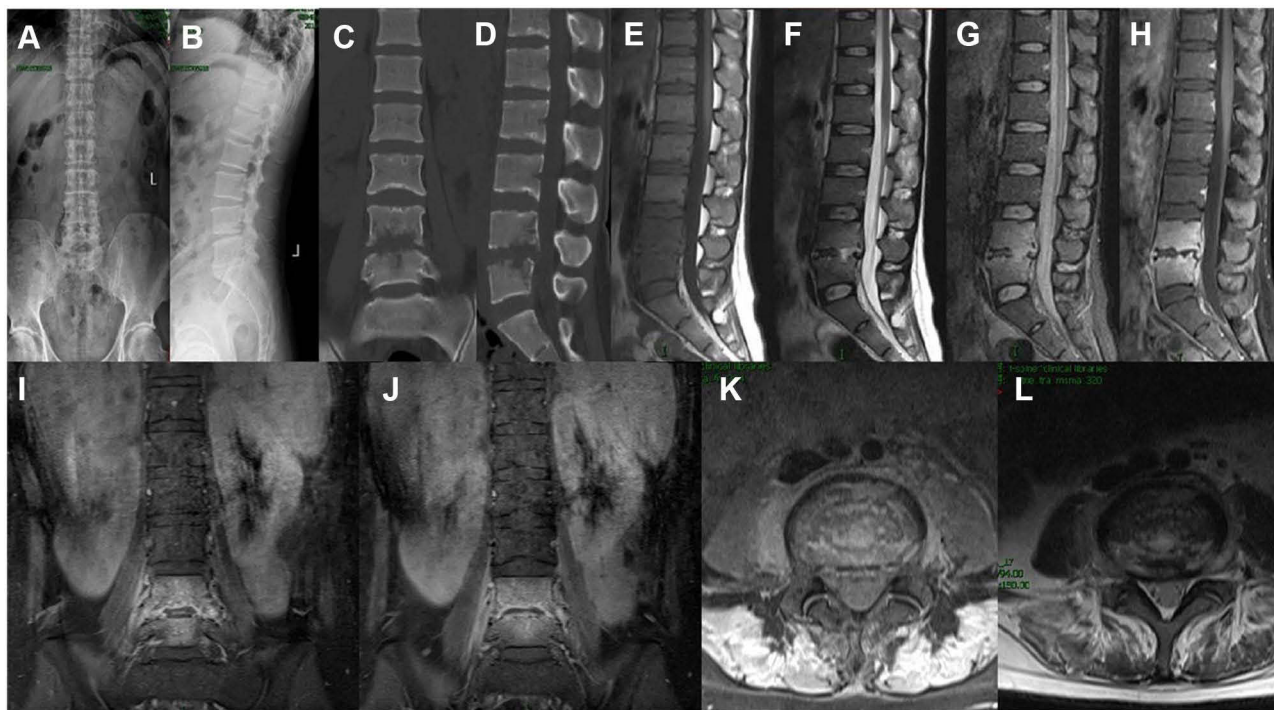


Figure 1 Radiological studies before operation. Plain radiograph showed narrowing of lumbar space 4–5 (A and B). CT showed dense pore-like destruction of the 4–5 lumbar vertebrae and intervertebral discs (C and D). Sagittal MRI showed vertebral and intervertebral disc lesions with low signal in T1, high signal in T2, and high signal in fat compression image, which was significantly enhanced after enhancement (E–H). Coronal MRI demonstrates a large, marked paravertebral abscess with unclear margins and enhancement (I and J). Axial MRI showed destruction of vertebral bodies and intervertebral discs, and significant strengthening of psoas after enhancement (K and L).

