Peer Review File

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Reviewer Comments

The authors present an interesting report of a patient who presented with T-ALL and subsequently developed AML and was found to have heterozygous mutations in FANCC and AKAP9 genes. Genomic alterations in Fanconi's anemia are rapidly evolving with advances in genetics and NGS, and this case report describes a novel mutation.

Comments - General:

The manuscript has many grammatical errors, and many sentences are difficult to follow. The manuscript will benefit tremendously from English editing, formatting, and grammar corrections. I would request the authors to review each sentence and make appropriate changes.

Some specific examples from the abstract: "Fanconi anemia (FA) is the most common inherited bone marrow failure disorder which is predisposition to neoplasm", can be changed to "Fanconi anemia (FA) is the most common inherited bone marrow failure disorder, with a predisposition to neoplasia".

"Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are remarkable in FA related hematologic malignancies, limited cases of FA with acute lymphoblastic leukemia (ALL) have been described." Can be changed to "While Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are the most common hematologic malignancies seen in patients with FA, cases of acute lymphoblastic leukemia (ALL) have also been described in the literature.

It will also be helpful to label figures with legends, and arrows/boxes to show the reader what each figure is alluding to.

Reply-1:

Thanks for your work, the grammar and words had been revised by AJE (academic journal edting) Scholar, we have modified our words and grammar as advised (see Page 1, line 10-13, Page 2, line 37-40, we had highlight it with red)".

Comments - Introduction:

Lines 25 – 'Characterized by' instead of 'related to'

Reply-2

Thanks for your work, twe have modified our words as advised (see Page 2, line 35 and, we had highlight it with red)".

Lines 26-27– The sentence may not be accurate. Based on reference 2 that is quoted, the paper describes 16% of patients to develop a hematologic malignancy which is more common and 10% of patients developed a solid tumor. The use of the word secondary in the context of malignancy is confusing as 'secondary' is typically referred to a malignancy that developed due to treatment.

Reply-3

Thanks for your alert, we had revised the sentence (see Page 2, line 37, we had highlight it with red)

Line 30 – Does bilateral mutation mean compound heterozygous? Please review occurrence throughout the manuscript.

Reply-4

Thanks for your alert, indeed "compound heterozygous" is more acurate than "bilateral", we had revised it in the sentence (see Page 2, line 40, we had highlight it with red).

Line 32- Would verify the use of the term secondary malignancy in the manuscript.

Reply-5

Thanks a lot, the patient was diagnosed with T-ALL at onset, AML immunophenotype was presented at relapsed, we think "secondary malignancy" is reasonable, or could you give us better advice? thanks a lot.

Comments- Case Presentation

Lines 37-38: Would be helpful to know if the patient had any congenital abnormalities related to FA that were initially or subsequently identified in the patient. Similarly, if there was any history that would suggest of Fanconi anemia in the family?

Lines 41-45: It will be helpful to note markers that were positive that led to diagnosis of a T-ALL. And if there was any presence of myelodysplasia in the bone marrow evaluation or abnormal myeloid markers on flow cytometry at the initial presentation.

Line 47 – I am also curious why a whole skeleton Xray was done initially at the time of diagnosis. Were there clinical features of a congenital/bone abnormalities on presentation?

Reply-6

Thanks for your alert, we tried to investigate Symptoms, signs and lab findings in the patient and his family but failed. BM sample was obtained from the patient, BM biopsy and flow cytometry were done at diagnosis, but myelodysplasia or myeloid biomarkers were not found by our knowledges, we had revised in manuscript and motioned it (see Page 2, line 52-55, we had highlight it with red). We had been received several ALL patients with pathological fracture but whole skeleton X-ray was ignored at that periods, and we compensate for uncoved fracture, whole skeleton X-ray is regular exam for ALL paitnets from then on. But the patient had not feathers of congenital bone abnormalities.

Lines 47-51 – It will be helpful for the reader to know what chemotherapeutic agents were used. Also, patients with Fanconi's anemia tend to develop significant toxicities during treatment with conventional chemotherapy. How did the patient respond to the initial phases of chemotherapy? Did he get very sick during induction/consolidation? Did his therapy need to be changed during initial chemotherapy?

During the course – did any other bone marrow evaluations suggest myelodysplasia or presence of other clones? Did he have more cytopenia's than expected?

Reply-7

Thanks for your alert, the total protocol had been listed in reference-5 for limited length of the manuscript; you are correct, the patient presented with severe cytopenia, sepsis and fungi infection at course of induction, we had motioned it in manuscript (see Page 3, line 61-63, we had highlight it with red).

Comments – Discussion and conclusions:

This is an interesting case as lineage switching from lymphoid to myeloid is rare to begin with. What do the authors think about occurrence of AML- is it related to disease course, therapy related, combination? Was there any evidence of multiple clones at initial diagnosis of T-ALL?

The authors mention the role of AKAP9 gene, it will be helpful to discuss how it is thought to interact with the FANCC gene/mutation.

Reply-8

Thanks for your questions, we did not find evidences of multiple clones at initial diagnosis of T-ALL because of our limited ability, and we think that lineage switching was mainly related to underlying FA because chemotherapeutic agents the patient received included glucocorticoid, vincristine, daunorubicin, asparaginase, cytarabine,

methotrexate and mercaptopurine, treat related cancers were uncommon in these agents. AKAP9 gene was detected in the patient, the role in the patient was unclear, but the patient died of sepsis and we had not samples to explore its role, we had point it in article (see Page 5, line 127-131, we had highlight it with red).