Dear reviewers,

Thank you for the time and effort that went into reviewing our manuscript. We made some changes following your suggestions. Please find enclosed point to point responses to the issues that have been raised.

Reviewer's code: 03721184

1. The author indicated that "*The lack of response to corticoids and antihistaminic agents tips the balance towards a NAEB diagnosis - mesalazine discontinuation and the use of low-dose inhaled corticoids were in accordance with relevant clinical practice guidelines*" (line 12, page 9). I am wondering that since the curative effect of corticoids on NAEB is poor, then why did you choose low-dose inhaled corticoids in the subsequent treatment?

Response

The decision to use inhaled corticoids was based on ACCP Evidence-Based Clinical Practice Guidelines published in 2006 in Chest – inhaled corticoids and sensitizer avoidance are both recommended. Since mesalazine involvement was initially only suspected it seemed prudent to continue inhaled corticoids despite apparent lack of efficacy.

2. The diagnosis of ulcerative colitis was established only based on the medical history. It is recommended to supply some colonoscopy images to strengthen the work.

Response

Ulcerative colitis diagnosis was established on the basis of various medical reports and discharge papers. Colonoscopy images were not readily available as the gastroenterology department is not part of our medical setting. Pathology reports were available and were strongly suggestive of ulcerative colitis flareup.

3. Mesalazine serves as a standard medication in the treatment and remission maintenance of ulcerative colitis. As for this patient, it needs to be stated what medication was used in the further treatment.

Response

There were no serious digestive complaints during the six months follow up period; patient received no medication and was managed on dietary advice only.

Text was amended.

Reviewer's code: 03211772

1.The patient was previously diagnosed with UC and periodically treated with mesalazine, but there were no respiratory symptoms when using mesalazine before. Why did NAEB occur this time?

Response

We ruled out potential confounders such as excipients or different formulations. We do not have a clear explanation but late onset mesalazine adverse effects have been cited before – references 30 and 31 are relevant describing somewhat similar cases where adverse effects developed after 10 and 8 years respectively.

2.When the patient developed NAEB, whether she used drugs other than mesalazine, all drugs should be listed and checked one by one.

Response

Mesalazine was apparently the only documented drug the patient used prior to respiratory symptoms developed; apart from ulcerative colitis she was otherwise healthy.

3.What are the indications for the use of antibiotics when both chest radiographs and sputum cultures were negative?

Response

Antibiotics usage is mentioned as a history element – two courses one of amoxicillin clavulanate and clarithromycin were prescribed by her general practitioner – probably suspecting infectious bronchitis. Text was amended for clarity.

4.Antibiotics, antihistamine, inhaled beta 2 mimetic and corticoid were used in the early treatment of NAEB. Please indicate the time of use of these drugs. It is necessary to rule out the effect of previous medication on the treatment after discontinuation of mesalazine.

Response

Antibiotics and antihistamines were administered after respiratory symptomatology developed and apparently had no effect – that was the reason the patient was referred to our service. Text was amended.

Kind regards,

Andrei Tudor Cernomaz