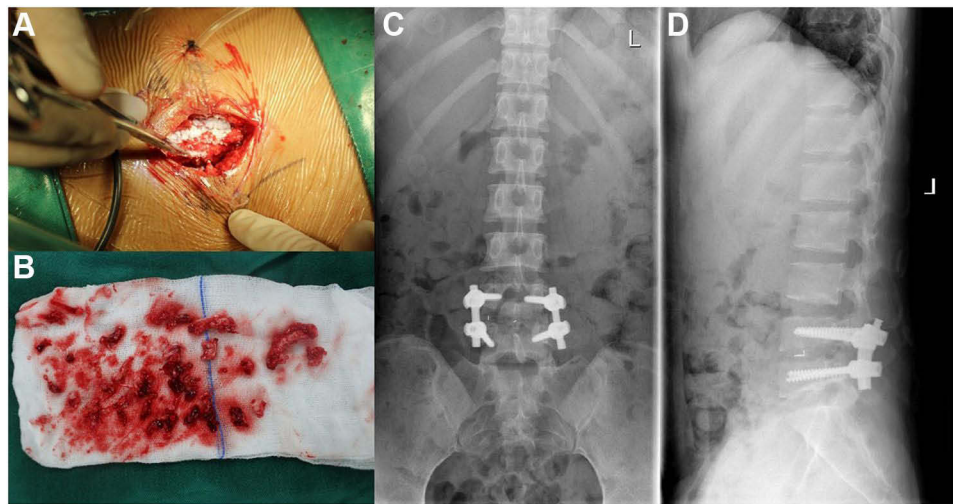


Figure 2 Intraoperatively, patients were treated with streptomycin to treat infection (A). Surgical specimens (B). Postoperative plain radiographs showed that the L4/5 vertebral space height was restored and the internal fixation was firm (C and D).

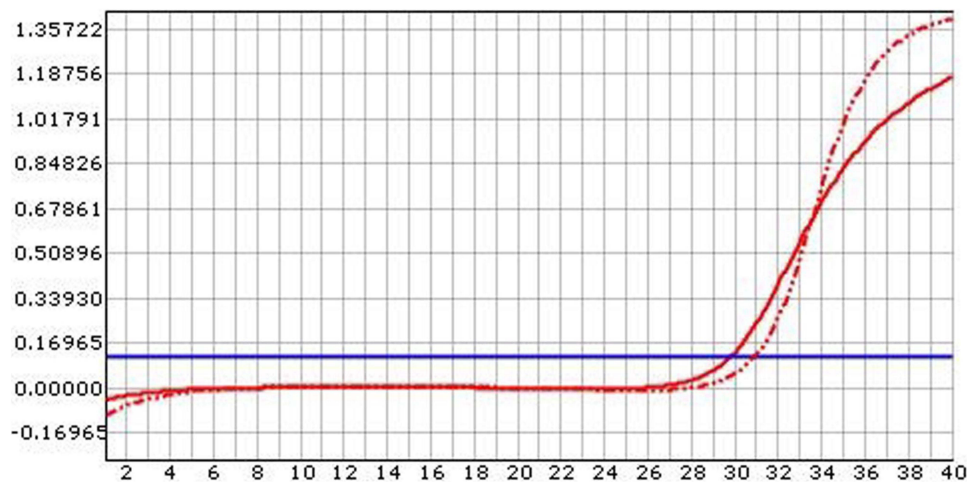


Figure 3 *Brucella melitensis* was detected by real-time PCR, real-time PCR showed that the DNA content of *Brucella melitensis* (dotted red line) increased in 30 cycles. The ordinate represents the fluorescence intensity, the abscissa represents the number of PRC cycles, the blue realization represents the baseline level, and the red realization represents the positive reference.

Salmonella enteritis was detected in intraoperative pus secretions 7 days after surgery, and the pathological Giemsa staining of intraoperative tissues (nucleus pulposus, endplate cartilage) showed *Brucella* contamination (Figure 4). Due to the long-term use of antibiotics, a stool smear revealed possible yeast growth. The patient was finally diagnosed with mixed spinal infection of *Salmonella enteritis* and *B. melitensis*. Afterwards, she was prescribed levofloxacin, rifampicin, and doxycycline. Antifungal fluconazole was administered orally. Oral ferrous sulfate tablets for the treatment of iron deficiency anemia. Two weeks after treatment, the patient was no longer experiencing fever or sweating, and was able to perform daily activities using a lumbar brace, CRP returned to normal and ESR (39mm/h) was significantly lower than before, Hb 112g/L and RBC $3.84 \times 10^{12}/L$, MCV 91.4 fL, MCH 30.2 pg, MCHC 326. A 6-month treatment course of levofloxacin, rifampicin, and doxycycline was continued after the patient was discharged. A follow-up 2 years later revealed normal CRP and ESR, Hb 119 g/L, and RBC $3.95 \times 10^{12}/L$; X-ray showed a good position of internal fixation (Figure 5A and B); CT showed well fusion of L4 and L5 vertebral body, suggesting the formation of new bone in L4/5 disc space (Figure 5C–F); MRI demonstrated a good repair of the lesion (Figure 5G–J).

