Author's response to reviews

Title: Diffuse duodenal nodular lymphoid hyperplasia: A large cohort of patients etiologically related to helicobacter pylori infection.

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Version: 2 Date: 29 January 2011

Author's response to reviews:

Editor BMC Gastroenterology,

Dear Sir,

Kindly find the enclosed revised document along with figures and tables. All the queries raised by the editors namely competing interests, acknowledgments, source of funding and authors contributions have been included in the revised document at appropriate place. Point to point answer of the queries raised by the reviewer 1 and 2 have been answered in the point to point document. The relevant changes in the revised document have been highlighted in red. We have had some concerns about questions raised by reviewer 2. The basis of our concern was lack of information of the reviewer about the protocol for diagnosis of H. Pylori infection and for H. pylori eradication. We have addressed them in our answer sheet appropriately and I hope this is taken in the proper perspective.

The revised manuscript has been read by all the authors.

Regards.

(Prof. M. S. Khuroo)

Dated Jan 29, 2011.

Reviewer's report

Title: Diffuse duodenal nodular lymphoid hyperplasia: A large cohort of patients etiologically related to helicobacter pylori infection.

Point to point answer to reviewer 1

Major Compulsory Revisions

None
Minor Essential Revisions

Q1: Ascaris lumbricoides was reported in 11 patients. Did these patients receive any treatment for this parasite?

Ans: Yes, all patients with Ascaris lumbricoides infection received anthelmintic therapy namely mebendazole 100 mg twice daily per oral for 3 days. This has been included in the text (Results para 2 line 18)

Q2. All patients (40 patients) with isolated diffuse duodenal nodular hyperplasia received H.pylori eradication therapy. The H.pylori status of these patients before therapy was not mentioned. Were they all H.pylori positive?

Ans: Helicobacter status of 40 patients with isolated diffuse duodenal nodular hyperplasia is mentioned in Results section para 3 line 10-12 as follows: < RUT was positive in all patients and H. pylori were seen in gastric biopsies in all patients. Density of H. pylori was moderate in 6 patients and heavy in 34 patients.>

Q3. Iron lack anemia is used as a term throughout the text. It will be better to use the term iron deficiency anemia.

Ans: We have changed the term as desired. See Results para 2.

Q4. The time period during which the study was carried out should be stated in the abstract section. From March 2005… is not enough.

Ans: Result section para one line 1 reads: <From March 2005 till February 2010, 44 patients with NLH of gastrointestinal tract were diagnosed.> The same statement has been included in Material and Methods study protocol line one: <From March 2005 till February 2010, we prospectively followed all patients with diffuse duodenal nodular lymphoid hyperplasia (DDNLH).> This has also been included in the abstract section.

Q5. In the last paragraph of the Results section, MAL was written instead of MALT lymphoma. It should be corrected.

Ans: Done as desired.

Q6. In the 4th paragraph of the Discussion section, It can be better to change the sentence “Chronic corpus atrophic gastritis with intestinal metaplasia caused by H.pylori infection is an initiating event in most cases of intestinal type
adenocarcinomas stomach” as “Chronic corpus atrophic gastritis with intestinal
metaplasia caused by H.pylori infection is an initiating event in most cases of
intestinal type gastric adenocarcinomas”.
Ans: Done as desired.

Q7. In table 1, some results are given in greater punto than others. For example
mean age of patients written in greater punto while the mean scores or follow-up
months of the patients were not. The number of Grade 1 nodular disease patients
(which is 4) was also given in larger punto. The punto of the variables in table 1
should be corrected.
Ans: Changed.

Q8) In the H.pylori eradication part of the methods section amoxicillin was
miswritten as amoxillin.
Ans: done as desired.

Q9. Discretionary Revisions
The prevalence of nodular lymphoid hyperplasia in the world and the prevalence
of nodular lymphoid hyperplasia, H.pylori infection and intestinal lymphoma in
the country where the study was conducted can be given within the text.
Ans: The epidemiology of either has been discussed in relevant sections.

Q10. Quality of written English: Needs some language corrections before being
Published
Ans: Gone over the text again and made necessary language changes.

Point to point answer to reviewer 2 questions

Title: Diffuse duodenal nodular lymphoid hyperplasia: A large cohort of patients
etiologically related to Helicobacter pylori infection.

Q1. Back ground and Introduction –
The authors state – “There are no published reports of association of nodular

Ans: The 2 references have been included. First reference deals with a case of gastric nodular hyperplasia causing gastric outlet obstruction and has been included in “Introduction” (Reference 23) The second reference is related to nodular gastritis related to H. pylori nad has been included in “Discussion” (Reference 38).

Q2. Material and methods –

Which classification was used to classify gastritis and duodenitis on histology?

Please give method of doing RUT.

Ans: Both these have been addressed in Material and methods. We have used modified Sydney classification for grading of gastritis and H pylori infection. Relevant references are included. (For RUT, 2 forceps punch biopsies were taken from gastric incisura and embedded in agar gel urea-rich medium (HP test™, Allied Marketing Corporation, Kolkata, India) and read as per manufacturer’s instructions. Multiple gastric biopsies (two from antrum; two from body and additional specimens from any visible endoscopic visible lesions, if needed) were taken and stained with Hematoxylin & Eosin to type and grade gastritis; Alcian blue to detect intestinal metaplasia and Giemsa stain for H. pylori detection and density.25,26)

Q3. It appears to be quite unusual that despite 100% biopsies showing presence of H. pylori (heavy in 34 patients), only 2 patients had MALToma and rest others had no evidence of lymphoid hyperplasia in stomach but all the cases had nodules in the duodenum.

