Author's response to reviews

Title: A patient with hypereosinophilic syndrome manifested with acquired hemophilia and elevated IgG4: a case report

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Version: 4 Date: 9 December 2011

Author's response to reviews: see over
December 10, 2011

Professor Michael Kidd, AM

Executive Dean of the Faculty of Health Sciences, Flinders University, Australia

Editor-in-Chief, *Journal of Medical Case Reports*

Dear Professor,

We are pleased to re-submit our manuscript entitled, "A patient with hypereosinophilic syndrome manifested with acquired hemophilia and elevated IgG4: a case report."

Written informed consent was obtained from all patients and healthy control individuals. All authors (Y. Nagao, H. Yamanaka, and H. Harada) had access to the data and had a role in writing the manuscript. There was no conflict of interest for any author.

We appreciate your further consideration of our manuscript.

Sincerely,

Yoshiro Nagao, MD, MSc, PhD

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Reviewer's report
Title: A patient with hypereosinophilic syndrome manifested with acquired hemophilia and elevated IgG4: a case report
Version: 3 Date: 29 October 2011
Reviewer: Hao-Wei Teng
Which of the following following best describes what type of case report this is?: An unexpected association between diseases or symptoms
Has the case been reported coherently?: Yes
Is the case report authentic?: Yes
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: No
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: Yes
Does the case report have diagnostic value?: No
Will the case report make a difference to clinical practice?: No
Is the anonymity of the patient protected?: Yes
Comments to authors:
- General comments
The author made every effort to produce a acceptable draft. We did not have any more comment.
Quality of written English: Acceptable
Declaration of competing interests: I declare that I have no competing interests

Our reply 1> We greatly appreciate that this reviewer carefully read the revisions, many of which were suggested by this reviewer. We believe these revisions have improved the clarity of the manuscript.

Reviewer's report
Title: A patient with hypereosinophilic syndrome manifested with acquired hemophilia and elevated IgG4: a case report
Version: 3 Date: 21 October 2011
Reviewer: Shinsaku Imashuku
Which of the following following best describes what type of case report this is?: Presentations, diagnoses and/or management of new and emerging diseases
If other, please specify: The case must be discussed under correct diagnosis, not by misdiagnosis.

Has the case been reported coherently?: No

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: No

Is this case worth reporting?: No

Is the case report persuasive?: No

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: No

Is the anonymity of the patient protected?: Yes

Comments to authors:

The authors revised the manuscript; however, it sounds like they do not correctly grasp the underlying pathogenesis of this case. The authors must understand that hypereosinophilia is just one of the symptoms, and that this case is not L-HES. The entire manuscript is better re-written from the viewpoint of IgG4-related systemic disease, including re-evaluation/analysis of all cytokine data, apart from HES.

Our reply 2>

We would like to remind this reviewer of the following three points:

First, this patient is clearly a case of lymphocytic variant of hypereosinophilic syndrome (L-HES). However, this reviewer objected in his previous review by stating that L-HES should be accompanied by only a single aberrant lymphocyte phenotype (e.g., CD3-CD4+). As we stated in reply 13 in our previous response, this knowledge is not up-to-date: diverse phenotypes have been reported in L-HES (e.g., CD3+CD4-CD8-, CD4+CD7-, and CD16+CD56+) [1-6]. Furthermore, many cases of L-HES are not accompanied by any aberrant phenotype [7]. Therefore, the absence or specific phenotype of the aberrancy does not exclude L-HES. Instead, the detection of T-cell monoclonality in our patient strongly supports the diagnosis of L-HES [8]. If the Journal of Medical Case Reports is skeptical of our diagnosis, we ask that they invite comments from other reviewers, such as Roufosse F, Kilon AD, Weller PF, or Tefferi A [6, 8-10], who are renowned researchers of hypereosinophilic syndrome (HES). Please be reminded that we communicated with Tefferi A, to discuss the diagnosis of this patient before the initial submission. According to Tefferi, this patient was clearly a case
of L-HES. Please see page 4 lines 2 – 17, and Table 1.

Second, this reviewer claims that L-HES does not explain the pathogenesis of the presented eosinophilia, while IgG4-related disease (IgG4RD) would explain it. However, IgG4RD does not explain the “pathogenesis” in terms of why and how only IgG4+ plasma cells damage organs, as reported by a proponent of this disease entity [11]. On the other hand, the pathogenesis of L-HES is relatively straightforward: IL-5-producing T-cells proliferate monoclonally [4]; the over-produced IL-5 stimulates the production and survival of eosinophils [4]; and these eosinophils damage target organs [12]. Please see page 9 line 18 – page 10 line 4.

Third, and most importantly, this reviewer maintains that IgG4 and hypereosinophilic syndrome must be mutually exclusive. However, we cannot find any reason that these two diseases cannot overlap in a single patient. Instead, overlap of multiple diseases in a single patient is not uncommon in clinical practice. In addition, there is a strong possibility that monoclonally-proliferated T-cells generated a milieu of cytokines that was favorable for eosinophilis and IgG4-producing plasma cells, both of which require Th2 cytokines for their expansion. Therefore, the reported patient is a very rare case in which L-HES and IgG4-related disease occurred simultaneously. Collectively, the importance to report this case is even more paramount. In this sense, we are grateful to this reviewer who reminded us of IgG4RD. Please see page 10 lines 1-4, lines 19 - 23, page 11 lines 1 – 9, and Figure 1 g

Quality of written English: Needs some language corrections before being published.

Our reply 3>
Our manuscripts have been corrected repeatedly by a U.S.-based manuscript editing company. In addition, we deleted less relevant information from the current submission so that the manuscript is maximally concise.

Declaration of competing interests: ‘I declare that I have no competing interests’

References for this file:


