Case Report

Anke Mittelstaedt*, Peter N. Meier, Eva Dankoweit-Timpe, Beate Christ and Joachim Jaehne

IgG4-related sclerosing cholangitis mimicking hilar cholangiocarcinoma (Klatskin tumor): a case report of a challenging disease and review of the literature

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Abstract

Background: Even though IgG4-related disease has gained increased attention worldwide, the diagnosis remains challenging. IgG4-related sclerosing cholangitis (IgG4-SC) is not well described in the western hemisphere and may mimic cholangiocarcinoma (CC), especially when occurring without other symptoms such as, e.g. concurrent pancreatitis or retroperitoneal fibrosis. We present a case to add further information to the diagnosis and treatment of this challenging disease.
Case report: A 60-year-old male patient presented with painless jaundice. Prior medical history showed diabetes mellitus type I, high blood pressure, and deep vein thrombosis. Diagnostic investigations were strongly suspicious of a Klatskin tumor, although biopsies were inconclusive. The tumor marker Carbohydrate Antigen 19-9 (CA 19-9) was elevated. Prior to the recommended surgery, the patient had two second opinions in two different university hospitals, both arguing for surgery as well. The patient received hilar resection with right hemihepatectomy. During the postoperative course, some major complications occurred, i.e. recurrent pleural effusion, abscess in the liver resection area, sepsis, ileus, and restricted liver metabolism. Treatment with prednisolone did not show any improvement. Approximately 3 months after surgery, the patient died in consequence of acute respiratory failure. Histology showed no signs of CC, but IgG4-SC could be diagnosed.
Conclusion: In the case of preoperative signs of CC, differential diagnosis of IgG4-SC needs to be considered, in particular, in cases with missing histologic proof of malignant disease.

Keywords: autoimmune biliary disease; cholangiocarcinoma; IgG4; IgG4-related disease; sclerosing cholangitis.

Abbreviations: AIP, autoimmune pancreatitis; CA 19-9, carbohydrate antigen 19-9; CC, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; IgG4-SC, IgG4-related sclerosing cholangitis; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis.

Introduction

IgG4-related disease is a newly recognized entity showing a chronic inflammatory process that involves many organ systems. Characteristic histopathological features are dense lymphoplasmatic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis [1, 2]. The disease was first described in the Asian population, and still, most of the research articles, such as reviews, guidelines, recommendations and studies including a larger number of patients, are from Japan [3–10]. In the western hemisphere, the disease entity is not as well described and recognized, and most of the articles are case reports [11–15]. In 2011, a consensus conference held in Boston named this entity "IgG4-related disease" [1]. Still, most members of this conference were from Asia and the USA. IgG4-related sclerosing cholangitis (IgG4-SC) belongs to this entity and may mimic cholangiocarcinoma (CC) [11, 13, 14, 16, 17], therefore, representing a challenging disease.

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Case report

In 2014, a 60-year old male patient noticed a first decrease in general performance. One year later, after a flight to Vietnam, deep vein thrombosis occurred in both legs. In April 2016, the patient presented with jaundice that appeared during a trip to Cuba. Prior medical history showed diabetes mellitus type I (initial diagnosis 1998) and high blood pressure, which were treated with insulin and an angiotensin II receptor blocker, respectively. Further anamnesis revealed an intermittent pruritus and minimal scleral icterus since approximately 10 years. During the first hospitalization, the patient developed an acute upper gastrointestinal bleeding (Forrest I b).

Diagnostic investigations such as endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance imaging (MRI) (Figure 1) showed intrahepatic PSC-like lesions and extended intrahepatic bile ducts but were also strongly suspicious of a Klatskin tumor type IV according to Bismuth. The MRI also showed an irregular configured and accentuated pancreatic duct, most likely post infectious. ERCP-based tissue sampling from the common hepatic duct revealed fibrosis and an unspecific inflammatory reaction but no signs of a malignant tumor. The tumor marker CA 19-9 was elevated with 148.40 IU/mL (normal range <39.0 IU/mL). Primary sclerosing cholangitis (PSC) and autoimmune hepatitis were excluded by measuring "antimitochondrial antibodies" (AMA), "anti-liver-kidney microsome antibody" (LKM), "soluble liver antigen" (SLA), "smooth muscle antigen" (SMA), "cytoplasmic anti-neutrophil cytoplasmic antibodies" (c-ANCA), and "perinuclear anti-neutrophil cytoplasmic antibodies" (p-ANCA), which were all negative.

In terms of a stenosis in the right as well as in the left hepatic duct and also high bilirubin, the patient received two self-expandable metallic stents (SEMS). Subsequently, the bilirubin serum level decreased, and an operation without higher risk of postoperative liver failure became possible.

Prior to the recommended surgery, the patient had second opinions in two different university hospitals specialized in liver surgery, both arguing for surgery as well.

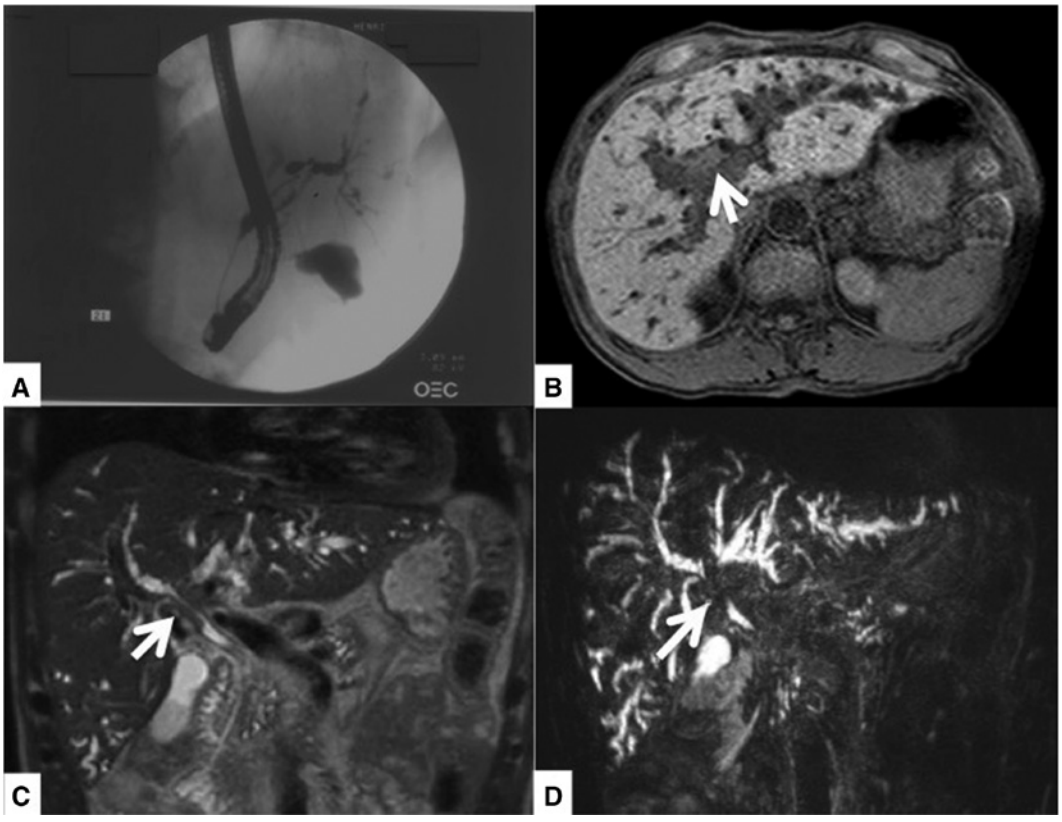

Figure 1: (A) ERCP; (B) (transversal), (C, D) (both frontal): MRI.
Cholangiographic findings show intrahepatic PSC-like lesions and extended intrahepatic bile ducts but are also strongly suspicious of a Klatskin tumor type IV of Bismuth. The arrows show a soft tissue thickening leading to a stenosis of the hilar bile duct region. There are also prestenotic dilatations of the bile duct. These findings correlate with type 4 of the cholangiographic classification of IgG4-SC.

The patient underwent explorative laparotomy. There were no signs of metastatic disease, so that a hilar resection with right hemihepatectomy was performed (Figure 2). Intraoperative frozen section of the left hepatic duct showed cell alterations suspicious of tumor infiltration requiring a re-resection in order to achieve an R0-status. Reconstruction of the bile duct system was achieved by a Roux-en-Y-loop.

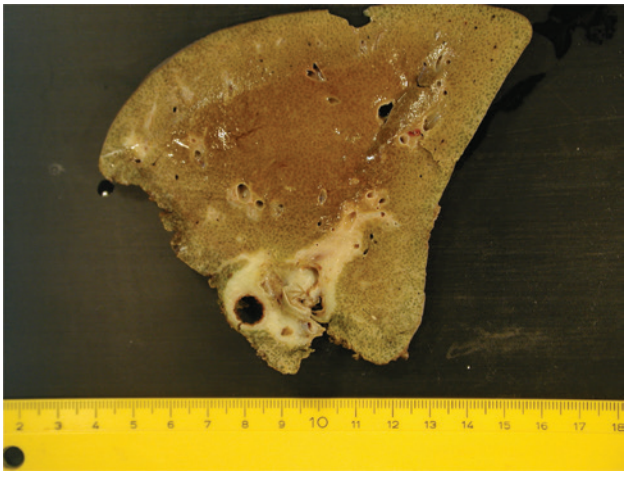

Figure 2: Cut section of the patients' liver: tumor-like prestenotic wall thickening of the right hepatic bile duct.

During the postoperative course, the patient developed some major complications, i.e. pneumonia, peritonitis, sepsis, abscess in the liver resection area, acute kidney failure, restricted liver metabolism with edema and ascites, and recurrent pleural effusion. Final histology, also proven by reference pathology, showed no signs of CC, but IgG4-SC could be diagnosed (Figure 3). Approximately 2 weeks after surgery, the serum IgG4 level was increased with 299 mg/dL (normal range 88–140 mg/dL). Because of decreased liver function, the patient was transferred to a university hospital for evaluation of liver transplantation. In terms of following stable liver function, transplantation was not necessary, and the patient was retransferred.

After diagnosis, the patient himself was reading articles about his disease and was begging for treatment with prednisolone. In the beginning, immunosuppressive therapy was not possible because of the several

