Title: Case report: Patient with occult dental abscess presenting with infective endocarditis caused by Brevundimonas vesicularis

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Version: 2 Date: 13 November 2006

Author's response to reviews: see over
Re: 2095928401146748 - Case report: Patient with occult dental abscess presenting with infective endocarditis caused by Brevundimonas vesicularis

Dear Editors,

A point-by-point response to the peer reviews of our original manuscript, #2095928401146748, is presented in this reply letter according to the editors’ suggestion. All authors have read and agreed to the re-submitted version of the manuscript. The reviewers’ queries and suggestions are addressed item by item as follows, highlighted in Bold format:
Reviewer Jacob Gilad

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Title + throughout paper – this paper adds two important points to our understanding of BV – (1) being the first case of SBE with BV; (2) a case that demonstrates the therapeutic challenges spanning antibiotic choice, determination of in vitro susceptibility and therapeutic failure in the context of a serious condition caused by a rare organism about which there are few or no data. The fact that the patient had an occult dental abscess is less important because this has been associated with SBE with other organisms and because the contribution of abscess to SBE is speculative. Therefore, the title, abstract and discussion should be revised to focus more on the situation described above rather than the dental abscess. The source of infection is important but is discussed adequately at the beginning of the discussion section.

As the reviewers’ suggestions, we have no enough evidence to support the relationship between endocarditis of the current case with the dental abscess, though dental lesions and dental procedures should always be evaluated for the origin of endocarditis. The title of the article will be corrected to be “Case report: Infective endocarditis caused by Brevundimonas vesicularis” And, the content of abstract was also corrected (page 1 & 2).

2. Abstract – therapeutic failure is mentioned in the conclusion but should be communicated to the reader also earlier in the abstract. Moreover, the conclusion regarding optimal regimens is not fully supported by the new data in this paper (see below). This should be revised into a less conclusive statement.

The therapeutic failure will be informed in the abstract of the revised article (page 2, line 10-11).

We agree that it is premature to conclude the optimal regimens for the pathogen by current treatment experiences of reported cases and revised the conclusion on the last paragraph of page 2.

3. p. 3 + table 1 - the authors rightfully review BV infection cases reported this far in the literature. There are two recent case reports that should also be added to the table and other parts of the paper (where relevant):

These two articles will be citated in the current report (page 3 & 8 and table1 & table 2). Thanks for your informations about these papers.

4. p. 3 + table 1 – reference 11 describes a case cluster in a dialysis unit and cannot be considered community-acquired infection.

We agree the infections of the patient with hemodialysis should be recognized as NOSOCOMIAL (healthcare-associated) INFECTION. The content of page 2 (line 8) and table 1 were corrected accordingly.

5. p.4, lines 1+8 – respiratory symptoms and pulmonary infiltrates are mentioned but we are not told whether they are a part of SBE? Is this a septic complication? Congestive heart failure? How do the authors explain these findings?

The respiratory symptoms and pulmonary infiltrates were supposed to
be parts of manifestations of endocarditis. For briefness of the article, the symptoms will not be further corrected in the revised paper.

6. p. 4, line 12 – should state according to Duke's criteria whether SBE in this case is definite, probable, possible... Findings in this paragraph should better ordered (e.g. major and then minor criteria).

The statements about the symptoms of the patient were corrected according to the major and then minor criteria of Duke's criteria (page 5, line 1-5). Definite SBE was diagnosed due to two major criteria (positive blood culture; positive echocardiogram) and two minor criteria (fever ≥ 38.0°C; Osler' nodes and Roth's spot)

7. p. 4, line 14 – how many blood culture vials were collected and how many of them did grew BV? This should be discussed since BV may be a contaminant and is an even more peculiar finding in a patient who lacks any risk factors.
&
8. Especially if only one culture vial is positive - were other causes of culture-negative SBE ruled out (e.g. Q fever, Mycoplasma, Bartonella, etc.).

Two positive results of the pathogen cultured from two blood collections by the standard procedure of blood collection (specimens obtained from different body sites via intravenous puncture in separated hour) were obtained.

The number of blood culture result will be presented in the revised article (page 5, line 2).

9. p. 4, last para – the author should report the %probability of organism ID in the API system used. Moreover, it is more important to report that the key features of BV were present and consistent with the biochemical gallery ID. These key features may include: orange pigment, weak oxidase activity, motility, no growth on MAC, sugar alkalinity, positive esculin hydrolysis, negative PYR, positive alkaline phosphatase, susceptibility results to vancomycin, polymyxin B and desferrioxamine. Indole production and nitrate reduction are typically negative in BV but listed AS positive in the paper. This should be explained or corrected .

The probability of organism ID in the API system was 99.6%. Indole production and nitrate reduction are typically negative in BV and also in our result. We have made the sentence clearer to understand (page 5, line 6-12)

10. p. 5, lines 6-10 – BV usually requires more than 24 hours to grow while CLSI guidelines for Pseudomonas require <24h of incubation. How did the authors overcome this? Did the organism grow well on standard susceptibility media (MHA) or did they test the organism on blood agar?

