Author’s response to reviews

Title: Acute exacerbation of idiopathic pulmonary fibrosis induced by pertussis: the first case report

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December 13, 2018

Cecilia Devoto
Senior Editor
BMC Pulmonary Medicine

Dear Editor:

On behalf of the co-authors, I wish to re-submit our case report for publication in BMC Pulmonary Medicine, titled “Acute exacerbation of idiopathic pulmonary fibrosis induced by pertussis: the first case report.”

We have made modifications in accordance with the reviewers’ comments, and have included those with the revised manuscript for your consideration. We thank the reviewers for their insightful comments, suggestions, and questions, which we believe have helped to significantly strengthen our article.

Thank you for your time in reviewing our re-submission. I look forward to hearing from you.
Sincerely,

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We sincerely express our heartfelt gratitude to all the editors who requested reviews from researchers with numerous achievements, especially in the field of interstitial pneumonia. Furthermore, we would like to express our heartfelt thanks to the reviewers for their careful reading of our manuscript and for providing useful comments. Based on this peer review feedback, we have modified the manuscript to further improve its quality. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions that were so graciously provided.

Reviewer reports:

Jean-Marc Naccache (Reviewer 1): The author described 2 cases of acute exacerbation that seem to be secondary to Pertussis infection. Acute exacerbation is a major concern in IPF and all therapeutical action that could prevent it should be emphasize. Vaccination against pertussis in this seating could be very interesting. However, the diagnosis of pertussis infection is poorly confirmed in this two cases and should be

Major comments

1) First of all, the cases did not encounter the CDC Case Definition of Pertussis. In the case definition of pertussis, Serologic testing can be used clinically to aid in diagnosis but are unfortunately not standardized. Is this test standardized in Japan.

Thank you for this information regarding the diagnosis of pertussis. First, we wish to apologize for the brevity of explanation in our case report. In Japan, the diagnosis of pertussis by serum is defined as valid. In Japan, pertussis is part of the disease surveillance notification system. Based on the current infectious disease guidelines in 2018 regarding pertussis, if any of the following
tests provide a definitive diagnosis, the attending physician should provide notification to the disease surveillance system.

① Detection of the pathogen

② Detection of genes of the pathogen

③ Increase in antibody titer in serum analysis (in case of single serum, PT antibody titer >100 EU/mL)

Similarly, another guideline in Japan indicates that serological testing is a standard test. It is also described in the adult cough guidelines in Japan, where pertussis is confirmed as definite diagnosis when PT antibody titer >100 EU/mL is confirmed.

Based on the above text, the following sentences have been added to the revised manuscript.

"In the Japanese infectious disease guidelines, if sputum cultures or Loop-Mediated Isothermal Amplification have not been done or are negative, an increase in antibody titer in the serum has been established as a diagnostic criterion for pertussis; in Japan, therefore, diagnosis by antibody titer is a standard evaluation method. Since a previous study indicated that cultures are unlikely to be positive in adults with more than 3 weeks of coughing, we suspect that a negative culture does not present a problem in the diagnosis of this case [13]."

2) The authors don't precise if exacerbation of cough have begun long term ago (at least 2 weeks). Did they have spasmodic cough?

Thank you for this comment regarding the patients’ symptoms. The patients were aware of uncontrolled cough deterioration and continuous cough at approximately 3 weeks before hospitalization. Although we did not describe their symptoms in detail, we agree that it is very important to include these details. We have added the following text to the revised manuscript.

“Both patients reported a chronic cough associated with the IPF, but they had been aware of uncontrolled cough deterioration and continuous cough beginning approximately 3 weeks before hospitalization.”

"3) If the infection is recent and explain the acute exacerbation of IPF, isolation of Bordetella pertussis from clinical specimen in culture or positive PCR should be showed. What about these tests in the two cases? Moreover, in this hypothesis, the serology should not be high.

As you noted in the above comment (No. 2), we agree that detailed description of the patients’ symptoms is extremely important. Although these patients exhibited an acute course of dyspnea, cough deterioration was present beginning several weeks before hospitalization.
On the basis of the worsening cough, we tested the patients for pertussis antibody, which showed an extremely high value. Based on the above timeline, we think that there is no problem with the increased antibody titer. Please accept our apology for omitting these details in the original text.

4) Whether the cases were epidemiologically linked to a case that was confirmed by culture or PCR it could be used as a diagnosis criteria. What about the two cases?

