



July 21, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 4211, a review article; Diagnostic Advances)

title: **Diagnosis of IgG4-related sclerosing cholangitis**

Author: Takahiro Nakazawa, Itaru Naitoh, Kazuki Hayashi, Katsuyuki Miyabe, Shuya Simizu, Takashi Joh

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4211

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Point to point reply to reviewer 1

(1) paragraphs are not really organized as a way to break up conceptually different topics.

We checked the manuscript again and rewrote.

(2) many sentences are disjointed.

We made the corrections to all the sentence pointed out by the reviewer.

1) Page 8: "We classified the etiology of SSC based on 3 reviews". What do the authors mean by saying "3 reviews"? ?

Thank you for your useful advise. We changed the sentence.

We classified the etiology of SSC based on [these 3 review articles \[13,16,17\]](#) (Table 1).

- 2) Page 10: The authors describe the findings from Oseini's study, saying "...some patients with CC, particularly PSC,...". Why PSC suddenly appeared here? ?

We inserted one sentence (red one)

They reported that among their 126 patients with CC, 17 (13.5%) had elevated (>140 mg/dL) and 4 (3.2%) had a >2-fold increase (>280 mg/dL) in serum IgG4 levels. **PSC was present 31/126 CC patients, of whom seven (22.6%) had elevated serum IgG4 level.** The authors concluded that some patients with CC, particularly PSC, had elevated serum IgG4 levels and diagnosis using a 2-fold higher cutoff serum IgG4 level may not reliably distinguish IgG4-SC from CC.

- 3) Page 11: What are "respective controls"? ?

We changed the words as follows (red one)

We have recently established a cutoff serum IgG4 level to differentiate IgG4-SC from **other three diseases (type 1 IgG4-SC versus Pca, type2 IgG4-SC versus PSC and type3 IgG4-SC versus CC)** using serum IgG4 levels measured in 9 Japanese high-volume centers [23].

- 4) Page 11: What "all types of CC" mean? ?

We deleted "all types of"

- 5) Page 16: What do the authors mean "the present series"? ?

We deleted the sentence and changed the order of one sentence.

Associated ulcerative colitis is suggestive of PSC. ~~In the present series, no IgG4-SC cases were associated with IBD.~~ IBD is present in only 0–6% of patients

with IgG4-SC [9,12,15]. IBD is usually not a feature associated with type 1 AIP, unlike the frequent association of IBD with type 2 AIP [22]. IBD associated with PSC represents a third phenotype, which has to be regarded without presumption in Western countries [38].

- 6) Page 18: I guess the authors wanted to say “1-mm thickness”, not “1- mm diameter”. ?

Thank you for correcting the mistake. “1-mm thickness” is appropriate.

- 7) Page 18: What is IgG4-associated cholangitis? Is this different from IgG4-SC? ?

Mayo group had insisted that “IgG4-associated cholangitis” is more appropriate terminology than “IgG4-related cholangitis”. However, international conference decided that we should use “IgG4-related cholangitis”. In order to incite the original terminology, we used “IgG4-associated cholangitis”. However, in order to avoid confusing by the reader, we used IgG4-SC in this review article.

- 8) Page 19: What is “non-PSC-related CC”? ?

We deleted “non-PSC-related CC”? and used “CC”.

- 9) Page 20: Nishio’s study. It is unclear that what made improvement. The readers have to guess it would be steroid therapy. ?

We changed the sentence as follows.

Nishino et al. [11] reported that bile duct stricture improved to various degrees in all 10 patients treated by steroid therapy but persisted in the lower part of the bile duct in 4 patients (4/10, 40%).

- 10) Page 21: Functional change of what?

We inserted a several words as follows.

Morphological and functional changes of liver and bile ducts in IgG4-SC

- 11) Abstract is written in a peculiar style for a review article. No needs for structural

abstract. One may be left with the impression that the authors did meta-analysis. Essentially abstract needs to be re-written.

We re-wrote abstract as follows

Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is recognized as one of IgG4-related diseases often associated with autoimmune pancreatitis (AIP). However, diffuse cholangiographic abnormalities seen in IgG4-SC may resemble those seen in primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma. IgG4-SC responds well to steroid therapy, whereas PSC is effectively treated only with liver transplantation and cholangiocarcinoma requires surgical intervention. Since IgG4-SC was first described, it has become a third distinct clinical entity of sclerosing cholangitis. The aim of this review was to introduce the possible diagnosis of IgG4-SC.

IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological, and histopathological features after cholangiographic classification and targeting of a disease for differential diagnosis. When intrapancreatic stenosis is detected, pancreatic cancer or cholangiocarcinoma should be ruled out. If multiple intrahepatic stenoses are evident, PSC should be discriminated on the basis of cholangiographic findings and liver biopsy with IgG4 immunostaining. Associated inflammatory bowel disease is suggestive of PSC. If stenosis is demonstrated in the hepatic hilar region, cholangiocarcinoma should be discriminated by ultrasonography, intraductal ultrasonography, bile duct biopsy, and a

higher cut off serum IgG4 level of 182 mg/dL.

- 12) Also Introduction has to be re-written. The authors should write what the problem is and why the objective of writing the review is.

We agree with the reviewer and re-wrote introduction.

Please see the revised manuscript.

- 13) Lastly one important ethical problem: Figure 1 is essentially the same as Figure 1 of the cited article #21. Figure 4 is very similar to Figure 2 of the cited article #21. The authors should obtain permission from the publisher, if applicable.

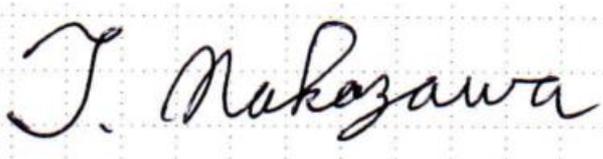
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author

I am pleased to be publishing our manuscript in the *World Journal of Gastroenterology*.

T Nakazawa

A handwritten signature in black ink that reads "T. Nakazawa". The signature is written in a cursive style and is placed over a light gray dotted grid background.

Takahiro Nakazawa, M.D.

Department of Gastroenterology and Metabolism,

Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

Phone: +81-52-853-8211, Fax: +81-52-852-0952.

e-mail: tnakazaw@med.nagoya-cu.ac.jp