We performed the disc diffusion susceptibility testing according to the CLSI guidelines for Pseudomonas but we actually read the result when incubation for 24 hours. The part is revised in Page 5, line 12-16.

11. CLSI breakpoints of 2006 rather than 1997 should be used.

The CLSI of 2006 was corrected accordingly. (reference 16)

12. p. 5, line 10 – the choice of initial therapy warrants clarification. First, cefazolin is hardly an antipseudomonal agent and the author should explain why ceftazidime or cefepime were not chosen as first-line agents. Second, the recommended gentamicin dose, especially in serious infections, in an adult with
normal renal function is 5.1 mg/kg that is 350mg/d for a 70kg man rather than 240mg/d. The author should elaborate on the dosing of gentamicin.

Cefazolin was just one of the empiric antibiotics for infection while admission. It was not the specific choice for Pseudomonas species.

The dosage of gentamicin (1mg/kg, q8h) for infective endocarditis was administered according to the suggestion from Table 109-4 on Harrison’s Principles of Internal Medicine, 16th edition. The body weight patient while admission was 78 Kg. Therefore, 80 mg/q8h of gentamicin was intravenously administered.

13. p. 5, line 11 – it is reasonable indeed to treat a presumed oral source of SBE during iv therapy for SBE, but the switch to A/S is unclear and should be addressed? What additional microbial coverage was sought?

Due to abundant anaerobes in oral cavity and the reason for A/S will be addressed in the revised article (page 5, line 19)

14. p. 5, line 16-18 – after A/S had supposedly failed, it was switched to ceftriaxone, and later to ciprofloxacin because of drug hypersensitivity. Again, the authors should comment on agent choice. This (hypersensitivity) might be a classic indication for aztreonam therapy.

We add the point that aztreonam may be considered as an alternative choice (the last paragraph of page 8). It is a clinician’s decision to use ciprofloxacin.

15. p. 6, line 2 – Pseudomonal endocarditis principally requires 6 weeks of combination therapy (e.g. see Mandell’s chapter on SBE). The authors should comment why did they choose a shorter protocol?

For there is no previous treatment experience for Brevundimonas endocarditis and the patient’s condition is afebrile and without symptoms of any heart failure and sepsis, the attending physician choose a 4-week treatment duration.

16. p. 8, line 3-7 – on the basis of a single case of therapeutic failure, one cannot conclude that disk-diffusion is unsuitable. The author should discuss the technical limitations of performing agar diffusion testing with fastidious organisms such as BV (see comment above) and lack of breakpoints (use of breakpoints for Pseudomonas is merely an assumption). The author should report the zone diameter measured with A/S in their case and clearly need to test this isolate for MIC, at least for A/S and other drugs administered to the patient, in order to elucidate whether the problem lies with disc diffusion method, or with the ability of susceptibility testing of BV to predict clinical outcome in general.

The viewpoint that “BV usually requires more than 24 hours to grow while CLSI guidelines for Pseudomonas require <24h of incubation.” is described in the discussion part. We are not able to do the MIC testing because the bacteria could not be recovered from storage at -70 °C.

17. p. 8, last para – statement regarding regimen effectiveness is premature. The current case, as opposing to this statement, does not prove that cephalosporin therapy is successful since this patient did not complete a course of cephalosporin therapy and because efficacy of SBE therapy is measured not only by initial improvement but also prevention of relapse. As for quinolones, this is the only case in which they were utilized for BV infection and one cannot issue a
therapeutic recommendation based on a single case. At most it might be stated
that current evidence and the presented case, favor these agents, but that
additional data are needed and close follow-up in order to detect treatment failure
is warranted.

We have revised the statement regarding treatment regimens in the
abstract (page 2) and discussion part (page 7).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use
of a term, which the author can be trusted to correct)
1. p. 4, line 5 – report patient hemodynamic parameters on admission.
   The hemodynamic parameters will be added in the revised article
   (page 4, line 6-7)

2. p. 4, line 6 – WBC count <10,000 is hardly an "elevated count".
   The statement will be corrected appropriately (page 4, line 11).

3. p. 4, line 10 – please report the TST (PPD) results of this patients.
   No routine PPD will be performed in our country due to almost of
   children had been vaccinated with BCG. It will be confused about
   interpretation of the PPD result. Serial AFS and TB culture of sputum were
   administered if suspect pulmonary tuberculosis. Additionally, PCR is also
   used for evaluating the infection of Mycobacterium tuberculosis sometimes.
   ASF and TB cultures of sputum from the patient were shown as negative.

4. p. 4, line 13 – echocardiographic findings should be more detailed (may be
   incorporated into legend of Fig 1), to include vegetation size, exact location,
   cardiac function (LVEF). Is this TTE or TEE? In figure 1, the vegetation should be
   pointed out with an arrow and normal cardiac structures surrounding it (LA, LV
   etc.) should be also marked.
   Fig 1 will be corrected according to the current suggestion.

