Author's response to reviews

Title: Necrotizing fasciitis caused by Haemophilus influenzae type b in a patient with rectal cancer treated with combined bevacizumab and chemotherapy: a case report

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Author's response to reviews: see over
Dear Dr. Harris

MS: 1931120475121429
Title: Necrotizing fasciitis caused by Haemophilus influenzae type b in a patient with rectal cancer treated with bevacizumab: a case report

We are grateful to you and the reviewer(s) for valuable comments and useful suggestions that have helped us to improve this manuscript. As indicated in the responses (in italics) in the following sheets, we have considered all of these comments and suggestions in the revised version. Changes to the accompanying manuscript are highlighted in red.

We hope that these responses are satisfactory and that the revised version of our manuscript is now suitable for publication in *BMC Infectious Disease*. Once again, thank you very much for your consideration.

Yours sincerely,

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Response letter to reviewer #1
Reviewer: Catriona Chalmers

Reviewer’s report:
1. Within the case report itself, we need to know whether this patient had any other risk factors for necrotising fasciitis - e.g. diabetes, use of steroids or NSAIDs. This could be achieved by including a brief medical history and relevant drug history, or stating at some point that there were no other identifiable risk factors. Without this detail your link to bevacizumab becomes more tenuous.

   Thank you for your comments. We agree to these comments. We added the following sentence in page 3, line 60-64.

   “She did not have a history of previous injury or the presence of other risk factors for necrotizing fasciitis such as a decubitus ulcer, diabetes, or liver cirrhosis. Her medications included a 5-HT3 receptor antagonist, which is an antiemetic, and a proton pump inhibitor; however, her medications did not include non-steroidal anti-inflammatory drugs, immunosuppressive drugs, or corticosteroids.”

2. It is unclear from the description whether the patient was taken to theatre for debridement, which was only completed on receipt of an intra-operative biopsy/frozen section, or whether biopsy was undertaken prior to the decision to operate. This should be made clear, ideally along with some indication of the timeframe from admission to debridement. This is important since it is recommended not to delay debridement while awaiting microbiological samples, and given the patient’s ultimate successful outcome (suggesting speedy treatment).

   We appreciate these comments. We agree to these comments. We changed “The advancing erythematous margin and her worsening clinical condition necessitated an orthopedic consultation for the biopsy of the fascia” to “The advancing erythematous margin and her worsening clinical condition prompted us to suspect necrotizing fasciitis and consult the orthopedics department for a fascia biopsy and debridement.” in page 3-4, line 73-75.

3. The second paragraph of the discussion begins: 'In a comprehensive safety review conducted by Roche.....'. A reference is required for this information - there is none at present.

   We apologize for not listing the correct reference. We added the correct reference.

4. In the same paragraph, the second sentence ('The majority of the patients
described in case reports.....’) is referenced by a single case report (ref 4). I have
not been able to gain access to the full-text version of that article, which may
in turn reference other case reports. However, I would suggest using a
reference(or references) which more clearly supports the statement.

We apologize for not listing the correct references. We added the correct
references.

Discretionary Revisions
1. The case report itself would read better with the addition of some paragraph
spacing.

Thank you for your comments. We agree to these comments. We added some
paragraph spacing in the case report section.

2. It is unusual to need such a long course of antibiotics (51 days) for a
surgically-debrided soft tissue infection. Was there a reason for this which would
add to the interest of the case?

Thank you for your comments. We should have mentioned about the reason. We
added the following words “because of residual intermuscular abscesses” in page 4,
line 87.

Response letter to reviewer #1
Reviewer: David Lung

Major Compulsory Revisions
1. Necrotizing fasciitis is an operative diagnosis, although I cannot say it’s wrong
to arrive to a diagnosis of NF with histopathology result, it’s rather odd to say so.
With operative finding of a positive finger test, dish-water pus and lack of
shininess of the fascia would be sufficient to make a diagnosis of NF. (a frozen
section would be unnecessary)

Thank you for your comments. We agree to these comments. However, at this
point we don’t know whether the orthopedics surgeon checked a positive finger
test or not. Therefore, we added the following sentences “Surgical exploration
revealed a murky dishwater-colored pus exudate from the incision site and the lack of a
shiny appearance of the fascia that also suggested necrotizing fasciitis.” in page 3-4,
line 75-76 and “On the basis of all of this information, we formally diagnosed the
patient with necrotizing fasciitis.” in page 4, line 79-80.

We changed “Necrotizing fasciitis was confirmed histopathologically with the debrided
tissue, resulting in a diagnosis of necrotizing fasciitis due to Hib” to “The
histopathological findings of the debrided tissue were compatible with a diagnosis of
necrotizing fasciitis due to Hib.” in page 4, line 82-84.

2. The main problem of this article is the author is unable to link up the drug, the disease and the organism into one story. I agree Hib NF is a rare occurrence and happening in a patient receiving bevacizumab is considered to be unique. However in the discussion, the author suggests several points which makes me re-think: “is it really related to bevacizumab?”

A. Immunocompromised and diabetic patients are at a higher risk of developing necrotizing fasciitis
B. Although Bevacizumab suppresses the immune system, chemotherapy administered concurrently with bevacizumab is more likely to be responsible for immune suppression.
C. Therefore the combined treatment modality is likely to place patients at an increased risk of developing necrotizing fasciitis.

So is it really related to the monoclonal Ab, or it’s a combination of factors? If so, then you will have to change the title and conclusion.

We appreciate these comments. We agree to these comments. As you told, we think that bevacizumab is one of factors for necrotizing fasciitis and invasive Hib infection, and that combination chemotherapy is really related to development of necrotizing fasciitis and invasive Hib infection.

We changed “bevacizumab” to “combined bevacizumab and chemotherapy” or “this combined treatment modality” in the title and the manuscript.

We changed “bevacizumab” to “the recent combined treatment of chemotherapy and bevacizumab” in page 5, line 109.

We changed “We caution physicians to consider invasive Haemophilus influenza type b disease in patients treated with bevacizumab.” to “Other factors conferring increased risk for H. influenzae infection include underlying immunocompromising conditions such as complement deficiency, hypogammaglobulinemia, sickle cell anemia, functional asplenia, malignancy, and human immunodeficiency virus infection. Although the association between bevacizumab and invasive Hib infection remains unclear, we caution physicians to consider invasive Hib disease in patients treated with the combination of bevacizumab and chemotherapy” in page 5, line 116-121.

Minor Essential Revisions
You have mentioned the mechanism of Bevacizumab which is inhibiting angiogenesis, but you have not gone further to discuss the relationship with
NF. As you have mentioned in the discussion, the role of Bevacizumab causing immunosuppression is probably not the main factor to predispose to NF, so there must be something else to link the drug and the infection. The main difference between NF and other types of SSTI is the septic thrombosis of vessels. So probably there’s something to do with the drug inhibiting angiogenesis?

We appreciate these comments. We added the following sentences."

Furthermore, one of the pathophysologic mechanisms of necrotizing fasciitis is subcutaneous artery thrombosis and tissue ischemia, to which bevacizumab can contribute” in page 4, line 96-97.

Discretionary Revisions
- Please comply with the typography of this journal.

We apologize for not complying with the typography of the journal. We changed the manuscript to the appropriate typography.

- Please make sure the fonts style are uniform. (there seems to be different fonts in the text and reference list, e.g. page 3, Case presentation line 15, “for the biopsy of the fascia” is in a different font style)

We apologize for not using the uniform fonts style. We changed the manuscript appropriately.