Responses To Reviewers

COMPANY EDITOR-IN-CHIEF'S COMMENT

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

RESPONSE TO COMPANY EDITOR-IN-CHIEF

Dear company editor-in-chief,

Thank you very much for your review and invaluable comments.

Current manuscript has been totally revised based on the editor and reviewers' valuable comments, which was insufficiently addressed in previous manuscript.

The more detailed information about 'final diagnosis', 'treatment', and 'outcome and follow-up' has been supplemented in the CASE PRESENTATION section. And we also added radiological follow-up images and more detailed descriptions in DISCUSSION section of revised manuscript.

We believe that this revised manuscript improved more by reflecting every editor and reviewer's important comments and is ready for your favorable reconsideration.

We are grateful for your helpful attention and await an excellent decision.

SCIENCE EDITOR'S COMMENT

1 Scientific quality: This manuscript is a case report, and it does not reach the publication standard of the WJCC. (1) Classification: Grade B, four Grade C, three Grade D; (2) Summary of the Peer-Review Report: Reviewer 05430304 pointed out that the title describes an epidural abscess, but this case should be diagnosed as lumbar tuberculosis. The paper only provided the MRI before the first operation. Methicillin-resistant S. epidermidis infection cannot explain the destruction of lumbar vertebrae and cold abscess. It is unreasonable to exclude tuberculosis based on pathological results; Reviewer 03207387 pointed out that the authors thought coinfection of bacteria and tuberculosis occurred in the case. However, the Staphylococcus hominis and methicillin-resistant Staphylococcus epidermidis were identified from preoperative blood culture and intraoperative abscess culture, respectively. Different bacteria were seen in blood culture and intraoperative abscess culture, so the possibility of contamination during culture could not be excluded. 2 Language quality: Classification: Three Grades A, four Grades B, and Grade C. 3 Recommendation: Rejection.

RESPONSE TO SCIENCE EDITOR

Dear science editor,

Thank you very much for your review and invaluable comments.

Current manuscript has been totally revised based on the editor and reviewers' valuable comments, which was insufficiently addressed in previous manuscript.

The more detailed information about 'final diagnosis', 'treatment', and 'outcome and follow-up' has been supplemented in the CASE PRESENTATION section. And we also added radiological follow-up images and more detailed descriptions in DISCUSSION section of revised manuscript.

We believe that this revised manuscript improved more by reflecting every editor and reviewer's important comments and is ready for your favorable reconsideration.

We are grateful for your helpful attention and await an excellent decision.

REVIEWER 05190615'S COMMENT

Epidural abscess is relatively rare, and the most common cause is puncture or injury. This patient had low back pain without other obvious symptoms, MRI showed epidural abscess, was suspected tuberculosis due to no improvement of initial treatment. The final diagnosis confirmed the coinfection of TB. Because the presentation of tuberculosis is becoming less typical, and spinal tuberculosis is more common than simple epidural abscesses, so when the cause of a spinal abscess is unknown, the abscess but not blood testing is more important, for example Tubercle Bacillus acid-fast staining. When systemic infection symptoms are not obvious, tuberculosis should be highly suspected, especially in patients with elevated ESR and CRP.

RESPONSE TO REVIEWER 05190615

Dear reviewer 05190615,

Thank you very much for your review and invaluable comments.

We totally agree with your opinion that abscess is more important specimen than blood when the causative pathogen of spinal abscess is unknown. Our patient had a history of spinal injection, which might have been the source of bacterial infection. In addition to bacteria, we also identified TB from spinal abscess based on following examinations; 1) acid-fast bacillus (AFB) stain, 2) AFB culture, 3) histopathological examination, 4) polymerase chain reaction (PCR). Because all of them showed same result, we believe our diagnosis for coinfection of bacteria and TB is certain. We have supplemented this description in 'FINAL DIAGNOSIS' section of our revised manuscript.