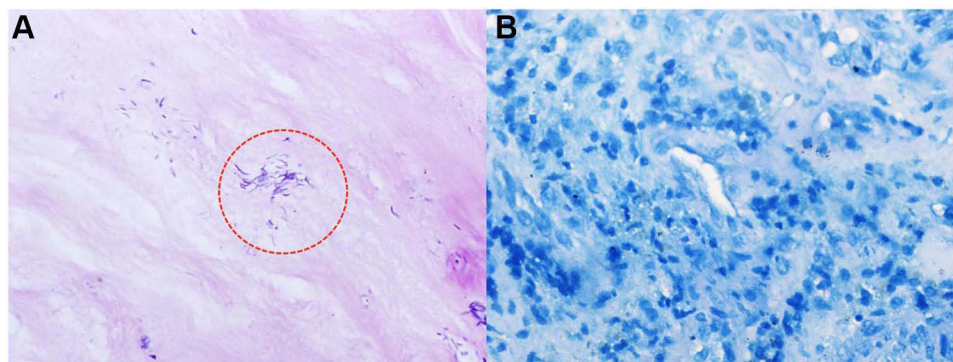


Figure 4 In postoperative pathology, *Brucella* (red circle) was positive for Giemsa staining (A). *Mycobacterium tuberculosis* was negative for acid-fast staining of the intervertebral disc of L4/5 (B).

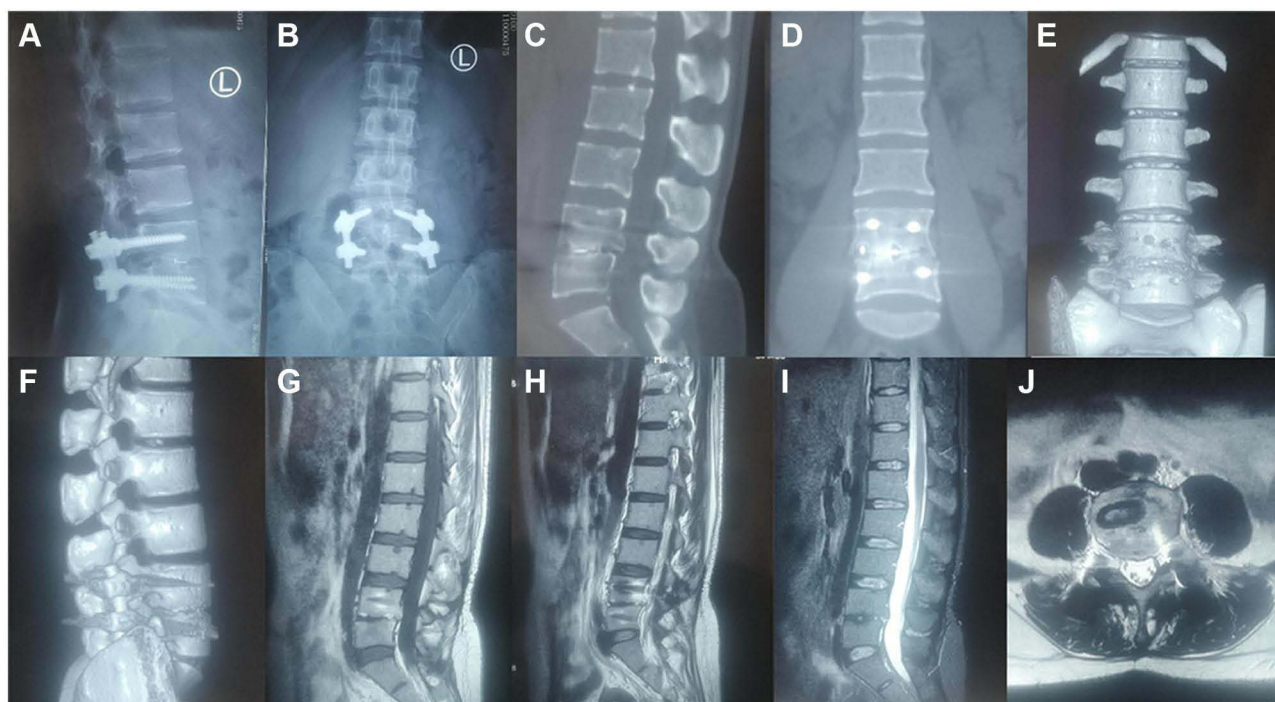


Figure 5 Radiological studies 2 years after discharge. Plain radiographs showed no abnormal changes in the fixed position of L4–L5 vertebral segments (A and B). No abnormalities on CT and MRI (C–J).

Discussion and Conclusions

Spinal infection is classified as specific infection (*B. melitensis*, *Mycobacterium tuberculosis*, *syphilis*, *fungi*) and non-specific infection (*Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus saprophyticus*, *Streptococcus pneumoniae*, etc).⁷ There has been an increase in *Salmonella*-induced spondylitis in recent years.^{6,8–16} Spondylitis caused by *Salmonella enteritidis* and *B. melitensis* has not been reported to date. An unusual mixed infection characterizes this case.

