Author’s response to reviews

Title: Chronic disseminated candidiasis manifesting as hepatospelnic abscesses among patients with hematological malignancies

Authors:

Chien-Yuan Chen (chienyuanchen@ntu.edu.tw)
Aristine Cheng (arischeng@ntuh.gov.tw)
Feng-Ming Tien (b92401007@gmail.com)
Po-Chu Lee (pclee@ntuh.gov.tw)
Hwei-Fang Tien (hftien@ntu.edu.tw)
Wang-Huei Sheng (whsheng@ntu.edu.tw)
Yee-Chun Chen (yeechunchen@ntuh.gov.tw)

Version: 1 Date: 06 Oct 2018

Author’s response to reviews:

INFD-D-18-00434

Resolution of abscess and outcomes of chronic disseminated candidiasis among patients with hematological malignancies

Editor Comments:

I perfectly agree with the reviewer and before the manuscript can be reconsidered for publication, all six major issues pointed by the reviewer must be addressed.

In particular, due to the disproportionate numbers between possible and proven/probable cases, it is very important to know how many patients underwent CT or MR rather than ultrasounds.

As expected, septic shock was an independent factor associated with mortality (the only one in this study). Since this conclusion can be easily anticipated (the more sick is the patient the higher is the probability to die), it should be very interesting to reanalyze all the data after exclusion of those patients suffering from septic shock.

Reviewer Loredana saemati:
The article reports results of a retrospectively studied of hepatosplenic candida abscesses in hematologic patients in a historical period in which, in Taiwan, the fungal prophylaxis during neutropenia was not indicated. 61 out of more than 2000 patients were identified, of which 30% resolve at 3 months and >50% at six months. Septic shock was the only factor associated with death. The article is interesting even if some major points need to be reviewed:

1. about 74% of CDC diagnosis were possible that means suspicion on radiological findings. What are the more common radiological (TC) findings associated with CDC diagnosis? How many patients had TC findings not common? All patients underwent TC scan? How many underwent only to echography?

Reply: Definition of EORTC 2002 of Chronic disseminated candidiasis:

Small, peripheral, target like abscesses (bull’s-eye lesions) in liver and/or spleen demonstrated by CT, MRI, or ultrasound, as well as elevated serum alkaline phosphatase level; supporting microbiological criteria are not required for probable category.

According to the EORTC 2008 clinical criteria of disseminated candidemia: At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks: Small, target-like abscesses (bull’s-eye lesions) in liver or spleen; Progressive retinal exudates on ophthalmologic examination. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

We add the description in the text of method (Page 8, Line 8)” According to the EORTC 2008 clinical criteria of disseminated candidemia: At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks: Small, target-like abscesses (bull’s-eye lesions) in liver or spleen; Progressive retinal exudates on ophthalmologic examination. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD. In this study, we followed the criteria of EORTC 2008 [10] and defined biopsy proved cases as proven, both blood candidemia culture and image study were positive as probable, and only image study was positive as possible cases of CDC.”

We did not suspect these image findings in CT scan or ultrasound. In the 45 cases of possible CDC, 43 of 45 had CT scan study. Their typical findings were several small, target-like abscesses (bull’s-eye lesions) in liver or spleen. Only two cases were negative for CT finding, but both were positive in Ultrasound. Ultrasound also performed in 43 of 45 cases.

2. there are any data on beta-glucan study?

Reply: Beta-glucan is not performed at NTUH laboratory test.
3. At univariate analysis, CDC population was younger than no-CDC population, is a bias or you could explain this result?

Reply: Only 5 of 397 patients received allogeneic stem cell transplantation were more than 65 years (p<0.001). The chemotherapy is heterogeneous, however, young people received more intensive chemotherapy. We add the description in the discussion (Page16, Line 14). “Young people received more intensive chemotherapy and allogeneic transplantation, and they had more CDC than the elder patients.”

4. A higher number of patients with invasive fungal pulmonary infection had also CDC. The authors considered this data associated with a possible genetic defect in the fungal immune response. Is a patient selection bias possible? Could other factors as type of chemotherapy, clinical stage severity (advanced disease, recurrence) or other factors of increased risk influenced CDC in this group of patients?

Reply: To clearly focus on CDC, we decided to delete the description of invasive fungal lung (IFI) in this manuscript. We revised the IFI part in this manuscript. (Page11, Line13; Page16, Line 16; Table 1).

5. Again, at univariate analysis younger age, less than 65y, was positively associated with CDC. How the authors explain these data?

Reply: We add the description in the discussion (Page16, Line 14). Young people received more intensive chemotherapy and allogeneic transplantation. They had more risks of CDC than the elder patients.

6. Surprisingly neutropenia at CDC diagnosis was associated with resolution also this need a more profound explanation.

Reply: We revised and add in the part of discussion (Page 19, Line 4). Neutrophil reverse migration plays a role in wound repair and abscess resolution. de Oliveira, et al. (Nat Rev Immunol. 2016; 16: 378-91) described “More recent studies have demonstrated that neutrophils can leave sites of tissue damage in a process termed neutrophil reverse migration which describes the interstitial migration of neutrophils away from inflamed sites. Neutrophils that encounter the fungal cell wall component zymosan have decreased reverse migration, and it is tempting to speculate that neutrophils are less likely to reverse migrate away from sites of infection, at least in part to prevent the dissemination of intracellular pathogens.” Neutropenia at diagnosis of CDC recruited less neutrophil possibly contributed the earlier resolution of abscess.