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The concurrence of an enterocutaneous fistula and granulomatosis with polyangiitis: The role of immunosuppression as a bridge to definitive surgical treatment

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Enterocutaneous fistula as a manifestation of granulomatosis with polyangiitis: The role of immunosuppression as a bridge to definitive surgical treatment
Journal of Clinical and Translational Research

Dear Dr. Hajjar,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Sep 24, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author.

You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I read with interest your case report on a successfully managed enterocutaneous fistula. However, I am still intrigued by immunosuppressive therapy initiation as wound dehiscence from ECF is a concern on steroids and there is risk of sepsis as well. You have mentioned that "Culture of the abdominal subcutaneous abscess revealed the expected presence of Enterococcus sp. and multiple species of Candida". This goes in favor of infectious etiology quite evidently. However, lung nodules were concerning and appropriately the patient was bronchoscoped. Moreover, there needs to be an elaboration on the false positivity of ANCAs in sepsis in the discussion. Please review Dr. Edgar's paper.
Edgar JD. The clinical utility of ANCA positivity. Annals of the rheumatic diseases. 1996 Aug;55(8):494.

The evidence in favor of pulmonary ANCA associated vasculitis is the presence of necrotizing small vessel vasculitis on the transthoracic biopsy. It seems to be an active disease process in the presence of nasal crusting and epistaxis. The discussion on the novelty of association and aspects of clinical management have highlighted critical issues of managing the two diseases with divergent treatment trajectories.The case description included pertinent details of the case although more demographic information may have been added, particularly occupation because of the lung findings which ensued and whether or not he smoked. As the clinical course mentioned surgical repair of the fistula followed by cholecystectomy and repair of leaking wound, the timings and dose of antimicrobial and immunosuppressive therapy with the therapeutic considerations at that point necessitate more elaboration. The decline in the fistula output could also be attributed to prolonged antibiotics course that this patient must have received. In the abstract, key words incorporating MeSH are missing and should be included. Overall, I feel that it should be reported as a concurrence of enterocutaeous fistula in a patient with pulmonary C-ANCA vasculitis.

Reviewer #2: in this case report, the authors provide information about a known case of GPA which presented with enterocutaneous fistula(ECF), However, this report suffering from some potential limitations such as below;

1-The first principle in the management of ECF depends on the daily output of fistula (low output vs high out put), in this case, the authors didn't explain more about it,since the control of these two types of fistula are different from each other
2-No clinical or laboratory data has been provided about the patient's sepsis status, although in this report has repeatedly stated that the patient was in sepsis situation.
3-as the main objection to this report, as the authors themselves have pointed out, a large

percentage of ECF will close and manage spontaneously, and there is no definitive correlation between attributing fistula closure to immunosuppressive drugs.Many other interfering factors are involved in fistula handling.

Reviewer #3: I think this is a very interesting case, and presentation, but there are a few comments that I have regarding the article that I think would make it a little more clear/complete.

1. I think that there are some grammatical issues in this article. It may be worth while to have someone else review the article to edit some of the grammar
2. Was there any follow up to the lung nodules noticed before the steroid therapy? Did they also shrink?
3. It would be nice to see more about the pathophysiology of GPA, and age onset. Is it common to see this first appear in a 60-something male?
4. Why did the fistula develop there and why was it thought to be from GPA vs some sort of failure from mesh - why would it happen at site of mesh vs anywhere else? Any chance the ECF was a coincidence since there was no sign of vasculitis at the site, or could he for some reason have had chronic inflammation or rejection of the mesh which prompted the formation of the fistula
5. Was there suspicion for an autoimmune disease (ie Crohn's) that prompted the ANCA testing. Why was this autoimmune testing ordered in the first place?
6. Was there any kidney involvement? Crescentic necrotizing glomerulonephritis? There were only 2 of the 3 typical presentations that were seen in this patient (GPA Triad)
7. Was the patient actually septic? How so, what were the vitals (SIRS criteria?), values that indicated that (WBC elevation, lactic acid?). Not all fistulas indicate sepsis, and if it's an abscess, not all lead to sepsis either since it is walled off.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

We thank the reviewers for taking the time to review the manuscript and for outlining the improvements that will enhance the quality and clarity of the work.

Please find below a detailed response to each one of the issues raised by the reviewers.

Reviewer 1

I read with interest your case report on a successfully managed enterocutaneous fistula. However, I am still intrigued by immunosuppressive therapy initiation as wound dehiscence from ECF is a concern on steroids and there is risk of sepsis as well. You have mentioned that "Culture of the abdominal subcutaneous abscess revealed the expected presence of Enterococcus sp. and multiple species of Candida". This goes in favor of infectious etiology

quite evidently. However, lung nodules were concerning and appropriately the patient was bronchoscoped. Moreover, there needs to be an elaboration on the false positivity of ANCAs in sepsis in the discussion. Please review Dr. Edgar's paper. Edgar JD. The clinical utility of ANCA positivity. Annals of the rheumatic diseases. 1996 Aug;55(8):494.

We thank the reviewer for the relevant comments. As suggested, the potential false positivity of ANCAs in sepsis and the need for additional investigations to confirm the diagnosis were added to the discussion. The suggested reference was reviewed and cited as well.

