Author’s response to reviews

Title: Hydroxyurea and colonic ulcers: a case report

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Author’s response to reviews: see over
Dear Editor,

Thank you very much for your valuable comments.

Followings are the responses:-

To the 1st reviewer, Dr. KONSTANTINOS KATSANOS

1. Please use standard journal abbreviations, ie Ref 12
   - Done as suggested
2. Please discuss more extensively endoscopic differential diagnosis
   - Differential diagnosis of the endoscopic findings was done in line 80
3. Please discuss if any preventive measure could be taken in order to avoid colon or GI tract ulceration in your patient.
   - To the best of our knowledge, there is no preventive measure aside from drug discontinuation. Unawareness of this adverse event will unfortunately lead to a progressive disease as seen in this patient.

To the 2nd reviewer, Dr. LAJOS KISS

1. One month after initiation of hydroxyurea therapy in line with naproxen usage massive hematochezia begun and periodic epigastric pain with mucous diarrhea persisted. The author advice was avoidance of naproxen, but really discarding of this therapy are unofficially on the text.
   - Naproxen was discontinued after LGIB. Changed in line 74
2. After first colonoscopy findings the area of ulcers are thriven based on the second and third colonoscopy. These concerned parts of the bowel ancillary superior mesenteric artery and vein system, but CT angiography was not made for separation of thrombo-embolic disorders.
   - The patient’s symptoms were not those of ischemic bowels. As a support, there was no evidence of thrombosis in both macro- and microscopic findings.

3. According to authors after discontinuation of hydroxyurea therapy all GI symptoms disappeared in 2 months. The text not contains what was the gastric or bowel complain of the patient after surgery. The hydroxyurea induced stomach erosions or ulcers well known, so it may regrediated after discontinuation of
hydroxyurea therapy. However, the association between colon symptoms and therapy discontinuation is not affirmable.

- All epigastric pain and mucous diarrhea also disappeared as indicated in line 112.
- To our knowledge, hydroxyurea induced GI ulcer is extremely rare. There were only few reports of oral ulcers but not GI ulceration as mentioned in the references. The prescribing information of this drug has no mention of the ulcer. We also asked the pharmaceutical company for any reports of this effect and found none. The pharmacological basis of therapeutics text book (Goodman & Gillman, 11th edition) mentioned only rare stomatitis and common GI disturbance as the GI side effects, but not GI ulceration.

4. Histo-pathologic findings of oro-pharyngeal ulcers shows similarity with colon ulcers, but oro-pharyngeal deviation appeared one month later when colon ulcers was eliminated by surgery. In spite of similarity the common procession is not verifiable.

- We did not confirm the side effect by re-challenging hydroxyurea due to ethical issue. By circumstantial evidence, hydroxyurea is considered to be the culprit. According to the Naranjo ADR probability scale, our patient’s score is 5, which is probable.

5. Discontinuation of hydroxyurea therapy was after colon surgery procedure, so it may not known colon ulcers would have disappeared or not.

- We did not repeat endoscopy because there was no GI symptom.

Thank you very much for your kind consideration.

Yours Sincerely,

Sansanee Wongwaisayawan, MD