

Cover letter:

Dear Editor-in-Chief,

On behalf of all the authors, I would kindly request you to consider our manuscript entitled “**A case report of IgG4 associated autoimmune cholangitis and pancreatitis following the administration of nivolumab.**” for publication in World Journal of Clinical Cases.

Immune checkpoint inhibitors have significantly improved survivals for or an increasing range of malignancies but at the cost of several immune-related adverse events, the management of which can be challenging due to its mimicry with other autoimmune related disorders such as IgG4 when the pancreaticobiliary system is affected. Nivolumab an IgG4 monoclonal antibody has been associated with cholangitis and pancreatitis, however its association with IgG4 has not been reported to date.

We present a case of immune-related pancreatitis and cholangiopathy in a patient who completed treated with Nivolumab for anal squamous cell carcinoma. Patient's IgG4 levels were normal on presentation. She responded to steroids but due to concerns for malignant biliary stricture, she opted for surgery, the pathology of which suggested IgG4 related disease.

We propose that the IgG4 related cholangitis and pancreatitis was likely triggered by Nivolumab. Our hypothesis suggests a possible role of these medications in the expression of an overt autoimmune process.

We feel that this case report will be of interest to the readers. The manuscript has not been published and is not under consideration for publication elsewhere. All authors have read the manuscript, declared no conflicts of interest and have approved this submission.

Thanks for your kind consideration.

Sincerely,

Rohit Agrawal,
Department of Medicine,
Department of gastroenterology and hepatology,
University of Illinois at Chicago
Email: ragraw7@uic.edu
Work: 4433267647

Revision:

Reviewer #1:

1. I would like to suggest the authors to revise the title, it is too complex. "A case report of IgG4 associated autoimmune cholangitis and pancreatitis followed by nivolumab" is enough, real, and easy to understand. It is not a good idea in the title to illustrate an unclear mechanism.

Comment: We have revised the title as you suggested. The new title is as follows:

"A case report of IgG4 associated autoimmune cholangitis and pancreatitis following the administration of nivolumab."

2. Please clarify whether the lesion was not related to HIV?

Comment: We do not think the patient's pathology was related to HIV due to her undetectable VL and normal CD4 counts. She was compliant with her ART. We have added this comment to the discussion.

3. What is the potential mechanism of nivolumab led to IgG4 associated autoimmune cholangitis and pancreatitis, or have you seen other drugs induced IgG4 associated autoimmune cholangitis in literature? Please specify.

Comment: We have briefly mentioned in our introduction regarding the mechanism of these immune check point inhibitors: "These medications enhance immune activity against tumor cells by blocking down regulators of the immune system. However, normal cells may suffer collateral damage causing a host of inflammatory disorders. These have been referred to as immune-related adverse events (irAEs), the management of which can be challenging due to their varied and delayed manifestations.". The immune hyperactivity is the likely result of all autoimmune side effects and we hypothesize that the same activity triggered IgG4 related process. We have added this comment to the discussion.

We could not find any medications that have been associated with IgG4 related disease.

4. Did you have any consultation or MDT from the department of rheumatology and immunology since it is a autoimmune disease. If yes, what were their advice for the diagnosis and treatment? Please specify.

Comment: Patient was not seen by immunology. However, rheumatology agreed with the assessment and treatment plan.

Reviewer #2:

1. The abbreviations should be consistent from beginning to end, as far as immune checkpoint inhibitors are concerned, there is a mixed use of "ICPI" and "ICI" in the discussion part.

Comment: The required corrections have been made. We are only using ICPI for immune checkpoint inhibitors.

2. The discussion part was not organized well to fully discuss the possible reasons for the IgG4 related pancreatic and cholangitis caused by nivolumab, and the description of relevant literature is also not comprehensive.

Comment: Please refer to revised discussion. Comments have been added to elucidate the reasons for IgG4 related disease with nivolumab. As we are reporting a novel case, there is not much literature regarding ICPI triggered IgG4 disease.