DEAR PROFESSORS:

THANKS FOR YOUR EFFORT IN REVIEWING OUR PAPER.

BELOW IS THE REPLY TO YOUR VALUABLE COMMENTS.

<table>
<tr><td colspan="2">Reviewer #1: Code 00506472
It is a well written paper regarding a case report of acute leukemia in a 15-year-old girl with B-thalassemia-intermedia.</td></tr>
<tr><td>1. Although sporadic cases of malignancies in B-thalassemia-intermedia were noted, no evidence for increased rate of malignancies in B-thalassemia-intermedia patients was provided. Is there any data on this?</td><td>Thanks for your valuable comment.
We totally agree with the that sporadic cases are detected.
However, there are some available evidence discussed thoroughly in the report published in the Pediatric blood and cancer Journal by Karimi and his colleagues in 2009, who discussed the hypothesis that malignancies are more common in patients with thalassemia because of predisposing factors such as iron overload resulting in iron-induced oxidative damage, high levels of oxygen free radical, and high cellular turnover (especially in thalassemia intermedia).
In their study, they found a higher proportion of cancer in patients with thalassemia intermedia</td></tr>
</table>

	(BTI) than thalassemia major (BTM). They stated that this may result from the fact that bone marrow in BTM is suppressed due to regular transfusions, in contrast to the high bone marrow cell turnover in patients with BTI. This in turn can lead to a higher rate of DNA repair faults and mutations and therefore a higher rate of hematologic malignancies. N.B: We added more clarification on this point in the manuscript discussion. Karimi et al 2009 is reference number 6 in the article references list.
2. Hydroxyurea was administered for 7 years in the patient. There are data on increased rates of malignancies and potential mechanism is described in the literature. Please provide relative data from the literature in the Discussion and add hydroxyurea as a potential factor for	***Thanks for the comment.*** We provided the data about the role of hydroxyurea in the discussion and we added the related reference to the references list. N.B: Added data were highlighted in yellow.

malignancy in B-thalassemia-intermedia patients.	
Reviewer #2: Code 03285337 The case presentation is nice, and the case itself is very important. Even in TI, the physicians should think about the occurrence of malignancies.	
However, the hypothesis of iron overload is too speculative for me. In this mean, the adopted therapy could be the trigger of leukemia, which might be big issue. To hypothesize such kind of hypothesis, more strong evidence or multiple patients experience are crucial to rule out the possibility of coincidence. I recommend the authors not to discuss about hypothesis but to describe more previous similar report likewise literature reviews....	***Thanks for the comment.*** ***We understand totally your valuable point of view.*** We responded to that by removing the term hypothesis and instead as suggested with did literature review on the possible factors underlying the predisposition to malignancies especially hematological malignancies in BTI. In the discussion we changed our way of handling this issue highlighting that this might be a simple coincidence, but a multifactorial possibility may be underlying and then we discussed those factors one by one based on literature review. All the changes were done using track changes in the revised version.

	We used reference 6 and we added two new references; 15 and 16. Review of reported cases was summarized in table 1. N.B: A paragraph about the possible role of hydroxyurea in predisposing to malignancies which was highlighted yellow in the revised version as requested by reviewer 00506472.

THE LIST OF ISSUES RAISED BY THE EDITOR WAS DONE USING TRACK CHANGES.