Infections in the gastrointestinal tract are usually caused by *Salmonella enteritidis*, a gram-negative bacterium. Microorganisms in contaminated water and food can cause *Salmonella enteritidis* infection. There are usually conservative treatments available for symptoms of acute infections, such as diarrhea, vomiting, and abdominal pain. *Salmonella enteritidis*, however, can persist in host cells and cause chronic infections. Those suffering from anemia (especially sickle

cell anemia), systemic lupus erythematosus, diabetes, and those receiving immunosuppressive medications are more likely to contract *Salmonella enteritis* spondylitis.^{17,18}

In patients with low immunity, *Salmonella enteritis* can cause extraintestinal infections; non-typhoid salmonellosis does not always present with gastrointestinal symptoms, especially in patients with low immunity, because diarrhea is a defense mechanism that depends on a normal immune response.¹⁹ Spinal tuberculosis and *Salmonella* spondylitis are easily confused—It has been shown that fever, a higher white blood cell count, CRP, alkaline phosphatase, and a higher proportion of neutrophils are all indications of suppurative spondylitis; the symptoms and signs of spinal tuberculosis are less obvious than those of *Salmonella* spondylitis.^{20,21} It is possible to distinguish tuberculous spondylitis from suppurative spondylitis with MRI—There are often paraspinal abnormalities, paraspinal abscesses with thin and smooth walls involving thoracic vertebrae in tuberculous spondylitis.²² A blood culture is essential for diagnosing spinal infections, but only 20% to 60% of the patients have a positive culture, the gold standard for diagnosis is percutaneous biopsy, culture of the lesion site, and histopathological examination.²³

Salmonella osteomyelitis is commonly treated with chloramphenicol, third-generation cephalosporins, and fluoroquinolones, although there are no standard antimicrobial treatment guidelines, antibiotic treatment should be continued for at least 6 weeks to avoid recurrence and failure.^{24,25} Surgical indications of *Salmonella* spondylitis include neurological impairment, large intraspinal and paraspinal abscesses, extensive bone destruction and spinal instability.^{26,27}

Around 500,000 cases of brucellosis spondylitis occur each year worldwide, making it the most common zoonotic disease; infection occurs mainly through contact with animals or through consumption of unpasteurized milk and fresh cheese.²⁸ Brucellosis spondylitis is a nonspecific disease that causes fevers, night sweats, fatigue, and is mainly found in northern provinces of China.²⁹ It is difficult to differentiate from spinal tuberculosis based on these non-specific symptoms. Thus, brucellosis spondylitis is often misdiagnosed as spinal tuberculosis in areas with low brucellosis incidence. There are many subtle differences between the two diseases: intermittent high fever of brucellosis spondylitis is more common than low fever of spinal tuberculosis; patients with spinal tuberculosis were more likely to experience vertebral body destruction, kyphosis, paraspinal abscess, and spinal cord compression.^{30,31} The RBPT is mainly used for *Brucella* infection screening.³² Presently, blood culture is the gold standard for diagnosing brucellosis, but positive detection rate in chronic bacteremia is low.³³ As compared with other detection techniques, PCR is highly sensitive and specific for identifying *Brucella* species from peripheral blood and other tissues.³⁴

In the acute phase of Brucellosis, rifampicin and doxycycline are the most commonly used drugs. The clinical treatment of brucellosis in China is mainly a triple-drug regimen, and enduring drug treatment for more than 3 months can reduce the risk of recurrence.^{35–37} When drug treatment does not seem to be working, surgical intervention may be necessary for patients with brucellosis spondylitis. The surgical treatment has been demonstrated in clinical studies to be effective in removing lesions, relieving pain, improving local blood flow to lesions, maintaining and rebuilding spinal stability, reducing complications, promoting early rehabilitation and cure of lesions, and improving clinical outcomes.^{38,39}

Anemia, a risk factor for *Salmonella*, was moderate in our case. As we speculated, the patient probably had *Salmonella enteritis* and *B. melitensis* infection through the digestive tract after eating a burger from an unidentified vendor prior to the fever. After antibiotic treatment, the patient's symptoms were not relieved, and the preoperative laboratory examination was unable to identify the infection bacteria. The infectious bacteria were finally identified through surgery and laboratory tests. Our case is characterized by the following points: 1) *Salmonella enteritis* spondylitis complicated by *B. melitensis* infection is extremely rare; 2) This patient had no obvious gastrointestinal symptoms; 3) All preoperative tests were negative, and pathogens were not detected; 4) Due to atypical manifestations, the patient was originally misdiagnosed as having spinal tuberculosis.

As a result, patients with spondylitis who are clinically immunocompromised should be cautious of *Salmonella* infections. In spite of the fact that Brucellosis spondylitis often complicates with *Mycobacterium tuberculosis*, when the diagnosis is unclear and conservative treatment is ineffective, surgical intervention should be considered as soon as possible.

Patient Consent and Ethics Statement

The patient provided informed consent for publication of this study and accompanying images. The Ethics Committee of the Beijing Ditan Hospital of Capital Medical University approved the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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