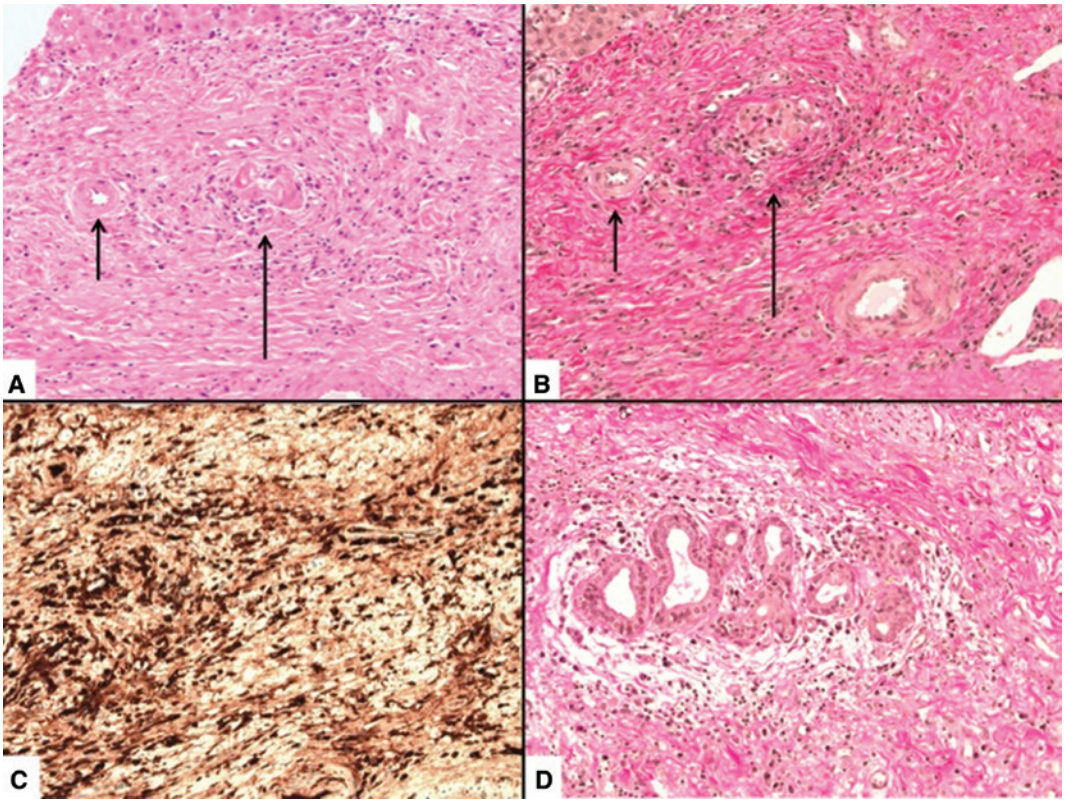

Figure 3: Histopathological sample of the patient.
(A) Hematoxylin and eosin. (B) Elastica van Gieson: small artery (short arrow) next to an inflammatory occluded vein (long arrow). (C) Immunostaining: IgG4-positive plasma cells. (D) Elastica van Gieson: IgG4-sclerosing cholangitis: Accessory gland in the wall of a bile duct with periductal lymphoplasma cellular infiltrate.

complications and imminent organ failure. Prednisolone was started 7 weeks after the first surgery when the patient slightly recovered. Steroid treatment did not show any great improvement. The patient was in a poor general condition and suffering from fatigue. Always, when the patient seemed to be on the mend, another complication occurred. Two months after the initial surgery, the patient developed an adhesive ileus with the need for reoperation following wound dehiscence with burst abdomen and the need for abdominal vacuum therapy. Even though GOT (glutamic oxaloacetic transaminase), GPT (glutamate-pyruvate transaminase), quick, total protein and albumin normalized, cholinesterase remained low with 0.6 and 1.0 kU/L (normal range 5.3–12.9 kU/L).

Approximately 3 months after initial surgery, the respiratory situation deteriorated unpredictably fast, and the patient was soon in need of reanimation in cause of ventricular fibrillation. The patient was transferred to a university hospital and received extracorporeal membrane oxygenation (ECMO). A few days later, the patient died due to pneumonia-induced septic-associated acute respiratory failure.

Discussion

IgG4-SC is the biliary manifestation of the IgG4-related disease, which can be defined as a syndrome characterized by increased levels of serum IgG4 and multifocal IgG4-rich lymphoplasmatic infiltrate associated with intense sclerosis [18]. Although the fibrosis may destroy the affected organ, clinical and radiological features of IgG4-related disease, in this case IgG4-SC, are usually resolved by steroid therapy [9, 19–21].

IgG4-SC displays various cholangiographic features similar to those of pancreatic cancer, primary sclerosing cholangitis (PSC), or cholangiocarcinoma (CC). There is a classification into four types based on the stricture regions revealed by cholangiography and differential diagnosis. Cholangiographic findings of types 3 and 4 should be discriminated from CC [3, 10]. According to MRI and ERCP, the patient had been a type 4 (Figure 1). Deep vein thrombosis in prior medical history and the elevated CA 19-9 supported the suspected diagnosis of CC in the patient.