As you noted, it is desirable to confirm whether these cases involved the same isolate of the pathogen; however, in this case, the culture test was negative. In England's Guidelines for the Public Health Management of Pertussis, it is stated that if time has elapsed since the patient developed symptoms, the likelihood of a positive culture for pertussis decreases. In the adult cough guidelines in Japan, it is stated that if a facility is available for the examination of pertussis by the LAMP method, this method should be performed. Because there was no insurance coverage for LAMP examination of pertussis, and because there were few facilities available for this analysis, examination of pertussis using the LAMP method was not a general exam at the time of these cases. Therefore, at that time, we did not search for pertussis using the LAMP method. However, since November 2016, the LAMP method for pertussis detection has received insurance coverage; therefore, we think that this method will be widely used in Japan in the future. We have added the following text to the revised manuscript.

“Neither patient had Bordetella pertussis detected from sputum; moreover, PCR analysis was not performed, so the patients did not directly show presence of pathogen.”

As we indicated in the manuscript, previous studies have shown that, when the pertussis antibody titer is increased, there is an extremely high probability that the patient has recently been infected with pertussis [9-12]. However, although the specificity of pertussis by antibody titer is high, the detection rate is low; therefore, other tests must be used in combination with the antibody titer analysis.

Thus far, no report has shown that pertussis is involved in AE-IPF, so we suspect that routine PCR testing for pertussis in patients with AE-IPF is not performed in all countries. In order to investigate the rate of pertussis infection as the cause of AE-IPF, high-precision testing, including PCR, may be necessary. Based on this case report, we expect that such tests might be conducted widely. We have summarized the above text and included it in the revised manuscript, as shown below.

“To epidemiologically investigate the extent to which pertussis is involved in AE-IPF, it is necessary to consider serological and culture examination methods, as well as examination by PCR, which shows high sensitivity. This additional method is needed because the specificity of pertussis is high with serological and culture examination methods, but the corresponding detection rates are low.”

Minor comment
Concerning the antibody titer, the cut off is very variable in different countries. The cutoff in Japan population should be precise.

As you noted, we did not include the exact cutoff value used in Japan. In Japan, the cutoff value is established based on the literature (12): PT antibody titer > 100 EU/mL is used to confirm pertussis infection. We have added this in the revised text, as follows:

"In Japan, the cutoff value is established based on the literature [12]: PT antibody titer > 100 EU/mL is used to confirm pertussis infection."

Paolo Spagnolo (Reviewer 2): Hirai and colleagues reported on two patients with IPF who developed an acute worsening - referred to as acute exacerbation (AE) - following Bordetella Pertussis infection. Both patients were discharged home after treatment with macrolides and systemic corticosteroids. To the best of my knowledge, such etiology for AE-IPF has not been reported before. IPF patients experiencing an AE have a poor prognosis, generally because the worsening is generally "idiopathic" or, at least, no clear cause for such worsening is identified. Therefore, treatment of AE-IPF is generally supportive. I found the manuscript interesting and well written.

My only comment relates to the diagnosis of pertussis, which in this case was diagnosed based on serological testing. The US CDC considers culture the diagnostic gold standard for pertussis, although PCR and serology are accepted alternative diagnostic modalities. The Authors may want to expand on this.

We appreciate your polite peer review and suitable interpretation of the essence of our thesis. Thank you for explaining the gold standard based on CDC guidelines. In Japan, pertussis is part of the disease surveillance notification system. Based on the current infectious disease guidelines in 2018 regarding pertussis, if any of the following tests provide a definitive diagnosis, the attending physician should provide notification to the disease surveillance system.

① Detection of the pathogen
② Detection of one or more genes of the pathogen
③ Increase in antibody titer in serum analysis (in case of single serum, PT antibody titer >100 EU/mL)

Similarly, another guideline in Japan indicates that serological testing is a standard test. It is also described in the adult cough guidelines in Japan, where pertussis is confirmed as definite diagnosis when PT antibody titer >100 EU/mL is confirmed.

Based on the above text, the following sentences have been added to the revised manuscript.

"In the Japanese infectious disease guidelines, if sputum cultures or Loop-Mediated Isothermal Amplification have not been done or are negative, an increase in antibody titer in the serum has
been established as a diagnostic criterion for pertussis; in Japan, therefore, diagnosis by antibody titer is a standard evaluation method. Since a previous study indicated that cultures are unlikely to be positive in adults with more than 3 weeks of coughing, we suspect that a negative culture does not present a problem in the diagnosis of this case [13]."