Author's response to reviews

**Title:** Disseminated Fusariosis and Endogenous Fungal Endophthalmitis in Acute Lymphoblastic Leukemia following platelet transfusion possibly due to Transfusion-Related Immunomodulation

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**Author's response to reviews:** see over
To,

The Editor in-charge,
BMC Ophthalmology 18th June 2011

Dear Sir,

Point-by-Point response for MS: 9110988385348001 - Disseminated Fusariosis and Endogenous Fungal Endophthalmitis in Acute Lymphoblastic Leukemia following platelet transfusion possibly due to Transfusion-Related Immunomodulation

Reviewer’s report:
Major Revision
1. There still is no evidence from the report for TRIM
2. Please elaborate on how the hypothesis is generated.
Reviewer’s comment #1:
1. There still is no evidence from the report for TRIM

Response:

WE agree with the reviewer that it is no evidence from the report (absence of evidence) for TRIM.

However “absence of evidence is not evidence of absence”. The challenge in this case thus becomes a choice between lacks proper means of detection of TRIM (absence of evidence), and the non existence of TRIM (evidence of absence).

The confounding factors in this patient were the presence of immunosuppressive state, hematologic malignancy, bacterial sepsis and systemic antibiotics usage. In fact, TRIMs are frequently reported in debilitated patients with multiple systemic confounding factors. Even in credible studies of TRIM (to investigate between the association of allogenic transfusion and perioperative infection) by Carson et al,¹ Vamvakas et al² and Chang et al,³ after adequate adjustments made for confounding factors, the authors acknowledge that there still may be unrecognized residual confounders that could affect the results of their studies.
Reviewer’s comment #2:
2. Please elaborate on how the hypothesis is generated.

Response:
The thought of TRIM after platelet transfusion arose when the patient developed systemic fungal infection within 48 hours of platelet transfusion.

This hypothesis came when we ask ourselves the question: “Could platelet transfusion be somehow related to the systemic fusariosis of this patient?”

Possible hypotheses were:

1. Contamination of transfused platelet by fungal element.
   This was ruled out (evidence of absence) due to the stringent quality control of in the preparation of blood products (Discussion, paragraph 1), and negative culture of residual platelet concentrate transfused to the patient.

2. HLA incompatibility.
   This was ruled out (evidence of absence) because the patient was transfused with irradiated apheresis platelet. Treated platelets significantly reduced the development of lymphocytotoxic antibodies and alloimmune refractoriness to platelet transfusions. The patient’s platelet increased from 19 x 10^9/L to 110 x 10^9/L after platelet transfusion. The points against HLA incompatibility was outlined in Discussion, paragraph 2.

Changes made to manuscript, Case presentation, Paragraph 3, Last Line:
“After five days, the white cell count increased from 0.4 x 10^9/L to 7.1 x 10^9/L, while the platelet count was 110 x 10^9/L.”

3. Transfusion associated graft versus host disease (TAGVHD)
   This is ruled out (evidence of absence) because TAGVHD occurred 10 to 14 days after transfusion with multisystem organ failure.
4. Transfusion related immunomodulation (TRIM)

The supporting points for TRIM were outlined in Discussion, Paragraph 4 and 5. The article by Blumberg et al entitled: The platelet as an immune cell—CD40 ligand and transfusion immunomodulation, provides detail discussion of role of platelet-derived CD40L in transfusion-related acute lung injury (TRALI) and milder transfusion reactions such as fever and rigors. These effects come under the rubric of transfusion related immunomodulation (TRIM).^5

However, the evidence of TRIM was masked by the presence of multiple confounding factors (absence of evidence).

and lastly, in there presence of conclusive evidence of absence of TRIM

5. Superinfection in the presence of immunosuppressive state, hematologic malignancy, bacterial sepsis and systemic antibiotics usage.

Changes made to manuscript, Conclusion,Line 3-6:

TRIMs are usually reported in debilitated patients. The evidence of TRIM in this case was masked by the presence of multiple confounding factors (absence of evidence); but the absence of evidence is not evidence of absence.
Reference


WE sincerely thank both reviewers for their time and constructive input into our manuscript. WE hope BIOMED CENTRAL OPHTHALMOLOGY will accept our manuscript for publication.

With kind regards,

Tan Aik Kah,
Ku Chui Yong,
Ropilah Abdul Rahman