IgG4-SC is most common in elderly men, and obstructive jaundice is frequently observed [5, 22], both applicable to the patient. Frequently, IgG4-SC is associated with autoimmune pancreatitis (AIP) and occasionally with IgG4-related dacryoadenitis/sialdenitis and IgG4-related retroperitoneal fibrosis [23–26]. However, some cases do not involve other organs [27]. The MRI of the patient showed an irregular configured and accentuated pancreatic duct, most likely post infectious. At least, there were some radiological abnormalities in the pancreas. We have never collected a histopathological sample. The diagnostic criteria for AIP according to the HISORt criteria are: (1) histologic evidence of IgG4-positive cells, (2) evidence of pancreatitis on imaging studies, (3) high serum IgG4 concentrations, (4) other organ findings, and (5) a response to steroids [28]. The patient also suffered from a diabetes type I since 1998. Even though diabetes can occur due to a pancreatitis as a diabetes type III, it is most likely that the diabetes already existed before.

An elevated serum IgG4 level is also a characteristic feature of IgG4-SC [18]. A cutoff level of 135 mg/dL seems to be useful in discriminating IgG4-SC from pancreatic cancer and PSC. However, it has a lower specificity in discriminating IgG4-SC from CC [8]. Ohara et al. [7] established a cutoff level to distinguish IgG4-SC from CC using serum levels measured in nine Japanese high-volume centers. A cutoff level of 182 mg/dL has a specificity of 96.6% for distinguishing types 3 and 4 IgG4-SC from CC. A cutoff level of 207 mg/dL might be useful for completely distinguishing types 3 and 4 IgG4-SC from CC. We do not know the preoperative IgG4-serum level of the patient, but 2 weeks after surgery, the serum IgG4 level was increased with 299 mg/dL, which is even higher than the cutoff level auf 207 mg/dL. So most likely, the preoperative serum level was equally as high as the postoperative one. However, there are other cases were the IgG4 serum level was not measured [29] or the level was in the normal range [14]. Because of the clinical rarity and poor recognition of IgG4-SC, it is not surprising that measuring the serum IgG4 level could be missed, especially without manifestation of the extra-biliary organs. Additionally, high IgG4 levels do not exclude CC completely [12]. Therefore, it is absolutely reasonable that the patient had two second opinions in two different university hospitals specialized on liver surgery, both arguing for surgery as well. Lately, Doorenspleet et al. [30] developed a novel quantitative PCR test measuring the IgG4/IgG RNA ratio in the peripheral blood that accurately distinguishes (94% sensitivity, 99% specificity) IgG4-SC from CC and PSC. Although not widely available yet, this test may be a potential support in clinical decision making in biliary tumors [31].

The histopathological features are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis [1]. All these features showed the histopathological sample of our patient (Figure 3). However, the first intraoperative frozen section of the left hepatic duct was misdiagnosed as tumor infiltration, and a re-resection was performed in order to achieve an R0-status.

The frozen section is not as significant as the final histopathological diagnosis. Nevertheless, again, due to the clinical rarity of the differential diagnosis IgG4-SC, tumor infiltration seemed to be obvious. Approximately 2 weeks after surgery, the final histology, proven by reference pathology, showed no evidence of malignancy but the pattern of IgG4-SC.

Glucocorticoids remain as the first-line agents for symptom improvement and organ function restoration. As an alternative, surgical resection or biliary drainage proved to be effective for symptom relief. Ghazale et al. [18] reported the clinical courses after steroid treatment, surgical resection, and conservative management. Relapses occurred in 53% of cases after steroid withdrawal, whereas 44% relapsed after surgery and were further treated with steroids. Proximal extra/intrahepatic strictures were predictive of relapse. The authors indicate that these patients may need maintenance therapy over the long term. The role of immunomodulatory drugs such as azathioprine or rituximab needs further studies. Topazian et al. [32] reported a case where biliary strictures improved after rituximab therapy. Hart et al. [33] reported no difference in the relapse-free survival of patients treated with immunomodulatory drugs and steroids compared to steroids alone in patients with AIP. The herein reported patient himself was arguing for steroid therapy and finally treated with prednisolone, which started 7 weeks after surgery. Steroid treatment, however, did not show any great improvement. After 3 months, the patient died in consequence of acute respiratory failure in cause of sepsis and pneumonia.