Ans: The reviewer is mixing up the entity of low grade MALT lymphoma and Mucosa Associated lymphoid tissue. Low grade MALT lymphoma is a malignant disease of stomach related to H. pylori infection and potentially reversible disease after H. pylori eradication as seen in 2 of our patients. Low grade MALT lymphoma can evolve in to high grade gastric lymphoma with local and distant spread. Mucosa Associated Lymphoid Tissue (MALT) is a very common
association of H. pylori gastritis. In fact most of patients with H. pylori gastritis (in our study as well) have lymphoid follicles in the gastric mucosa and this is a hallmark of gastritis caused by H. pylori.

Q4. How many duodenal biopsies had evidence of gastric metaplasia and evidence of H. pylori?

Ans: This has been dealt with in the Results section. In fact duodenal mucosal changes have been dealt with in detail in this section. H. pylori was rarely seen in the section of duodenal biopsies and was very sparse.

Q5. How the H. pylori present in the stomach led to nodular lymphoid hyperplasia in the duodenum without producing any change in the gastric mucosa – please explain

Ans: H. pylori can cause lot of extragastric manifestations such as Idiopathic thrombocytopenic purpura (ITP), iron deficiency anemia etc. The reviewers comments that there were no changes in the stomach is incorrect. Refer to endoscopic and histologic findings of gastric mucosa in results section which reads as follows < Examination of stomach showed no endoscopic abnormality in 8 patients; linear erythematous antral gastritis in 20 patients; exudative fundic gastritis in 6 patients and atrophic gastritis in 4 patients. Two patients had diffuse ulcerative nodular lesions limited to the antrum. None of the patient had pyloric or duodenal ulcer. RUT was positive in all patients and H. pylori were seen in gastric biopsies in all patients. Density of H. pylori was moderate in 6 patients and heavy in 34 patients. Histology of gastric biopsies revealed chronic superficial gastritis in 24 patients, and chronic atrophic gastritis with intestinal metaplasia in 14 patients. Two patients with diffuse ulcerative nodular disease of antrum showed histologic features of low grade MALT lymphoma>

Q6. Diagnosis of H. pylori was made by RUT and histology but after treatment only Breath test was used

Ans: It seems that reviewer is not aware of diagnostic protocol of H. pylori infection. Prior to antibiotic therapy H. pylori infection uniformly affects antrum (not patchy) and grows up to body, and fundus. In such a situation endoscopic forceps biopsies are very useful for diagnosis of H. pylori (histology and RUT). Both tests need to be done for diagnosis and we have meticulously followed the protocol for taking correct site and number of biopsies. However, after antibiotic therapy H. pylori infection persists (in resistant cases) in small pockets and is scattered as small islands of infection in gastric epithelium. Thus forceps biopsies cannot be used to diagnose H. pylori eradication. In such a situation we need a
global test for H. pylori eradication and these are either 14C-UBT or fecal H. pylori antigen. In this study we have employed 14C-UBT to check for H. pylori eradication.

Q7. How can you compare the three different methods for showing eradication.

A: A pre and post Urea breath test should have been done to show the eradication.

Ans: It seems that reviewer is not aware of diagnostic protocol of H. pylori infection. Prior to antibiotic therapy H. pylori infection affects antrum and grows up to body, and fundus. In such a situation endoscopic forceps biopsies are very useful for diagnosis of H. pylori (histology and RUT). Both tests need to be done for diagnosis and we have meticulously followed the protocol for taking correct site and number of biopsies. However, after antibiotic therapy H. pylori infection persists (in resistant cases) in small pockets and islands in gastric epithelium. Thus forceps biopsies cannot be used to diagnose H. pylori eradication. In such a situation we need a global test for H. pylori eradication and these are either 14C-UBT or fecal H. pylori antigen. In this study we have employed 14C-UBT to check for H. pylori eradication. The reviewers contention of comparing diagnostic tests for H.pylori infection and eradication is grossly misconceived as she needs to review proper protocol for diagnosis of H.pylori infection and for checking eradication of H pylori infection.

Q8. Discussion –

Authors try to state that the nodules in the duodenum were probably due to immune stimulation secondary to heavy H.pylori infection. If it was so, then how the stomach, small intestine and colon were spared

Ans: Pathogenesis of H. pylori induced nodular lymphoid hyperplasia of the duodenum need further studies. In fact selective involvement of the duodenum is characteristic and pathognomonic of this entity. This can only be answered by doing studies similar to those done on H. pylori induced ITP. This we are convinced will define the cause of selective involvement of the duodenum.

Q9. References – Most of the references are quite old. some new references should be added.

Ans: We have added 2 references of the reviewer in the list.

Q10. Photographs –

Histology photograph is not good. Getting a single lymphoid follicle is not unusual. A scanner or low magnification (10x) showing multiple large follicles
should be given

Ans: Reviewer is confusing this entity with nodular gastritis induced by H. pylori. In H. pylori induced gastritis numerous lymphoid follicles are seen in the gastric mucosa in the low power view. However, in DDNLH we have striking nodular lesions of 2 to 5 mm size and endoscopic view of these lesions is the basis of this entity. Forceps biopsy with a size of 2 to 3 mm can pick up one nodule of same or larger size. Characteristic of these biopsies is the large lymphoid follicles which cause these characteristic elevated lesions. It is possible to see numerous nodular lymphoid lesions only in surgically resected specimens and we have not surgically resected any of these lesions. We are enclosing a low power view of the duodenal biopsy to address this issue. In the low power view of the duodenal biopsy (around 3 mm in size) only one lymphoid follicle can be seen, the cause of the elevated nodular lesion. I hope this point is clear.