We also agree with your idea that when systemic infection symptoms are not obvious, TB should be highly suspected, especially in patients with elevated ESR and CRP. We also described only 20-30% of case of spinal TB had constitutional symptoms in the 3rd paragraph of 'DISCUSSION' section of revised manuscript.

We have revised current manuscript referring to your excellent comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your

helpful attention and await a superb decision.

REVIEWER 03227821'S COMMENT

This case report may provide reference for the diagnosis and treatment of patients in the future, and has certain clinical value.

RESPONSE TO REVIEWER 03227821

Dear reviewer 03227821,

Thank you very much for your review and invaluable comments.

We have revised current manuscript referring to your excellent comments. The more detailed information about 'final diagnosis' and 'treatment' has been supplemented in the CASE PRESENTATION section. And we also added radiological follow-up images (Figure 4) including more detailed descriptions in 'outcome and follow-up' section of revised manuscript.

We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await a superb decision.

REVIEWER 05430304'S COMMENT

1. The title describes an epidural abscess, but this case should be diagnosed as lumbar tuberculosis. 2. The paper only provided the MRI before the first operation. Methicillin-resistant S. epidermidis infection can not explain the destruction of lumbar vertebrae and cold abscess. It is unreasonable to exclude tuberculosis based on pathological results.

RESPONSE TO REVIEWER 05430304

Dear reviewer 05430304,

Thank you very much for your review and invaluable comments. We have revised current manuscript referring to your comments deeply and all of your comments

have been supplemented in our revised manuscript.

We totally agree with your comment that the destruction of vertebral body and cold abscess were typical findings in spinal tuberculosis (TB) rather than in *S. epidermidis* spondylitis. However, preoperative blood culture result strongly suggested bacterial infection and *S. epidermidis* was identified from multiple intraoperative abscess specimens. Although we knew this microbiological result was not compatible with MRI finding, we should have initiated vancomycin treatment. We were more tentative to diagnose the spinal TB, because chest CT scans preformed 2 and 6 months prior to first surgery failed to detect pulmonary TB and the patient did not have any symptom of it. After recognizing the recurrence of spinal abscess, we carefully suspected coinfection of TB. However, we could not confident of the coinfection of bacteria and TB until second surgery, because it was very rare and few cases had been reported. Its rarity caused our inattention to TB coinfection. We have supplemented this description in 'DISCUSSION' section of our revised manuscript.

Moreover, we provided MRI not only before the first operation (Figure 1), but also before second operation (Figure 2), which revealed recurrence suggesting TB spondylitis.

3. There is no images after the second operation.

We are very sorry for omitting follow-up radiological images after the second operation. We performed CT scan after second operation and have also conducted radiological follow-up using simple X-ray. We supplemented the follow-up CT and simple X-ray images in 'Figure 4' of our revised manuscript.

4. Although the article mentions a ten-year follow-up, there is no follow-up outcomes.

After completion of 1-year of antitubercular medication, the TB or epidural abscess never recurred. Serial chest X-rays and polymerase chain reaction (PCR) test, which was performed 10 years later were free from pulmonary TB.

CT scan and serial X-rays showed no change of spinal instrument until follow-up X-ray revealed rod fracture 10 years later (Figure 4D). However, low back pain never aggravated and the patient did not have additional medication for pain or spinal

intervention after second surgery.

ESR has been normalized within 1 week after second surgery, whereas CRP remained high until completion of antitubercular medication. We also supplemented this description in 'OUTCOME AND FOLLOW-UP' section of our revised manuscript.

We have revised current manuscript referring to your invaluable comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await an excellent decision.

REVIEWER 05353971'S COMMENT

The paper presents an interesting and rare case of SEA, which coinfected with bacteria and tuberculosis. And it is praiseworthy that the case had been followed up for ten years. This is a well-written paper. For the benefit of the reader, however, a number of points need clarifying and certain statements require further justification. My detailed comments are as follows: 1. Accurate diagnosis of tuberculosis has been rendered increasingly difficult. To our knowledge, T-spot is a test with high sensitivity for tuberculosis diagnosis, had it been conducted in the case? And if not, what was your consideration?