Various case reports with misdiagnosed IgG4-SC show different data regarding the effects of surgery and/or medical treatment [13, 16, 29, 32]. Some showed no recurrence after surgery without steroid therapy [29], some showed no improvement at all after resection plus steroids [13] as it was the situation in the herein reported patient. In another case, reported by Miki et al. [16], hilar cholangiocarcinoma could not have been ruled out even though serum IgG4 level was elevated. However, the patient did not respond to steroid pulse therapy and underwent explorative laparotomy. Partial resection of the upper bile duct was performed, and frozen section pathological diagnosis revealed no evidence of malignancy. Therefore, right hemihepatectomy was not performed. Final histologic examination revealed IgG4-SC, and the patient was treated with steroids again. In our case, the frozen section was misdiagnosed as malignancy, so we had to perform re-resection. However, if CC cannot be ruled out clinically, it seems to be an alternative to perform explorative laparotomy or even laparoscopy [34] in order to obtain a histopathological specimen. Another option performed in the case of Miki et al. [16] is the steroid trial. Although, generally, when diagnosis should be made before starting therapy, a steroid trial is needed in some cases relating to AIP [35]. In type 2 classified IgG4-SC, a steroid trial is recommended if a diagnosis cannot be clearly established. If malignancy is not confirmed by bile duct biopsy in types 3 and 4 IgG4-SC and bile duct wall thickening appears normal on a cholangiogram, a steroid trial is an option [5]. No reports on any steroid trial, especially for IgG4-SC types 3 and 4, have been published so far.

Recently, Roos et al. [31] investigated the incidence and long-term activity of IgG4-SC in patients resected for CC in a single tertiary center over a period of 30 years. Interestingly, the resection rate for benign disease remained 15% over the years despite improved imaging methods. The authors constitute this due to the lack of accurate diagnostic tests for IgG4-SC.

As there are also reports of concomitant IgG4-SC and CC [12], it seems justified to state that surgery should always be considered if there are diagnostic signs and features, which are highly suspicious for malignancy.

Conclusion

From the literature and our case report, it may be concluded that in the case of normal IgG4 serum levels and signs of bile duct strictures, surgical exploration may be indicated. In patients with increased IgG4 levels, steroids should be applied. If there are signs of recovery, long-term treatment seems to be justified. Without improvement, surgery appears to be indicated.

Nevertheless, IgG4-SC remains a diagnostic challenge, and there is a need for further studies to identify those cases with malignancy because these patients only benefit from surgery in early tumor stages.

Author Statement

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Author Contributions

Anke Mittelstaedt: conceptualization; data curation; formal analysis; writing original draft; Peter N. Meier: investigation; Eva Dankoweit-Timpe: visualization; Beate Christ: visualization; Joachim Jaehne: supervision; validation; writing review, and editing.

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Supplemental Material: The article (https://doi.org/10.1515/iss-2018-0010) offers reviewer assessments as supplementary material.

Reviewer Assessment

Anke Mittelstaedt*, Peter N. Meier, Eva Dankoweit-Timpe, Beate Christ and Joachim Jaehne

IgG4-related sclerosing cholangitis mimicking hilar cholangiocarcinoma (Klatskin tumor): a case report of a challenging disease and review of the literature

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Mar 26, 2018

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	80

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	3
Please rate the practical significance.	3
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The manuscript is well written and provides interesting information about an important topic. Although not new, the problem of IgG4 related disease in pancreato-bilary surgery is still evident and perhaps not very well recognized.
In summary, although the case report itself does not provide any new insides, I think that the review of the (very few available) literature is interesting.

Reviewer 2: anonymous

Apr 11, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	30

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	2
How adequate is the data presentation?	3
Are units and terminology used correctly?	N/A
Is the number of cases adequate?	2
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	2
Please rate the practical significance.	2
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

If the manuscript is acceptable for publication most recent reference PMID 29549357 Roos et al. should be included.

Authors' Response to Reviewer Comments

Apr 15, 2018

Reviewer 2:

The reference PMID 29549357 Ross et al. is included now as you can see in the highlighted text.