5. p. 5, line 4 – present all initial clinical data first, then microbiology data, and then
   treatment and outcome. The case report section should be organized better.
   The paragraph will be corrected according to the current suggestion
   (Page 4-5).

6. p. 5, line 5 – what did this "serial survey" include?
   The patient got admitted for intermittent fever for about 2 months.
   Fever of unknown origin (FUO) was impressed initially according to the
   DEFINITION derived by Petersdorf and Beeson. Serial survey for the
   etiologies of FUO, such as Infections, collagen-vascular diseases,
   malignancies and drugs, was evaluated by physical examination and lab
   analyses. For the briefness of the report, the detail will not be addressed in
   the article.

7. p. 8, line 11 – "standardized" is preferred over "simultaneous".
   The statement will be corrected according to the current suggestion
   (Page 8, line 16).

8. reference 1 is outdated. Refer to 8th edition of this textbook.
   The reference will be renewed in the revised article (reference 1).
9. p. 5, line 14 – a flare-up of fever is noted but no previous sentence describes defervescence.

   The statement will be corrected according to the current suggestion (Page 5).

10. p. 5, line 15 – how do the authors explain sudden femoral-inguinal involvement? Was this further investigated? Were possible complication such as septic arthritis / osteomyelitis / septic embolism ruled out?

   The femoral-inguinal lesion was supposed to be septic embolism and disappeared after treatment. Therefore, no further evaluation was administered.

11. p. 6, line 1 – make it clearer that gentamicin was discontinued and that cipro was given alone, as in table 1. Were gentamicin serum levels measured?

   When gentamicin given, the renal function of the patient was monitored closely and was noted as normal, but the serum levels of the antibiotic was not measured. As combined therapy for bacterial endocarditis, gentamicin was suggested for two weeks (Table 109-4 on Harrison’s Principles of Internal Medicine, 16th edition). Therefore, gentamicin was discontinued, which was not concerned with the serum level for the renal function impaired, for two week treatment of the case.

12. p. 6, line 2 – was a follow-up echocardiogram performed?

   Follow-up echocardiogram was performed one month after discharge. It will be addressed in the revised article (page 6, line 11).

13. p. 8, line 1 – authors discuss previous susceptibility data. This sentence should refer to table 2.

   The statement will be corrected according to the current suggestion (Page 8, line 1).

14. Table 2 – S, R, N need to be explained in table footnote.

   The abbreviations will be explained in table footnote (Table 2).

S: sensitive
R: resistant
N: not determined

We revised according to the above suggestions (minor essential revisions).
Reviewer Sanjay Shukla

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) What clinical samples were used to test for the Mycobacterium tuberculosis culture and acid-fast staining?

   Sputum specimens were sent for Mycobacterium tuberculosis culture and acid-fast staining. We have added the information in line 15-16 of page 4.

2) What tests (culture, PCR etc.) were done to isolate the B. vesicularis from the dental abscess? Did the dental abscess yield any other bacteria from any of the approaches (Gram stain, culture etc.) used?

   There is no microbiology study on the pus from dental abscess for the dentist did not collect the specimen and our not informing the importance to collect the abscess specimen for microbiologic study. We notice the inadequacy of evidence to correlate the abscess with the infective endocarditis and rewrite the title and article according to the reviewers’ comments.

3) Provide reference for the statement that 'B. vesicularis are reported with increasing frequency.' Certainly a search of PubMed suggests otherwise.

   As shown in Table 2, there was no reported case of infection due to B. vesicularis before 1992. Only one case infected by the pathogen was published in 1992 and 1994 respectively. Five cases, including the current one, were published during 2000 to 2006, and especially three cases have been reported in 2006. The above showed B. vesicularis are reported with increasing frequency.

4) Mention of ‘occult dental abscess’ in the title of the manuscript is somewhat misleading as it may have nothing to do with the endocarditis. Title of the manuscript needs to be modified.

   Indeed, we have no enough evidence to support the relationship between endocarditis of the current case with the dental abscess, though dental cavities and dental procedures should always be evaluated for the origin of endocarditis. The title of the article will be corrected to be “Case report: Infective endocarditis caused by Brevundimonas vesicularis”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) Explain the abbreviations such as ESR, AST and ALT.

   The abbreviations have been explained in the list of abbreviations of article.

ESR: erythocyte sedimentation rate
AST: aspartate aminotransferase
ALT: alanine aminotransferase
2) Table 1. There is no discussion of what criteria were used to define infections as ‘community-acquired’ and ‘nosocomial.’

Community-acquired and ‘nosocomial infection will be defined in the table footnote (Table 1)

3) Table 2. ‘S’, ‘N’, and ‘R’ are not defined.

The abbreviations will be explained in table footnote (Table 2).

S: sensitive
R: resistant
N: not determined

We revised according to the above suggestions (minor essential revisions).

Many thanks to both reviewers’ kindly instructive suggestions and corrections.

Yours sincerely,

Po-Liang Lu M.D.