RESPONSE TO REVIEWER 05353971

Dear reviewer 05353971,

Thank you very much for your review and invaluable comments.

We totally agree that T-spot test is very useful for diagnosis of tuberculosis (TB) because of its high sensitivity (81.8-100%). It quantitatively measures interferon-gamma producing T-lymphocyte after exposure of TB-specific antigens (ESAT-6, CFP-10) by enzyme-linked immune-spot analysis (ELISPOT).

However, T-spot test is not site specific and it can't determine the location of TB. It may have been positive because our patient had latent pulmonary TB. Even though it is positive, that just means the patient have TB and that does not mean it is

specifically involved with spine. In our case, the most important point is whether the spinal abscess was TB origin or not, not the presence of pulmonary or any other TB. Thus, we think the role of T-spot, in spinal TB like our case is relatively limited.
Although T-spot test is very useful diagnostic modality, it was approved by FDA in 2008. Unfortunately, we did not have opportunity to conduct T-spot test because of limited facility of our hospital 10 years ago. We heartily hope your generous understanding of our previous situation.

2. For bone infections, especially bacterial infections, it is controversial whether to perform internal fixation implantation after debridement. It would be catastrophic if the infection is not controlled. And posterior instrumentation was performed after debridement in the case, what was your consideration?
We totally agree with your idea that the spinal instrumentation is controversial issue especially in pyogenic spinal infection. We are also very cautious about internal fixation using metallic instrument after debridement of infective tissue or abscess. Thus, we did not performed internal fixation in first surgery to avoid foreign body related infection problem.
However, we had limited option in second surgery because of progressive bony erosion and risk of instability. Although we preferred staged surgery, the patient wanted the second surgery should be the final one. Moreover, we carefully suspected the possibility of TB, because of bony erosion and disappointing response to vancomycin. Looking back on such situation, it was very lucky that the pathogen was confirmed as TB after second surgery, because the bio-film formation and instrument-related problem are less frequent in TB spondylitis.

3. The normal reference value should be marked on the part of laboratory examination.
Thank you very much for your thoughtful advice. The normal reference values for ESR, CRP, and WBC count were 0-20 mm/hour, 0-0.75 mg/dl, and 3800-1000/μL, respectively. We supplemented them in 'Laboratory examinations' section of our revised manuscript.

4. Methicillin-resistant S. epidermidis was identified from intraoperatively acquired abscess culture at the first surgery. What was the type of bacteria at the second surgery? In addition to taking antitubercular medication after the second surgery, is there any oral anti bacteria drugs?

We acquired more than 10 intraoperative specimens from the abscess, bone and soft tissue for microbiological study in second surgery. However, no bacteria were identified from every specimen. We believed that causative bacteria (MRSE) were disappeared completely after weeks of vancomycin treatment. Thus, we administered only prophylactic intravenous antibiotics for days except for antitubercular medication. We supplemented this result in 'FINAL DIAGNOSIS' section of revised manuscript.

5. Did the patient undergo MRI imaging during the 10-year follow-up? If there were laboratory and Imaging examinations after the patient being cured, it would be more perfect.

We did not perform MRI after second surgery because of metallic artifact stem from internal fixation. However, we conducted CT scan postoperatively and simple X-rays during the 10-year follow-up in addition to serial laboratory examinations. We supplemented the follow-up CT and simple X-ray images in 'Figure 4' of our revised manuscript.

After completion of 1-year of antitubercular medication, the TB or epidural abscess never recurred. Serial chest X-rays and polymerase chain reaction (PCR) test, which was performed 10 years later were free from pulmonary TB.

CT scan and serial X-rays showed no change of spinal instrument until follow-up X-ray revealed rod fracture 10 year later. (Figure 4D). However, low back pain never aggravated and the patient did not have additional medication for pain or spinal intervention after second surgery.

ESR has been normalized within 1 week after second surgery, whereas CRP remained high until completion of antitubercular medication. As you recommended, we also supplemented radiological imaging and laboratory examination results in

'OUTCOME AND FOLLOW-UP' section of our revised manuscript.