The evidence in favor of pulmonary ANCA associated vasculitis is the presence of necrotizing small vessel vasculitis on the transthoracic biopsy. It seems to be an active disease process in the presence of nasal crusting and epistaxis. The discussion on the novelty of association and aspects of clinical management have highlighted critical issues of managing the two diseases with divergent treatment trajectories. The case description included pertinent details of the case although more demographic information may have been added, particularly occupation because of the lung findings which ensued and whether or not he smoked. As the clinical course mentioned surgical repair of the fistula followed by cholecystectomy and repair of leaking wound, the timings and dose of antimicrobial and immunosuppressive therapy with the therapeutic considerations at that point necessitate more elaboration. The decline in the fistula output could also be attributed to prolonged antibiotics course that this patient must have received. In the abstract, key words incorporating MeSH are missing and should be included. Overall, I feel that it should be reported as a concurrence of enterocutaneous fistula in a patient with pulmonary C-ANCA vasculitis.

As suggested by the reviewer, demographic data has been added to the case presentation, namely daily activities and the risk of lung infections or inhalation injuries, and smoking history. The details regarding the antimicrobial and immunosuppressive medication, and the concomitant changes in blood parameters and fistula output were also added for clarity. Keywords were added to the manuscript as suggested.

Furthermore, the title was modified to nuance the interpretation of this case. Despite the improvement in the fistula's output and patient's overall health when immunosuppression was initiated, the enterocutaneous fistula could not attributed beyond all doubt to the auto-immune process, and therefore, the title, and the overall message of the manuscript, were modified accordingly.

Reviewer 2

In this case report, the authors provide information about a known case of GPA which presented with enterocutaneous fistula (ECF), However, this report suffering from some potential limitations such as below;

1-The first principle in the management of ECF depends on the daily output of fistula (low output vs high output), in this case, the authors didn't explain more about it, since the control of these two types of fistula are different from each other.

We thank the author for the comment. The output was specified, as well as its changes in response to treatment.

2-No clinical or laboratory data has been provided about the patient's sepsis status, although in this report has repeatedly stated that the patient was in sepsis situation.

As suggested by the author, several clinical and blood parameters were detailed to describe the infectious status of the patient.

3- As the main objection to this report, as the authors themselves have pointed out, a large percentage of ECF will close and manage spontaneously, and there is no definitive correlation between attributing fistula closure to immunosuppressive drugs. Many other interfering factors are involved in fistula handling.

We thank the author for this relevant comment. We have clarified in the manuscript that the improvement in the fistula's output occurred after the initiation of immunosuppressive medication, while no changes occurred in antibiotic treatment. Nonetheless, we have modified several elements of the manuscript to nuance the main message, and to outline that despite the clinical improvement of the fistula after the initiation of immunosuppressive treatment, its etiology could not be absolutely attributed to the GPA, and it may be very well a concomitant infectious process. Therefore, the concurrence of the ECF with an auto-immune disease and the complexity of its management were highlighted, and the main message of the manuscript was oriented in that sense.

Reviewer 3

I think this is a very interesting case, and presentation, but there are a few comments that I have regarding the article that I think would make it a little more clear/complete.

1. I think that there are some grammatical issues in this article. It may be worthwhile to have someone else review the article to edit some of the grammar.

We thank the reviewer for this comment. The article was proof-read as suggested.

2. Was there any follow-up to the lung nodules noticed before the steroid therapy? Did they also shrink?

There was a significant improvement in the size of the pulmonary lesions during the weeks following the initiation of the immunosuppressive treatment. This information was mentioned in the manuscript as suggested.

3. It would be nice to see more about the pathophysiology of GPA, and age onset. Is it common to see this first appear in a 60-something male?

These details were added to the manuscript as suggested by the reviewer. Infectious processes, in addition to genetic predisposition and other environmental factors, may be potential etiological factors in the pathophysiology of GPA. This information was therefore added to complement the description of the relation between the fistula and the concomitant auto-immune process.

4. Why did the fistula develop there and why was it thought to be from GPA vs some sort of failure from mesh - why would it happen at site of mesh vs anywhere else? Any chance the ECF was a coincidence since there was no sign of vasculitis at the site or could he for some reason have had chronic inflammation or rejection of the mesh which prompted the formation of the fistula.

We thank the author for this highly relevant comment. The fistula could be potentially a cutaneous manifestation of GPA, and its improvement after the initiation of immunosuppressive therapy may suggest that it harbors an auto-immune process. However, this possibility cannot be confirmed beyond a reasonable doubt. The complexity of this presentation and challenges in its management were highlighted in the manuscript and detailed for more clarity.

5. Was there suspicion for an autoimmune disease (ie Crohn's) that prompted the ANCA testing. Why was this autoimmune testing ordered in the first place?

The patient did not present any gastrointestinal signs or imaging findings suggesting an inflammatory bowel disease. The complexity of the clinical presentation, and the inability to diagnose a neoplastic or an infectious process warranted an immunological investigation. This information was detailed as suggested for clarity.

6. Was there any kidney involvement? Crescentic necrotizing glomerulonephritis? There were only 2 of the 3 typical presentations that were seen in this patient (GPA Triad).

There seemed to be no kidney involvement in the case of our patient since the renal function was normal, and no formal kidney biopsies were performed to prevent complications.

7. Was the patient actually septic? How so, what were the vitals (SIRS criteria?), values that indicated that (WBC elevation, lactic acid?). Not all fistulas indicate sepsis, and if it's an abscess, not all lead to sepsis either since it is walled off.

We thank the author for this relevant comment. We added several parameters to the case presentation to support the septic process.

2nd Editorial decision
29-Sep-2021

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: