Peer Review File

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Reviewer A

Comment: This patient should have had a core needle biopsy followed by incision and drainage of the fluid collections at initial presentation.
This would have resulted in no delay in diagnosis of IGM.
It also would have led to resolution of the process much sooner than repeated aspirations and use of unnecessary treatments.
Reply: Thank you for your comment and I agree completely. This case highlights exactly the point you have made and shows that IGM is often misdiagnosed initially leading to delayed treatment. This treatment algorithm aims to raise awareness to IGM and help clinicians make a prompt diagnosis and avoid unnecessary investigations/treatments.
Changes: No specific changes were made but this point has been highlighted throughout the article and in the suggested treatment algorithm.

Reviewer B

Interesting case.
Comment: Would use "treatment algorithm" or "approach" instead of "pathway" line 13 and throughout the text/figures.
Reply: “Pathway” has been changed to “treatment algorithm” or “approach” throughout text and figures.
Changes: All changes throughout text, including title of the manuscript.

Comment: Line 53- "microscopy sample had no growth"- do you mean tissue culture? please clarify
Reply: Pus microscopy and culture had no growth of organisms
Changes: We have modified this in line 54 & 55.

Comment: Line 59- "grew sensitivities" - do you mean grew bacteria?
Reply: We mean grew bacteria with sensitivities to specific antibiotics.
Changes: We have modified this in line 60 & 61

Comment: Line 112- "four monthly"- do you mean once every 4 months? or 4 times a month?
Reply: We mean once every 4 months.
Changes: This had been modified in line 118 & 119

Comment: Can you discuss a bit more why allopurinol was used with azathioprine and not azathioprine alone in this patient and also specify the dose of the medications used? In inflammatory rheumatological diseases we avoid combination azathioprine with allopurinol due to risk of bone marrow suppression, though combination has been used in inflammatory bowel disease,

however this patient does not have IBD. also, is there data that azathioprine+allopurinol is safer than azathioprine alone in pregnancy?
Reply: Noted
Changes: Explanation of the use of a reduced dose of azathioprine with allopurinol cover is given in the Discussion paragraph 8

Reviewer C

This is an interesting case report and presents a management strategy for management of IGM in patients who wish further pregnancy.
A few general issues first:
Comment: Although there is mention of exclusion of infection, there should be more discussion on evaluation of underlying systemic inflammatory disease or immunodeficiency including consideration of CVID, RA, ANCA-vasculitis, SLE, sarcoid etc. This should be explored in the discussion and also the case report with investigation results mentioned
Reply: Noted
Changes: Modified in table 2

Comment: There is no mention of the role of corynebacterium kroppenstedtii which is a bacterium associated with IGM for which targeted therapy with prolonged doxycycline is effective. This should be mentioned in the discussion as well as case report. Was this looked for on specific cultures?
Reply: I have added this point to the introduction. The Corynebacterium species was not present on the cultures but from what I noted it was not specifically tested for in this case. Doxycycline was therefore not one of the antibiotics used.
Changes: Modified in Line 30 & 31. Further discussed in the Discussion paragraph 4

Comment: The combination of azathioprine and allopurinol is dangerous due to the effect of allopurinol on azathioprine metabolism. Simply saying 'low dose aza' is not enough - the exact dose in mg and relative to patient weight in mg/kg must be stated together with the allopurinol dose.
Reply: 50mg Azathioprine and 100mg Allopurinol was used.
Changes: Azathioprine and allopurinol doses has been included in lines 102&103 and then throughout the rest of the manuscript including Appendix 1.
Explanation of the use of a reduced dose of azathioprine with allopurinol cover is given in the Discussion paragraph 8

Comment: Was measurement of TGN metabolites undertaken prior to introduction of azathioprine?
Reply: The patient had subtherapeutic 6-TGN levels without any hepatotoxicity which therefore made her eligible to started on allopurinol 100mg (low dose)
Changes: Included in line 101 & 102.

Comment: What was the advantage of adding in the second drug in pregnancy which places the fetus at risk rather than just using a lower mg/kg dose of azathioprine?
Reply: Careful monitoring of metabolites and FBC throughout the pregnancy allowed allopurinol and azathioprine to be continued. This resulted in no harm to the fetus and the birth of a healthy baby.
Changes: No specific changes made in manuscript.

Specific comments:
Comment: Generic names of drugs do not require capitalization
Reply: Noted
Changes: Modified throughout text.

Comment: line 6 - should be more definitive ie with a known association with lactation etc rather than 'thought to have an association'
Reply: Noted
Changes: Modified in text on line 6

Comment: line 24 - same comment as for line 6
Reply: Noted
Changes: Modified on line 24

Comment: line 29 - exclude systemic inflammatory conditions also
Reply: Noted
Changes: modified in line 29

Comment: line 30 - should refer to C kroppenstedtii and its significance
Reply: noted
Changes: Modified in line 30&31. Further explained in the Discussion paragraph 4

Comment: line 49 and 53 - specify which antibiotics
Reply: Flucloxacillin and co-amoxiclav
Changes: Modified on line 52.

Comment: line 59 ' grew sensitivities' does not make sense
Reply: pus aspirations for microscopy and culture grew Staphylococcus aureus with sensitivity to clindamycin.
Changes: Modified in line 61 & 62

Comment: line 77 - requires exclusion of other systemtic inflammatory and granulomatous diseases prior to diagnosis
Reply: Noted
Changes: Modified in line 84 & 85. Further modified in Discussion Paragraph 5

and Table 2.

Comment: line 89 - it is unusual to include gastroenterology as co-managing specialty rather than immunology or rheumatology who have experience with azathioprine as well as the more commonly associated systemic diseases
Reply: Specialist teams with experience using azathioprine can be helpful in managing cases of IGM. This includes rheumatology, gastroenterology or immunology.
Changes: Discussion paragraph 9

Comment: line 94 - how much prednisone? for how long? doses of all drugs needed
Reply: 30mg prednisolone once daily for 4 weeks followed by a reducing regime of 5mg each week.
Changes: Modified in “Case” Paragraph 3 lines 87-95

Comment: table 1 - consider adding quanitferon gold and strongyloides serology prior to azathioprine
Reply: Noted
Changes: Modified in table 1

Comment: line 106 - state whether the fetus was a healthy infant
Reply: She had an uncomplicated labour and delivered a healthy baby.
Changes: Modified in line 119

Comment: figure 3 - could do with less time points
Reply: Noted
Changes: We have decided not to remove any time points and this gives a clear clinical course

Comment: line 153-156 - mention cystic neutrophilic variant histologically – CNGM
Reply: Noted
Changes: Modified in Discussion paragraph 4

Comment: line 172 - low dose prednisone can be used in pregnancy
Reply: Yes it can but this patient was experiencing significant side effects of the drug (diarrhea, abdominal discomfort, weight gain) which is why it was discontinued.
Changes: Modified in line 89-90

Comment: table 2 - tuberculous mastitis is an infectious not autoimmune cause. Wegener's is misspelt. There are more extensive autoimmune diseases requiring consideration as listed above

Reply: Noted
Changes: Modified in Table 2

Comment: line 238 - specify prednisone dose
Reply: noted
Changes: All drug doses have been specified throughout the manuscript

Comment: figure 4- a little complicated. Prednisone in such doses requires pre-immunosuppression safety checks also (hep b,c etc)_ as well as PJP prophylaxis and bone protection. Weaning after 5mg may require dose reduction by 1mg/month
Reply: Noted
Changes: Modified Figure 4