6. The author should give a detailed plan of antituberculosis treatment, including dose and drug adjustment plan.

We initiated combination therapy using Isoniazid (INH 300mg qd), Rifampin (RFP 600mg qd), Ethambutol (EMB 1200mg qd), and Pyrazinamide (PZA 1500mg qd). Because the patient experienced urticaria and skin lash in 3 weeks, PZA was replaced by Levofloxacin (500mg qd).

Whereas INH and RFP were continued without dose adjustment throughout 1-year of antitubercular treatment, EMB was reduced to 800 mg qd and Levofloxacin was discontinued in 4 months. As you recommended, we supplemented this detailed description in 'TREATMENT'section of our revised manuscript.

We have revised current manuscript referring to your excellent comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await a decision.

REVIEWER 05355553'S COMMENT

Good work，How to identify coinfection or postoperative infection?

RESPONSE TO REVIEWER 05355553

Dear reviewer 05355553,

Thank you very much for your review and invaluable comments.

Mycobacterium tuberculosis is slow-growing pathogen. Even in very optimal environment such as laboratory culture condition, its growth and identification usually takes over 6-8 weeks. In our case, the abscess recurred only 9-11 weeks after the operation. We think it is too short period for invasion, colonization, and fully-matured abscess formation. Thus, we believe our case should be regarded as coinfection rather than postoperative infection, considering the short time interval between the first operation and recurrence.

Additionally, the extent and location of recurred abscess was very similar to initial abscess which had been totally removed surgically. Thus, recurred abscess is likely to be the continuation of initial abscess, rather than new event.

Finally, our patient had latent pulmonary tuberculosis (TB), which was diagnosed after second surgery. Considering the major portal of entry for TB is respiratory and genitourinary system, it is very likely to be the source of spinal epidural abscess. We think it is more reasonable explanation rather than that postoperative TB infection resulted in spinal epidural abscess, which became the source of pulmonary TB.

We have supplemented this description in 'DISCUSSION' section of our revised manuscript. We have revised current manuscript referring to your excellent comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await a decision.

REVIEWER 03207387'S COMMENT

The authors reported a 75-year-old female complaining low back pain. MRI revealed an Spinal epidural abscess (SEA) at the lumbosacral segment. Staphylococcus hominis and methicillin-resistant Staphylococcus epidermidis were identified from preoperative blood culture and intraoperative abscess culture, respectively. The patient underwent treatment with vancomycin medication for 9 weeks after surgical drainage of the SEA. However, the low back pain recurred 2 weeks after vancomycin treatment. Then, MRI revealed an aggravated SEA in the same area in addition to erosive destruction of vertebral bodies. Revision surgery was performed for SEA removal and spinal instrumentation. The microbiological study and pathological examination confirmed Mycobacterium tuberculosis as the pathogen concurrent with the bacterial SEA. The patient improved completely after 12 months of antitubercular medication. The authors thought coinfection of bacteria and tuberculosis occurred in the case. However, the Staphylococcus hominis and methicillin-resistant Staphylococcus epidermidis were identified from preoperative blood culture and intraoperative abscess culture, respectively. Different bacteria were seen in blood culture and intraoperative abscess culture, so the possibility of contamination during

culture could not be excluded.

RESPONSE TO REVIEWER 03207387

Dear reviewer 03207387,

Thank you very much for your review and invaluable comments.

Staphylococcus hominis is a coagulase-negative member of the genus Staphylococuss (CoNS). As you commented, they are commonly encountered blood culture contaminants whose contamination rate is reported to be over 44%[1,2]. On the other hand, they also constitute an important cause of blood stream infection in the ever-expanding population of patients with biomedical devices, broad-spectrum antibiotics and indwelling catheters[1,2]. Thus, the isolation of CoNS from blood cultures remains a clinical dilemma in many cases, and it is difficult to determine with certainty the clinical significance of these isolates[3]. We understand it is difficult to completely exclude the possibility of contamination in blood culture, as you commented.

However, our result was derived from 2 sets of blood cultures and both were identical even in species level (Staphylococcus hominis genus and hominis species). Kirn et al.[1] recommended to identify CoNS to the species level (not just genus level) when more than one set of blood cultures are positive. If the CoNS from multiple blood culture sets are same not only in genus level but also in species level like our case, the odds of contamination decrease[1]. Weinstein et al.[3] also described if 2 or more blood cultures grow CoNS and they are identical in biochemical profile and susceptibility, the probability of true infection increases. Therefore, we think it is not reasonable to conclude our blood culture result as contamination, just because the identified pathogen is Staphylococcus hominis. Moreover, we believe that the intraoperative abscess culture was not contamination, because the methicillin-resistant Staphylococcus epidermidis were identified from multiple sites.

We have supplemented this description in 'DISCUSSION' section of our revised manuscript.

[1] Kirn T J, Weinstein M P. Update on blood cultures: how to obtain, process, report,

and interpret. Clin Microbiol Infect. 2013 Jun;19(6):513-20. doi: 10.1111/1469-0691.12180. Epub 2013 Mar 13.
[2] Zeng L, Wang S, Lin M et al. Evaluation of time to positivity for blood culture combined with immature granulocytes, neutrophil-to-lymphocyte ratio, and CRP in identifying bloodstream coagulase-negative Staphylococci infection in pediatric patients. J Clin Lab Anal. 2020 Nov;34(11):e23473. doi: 10.1002/jcla.23473. Epub 2020 Jul 19.
[3] Weinstein MP, Mirrett S, Van Pelt L et al. Clinical importance of identifying coagulase-negative staphylococci isolated from blood cultures: Evaluation of microscan rapid and dried overnight gram-positive panels versus a conventional reference method. J Clin Microbiol 1998 Jul;36(7):2089-92. doi: 10.1128/JCM.36.7.2089-2092.1998.

And T-spot, PPD and X-pert tests are necessary to confirm the diagnosis of TB. Besides, anti-acid staining of the abscess are needed.

We totally agree with your comment about the importance of T-spot, PPD (Purified protein derivative), and X-pert tests. However, they are not site specific and they can not determine the location of TB. They may have been positive because our patient had latent pulmonary TB. Even though they were positive, that just means the patient have TB and that does not mean it is specifically involved with spine.

In our case, the most important point is whether the spinal abscess was TB origin or not, not the presence of pulmonary or any other TB. Thus, we think the role of T-spot, PPD, and X-pert tests in spinal TB like our case is relatively limited.

We identified TB from spinal abscess based on traditionally verified methods; 1) acid-fast bacillus (AFB) stain, 2) AFB culture, 3) histopathological examination, 4) polymerase chain reaction (PCR). Because all of them showed same result, we believe our diagnosis for spinal TB is absolutely certain and we are sure it is not contamination. We have supplemented this description in 'FINAL DIAGNOSIS' section of our revised manuscript.

Although T-spot and X-pert test are powerful tools, we think they are not the exclusively necessary tests for spinal TB like our case. Moreover, PPD test is a skin

test which determines if the patient has developed an immune response to TB. However, it may cause false positive result for patient who received a BCG vaccine. Thus, it is not useful test in our country where a BCG vaccine is included in national immunization program.

T-spot is a test which detects interferon-gamma secreting T-cells after stimulation with TB-specific antigens. It can detect even latent TB with high sensitivity and specificity. X-pert test is also an innovative test for rapid TB diagnosis and drug resistance. It reduced time for diagnosis dramatically from several weeks to hours and saved much cost. However, we did not have opportunity to conduct them 10 years ago, because of limited facility of our institution. We heartily hope your generous understanding of our previous situation.

We have revised current manuscript referring to your invaluable comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await an excellent decision.

REVIEWER 05729651'S COMMENT

The idea of the paper is innovative, and they completed up to 10 years of follow-up, that is the excellent job. But There are some questions for the author to answer：1）I think the author must write down how many cases have been reported in the literature and conduct a small review.

RESPONSE TO REVIEWER 05729651

Dear reviewer 05729651,

Thank you very much for your review and invaluable comments.

We have found 2 cases of spinal abscess originating from coinfection of TB and bacteria[1,2]. The one was related with methicillin-resistant coagulase-negative staphylococcus and *Mycobacterium tuberculosis*[1]. Although the patient had a history of pulmonary tuberculosis (TB), the diagnosis of spinal TB has been delayed like our case. The other case was related with *Nocardia asteroids*, *Moraxella catarrhalis*, and

Mycobacterium tuberculosis[2]. The patient did not have a history of pulmonary TB. As you recommended, we supplemented this brief review in 'DISCUSSION' section of our revised manuscript.

[1] Kim YM, Cha JH. Delayed diagnosis of tuberculous spondylitis masked by concomitant methicillin resistant Staphylococcus aureus infection. J Korean Neurosurg Soc. 2010 Mar;47(3):235-8. doi: 10.3340/jkns.2010.47.3.235. Epub 2010 Mar 31.

[2] Mousa HA. Concomitant spine infection with mycobacterium tuberculosis and pyogenic bacteria: case report. Spine (Phila Pa 1976). 2003 Apr 15;28(8):E152-4.

2) Changes in all aspects of the patient during the 10-year follow-up should be described in detail, including the treatment plan, treatment outcomes, and changes in the patient's condition, etc.

After completion of 1-year of antitubercular medication, the TB or epidural abscess never recurred during the 10-year follow-up period. Serial chest X-rays and PCR test, which was performed 10 years later were free from pulmonary TB.

CT scan and serial X-rays showed no change of spinal instrument until the last follow-up X-ray revealed rod fracture 10 years later (Figure 4D). However, low back pain never aggravated and the patient did not have additional medication for pain or spinal intervention after second surgery.

ESR has been normalized within 1 week after second surgery, whereas CRP remained high until completion of antitubercular medication. As you recommended, we supplemented this more detailed description about 10-year follow-up in 'OUTCOME AND FOLLOW-UP' section of our revised manuscript.

3) Please provide your basis for the medication regimen after surgery.

After identification of methicillin-resistant staphylococcal epidermidis (MRSE) in first surgery, we started intravenous vancomycin treatment immediately and continued for 9 weeks. It was based on antibiotics susceptibility test for MRSE.

We acquired more than 10 intraoperative specimens from the abscess, bone and soft

tissue for microbiological study in second surgery. However, no bacteria were identified from every specimen. We believed that causative bacteria (MRSE) were disappeared completely after vancomycin treatment. Thus, continued only antitubercular medication for 1 year.

We initiated combination therapy using Isoniazid (INH 300mg qd), Rifampin (RFP 600mg qd), Ethambutol (EMB 1200mg qd), and Pyrazinamide (PZA 1500mg qd). Because the patient experienced urticaria and skin lash in 3 weeks, PZA was replaced by Levofloxacin (500mg qd). Whereas INH and RFP were continued without dose adjustment throughout 1-year of antitubercular treatment, EMB was reduced to 800 mg qd and Levofloxacin was discontinued in 4 months. As you recommended, we supplemented this detailed description in 'TREATMENT'section of our revised manuscript.

We have revised current manuscript referring to your excellent comments. We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await a decision.

REVIEWER 05345734'S COMMENT

authors have successfully addressed all comments.

RESPONSE TO REVIEWER 05345734

Dear reviewer 05345734,

Thank you very much for your review and invaluable comments.

We have revised current manuscript referring to your excellent comments. The more detailed information has been supplemented in the CASE PRESENTATION and DISCUSSION section. And we also added radiological follow-up images (Figure 4) in our revised manuscript.

We also believe that this revised manuscript improved more by reflecting your important comments and is ready for your favorable reconsideration. We are grateful for your helpful attention and await a decision.