



Relapsing immunoglobulin G4-related sclerosing cholangitis during maintenance treatment with low-dose steroids: a case report

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Background: Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) often has a good response to initial steroid therapy, but a high relapse rate during follow-up. Knowledge about the predictors and treatment strategy of relapsing IgG4-SC is of great significance.

Case Description: In this paper, we reported that a 57-year-old male was diagnosed with IgG4-SC accompanied by type 1 autoimmune pancreatitis (AIP) at the first onset of his diseases and had a good response to steroid therapy. However, during low-dose steroids maintenance therapy, IgG4-SC relapsed with clinical presentations related to severe bile duct stricture, but improved rapidly after re-administration of full-dose steroids, accompanied by resolution of jaundice, improvement of intrahepatic and extrahepatic bile duct stricture, and gradual recovery of liver function. At the last follow-up in December 2021, he was still stable with methylprednisolone tablets at 4 mg/day.

Conclusions: IgG4-SC is likely to relapse in patients who have high serum IgG4 level at initial onset and receive low-dose steroids maintenance treatment. The predictors of disease relapse also include steroids interruption, more severe bile duct stricture, long duration from diagnosis to treatment, history of allergy, and high serum tumor necrosis factor-alpha (TNF-alpha) and soluble interleukin-2 receptor (sIL-2R) levels. Re-administration or up-dose of steroids, immunosuppressors, and rituximab are effective for treating relapsing disease.

Keywords: Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC); immunoglobulin G4-related disease (IgG4-RD); relapse; steroid; case report

Received: 03 September 2021; Accepted: 22 February 2022; Published online: 17 March 2022.

doi: 10.21037/tgh-21-111

View this article at: <https://dx.doi.org/10.21037/tgh-21-111>

Introduction

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of immunoglobulin G4-related disease (IgG4-RD), which is an immune-mediated multi-system fibroinflammatory disease and related to an elevated serum IgG4 level and the infiltration of IgG4 positive plasma cells (1). Hepatopancreaticobiliary system

is the most frequently involved organ of the IgG4-RD with a proportion of 77% (2). Steroids are the first-line option of IgG4-SC with an initial remission rate of approximately 90% (3,4). The Japanese clinical practice guidelines recommend that the dosage of initial remission-induction therapy should be 0.6–1.0 mg/kg/day of prednisolone for 2–4 weeks, the dosage of prednisolone should be reduced

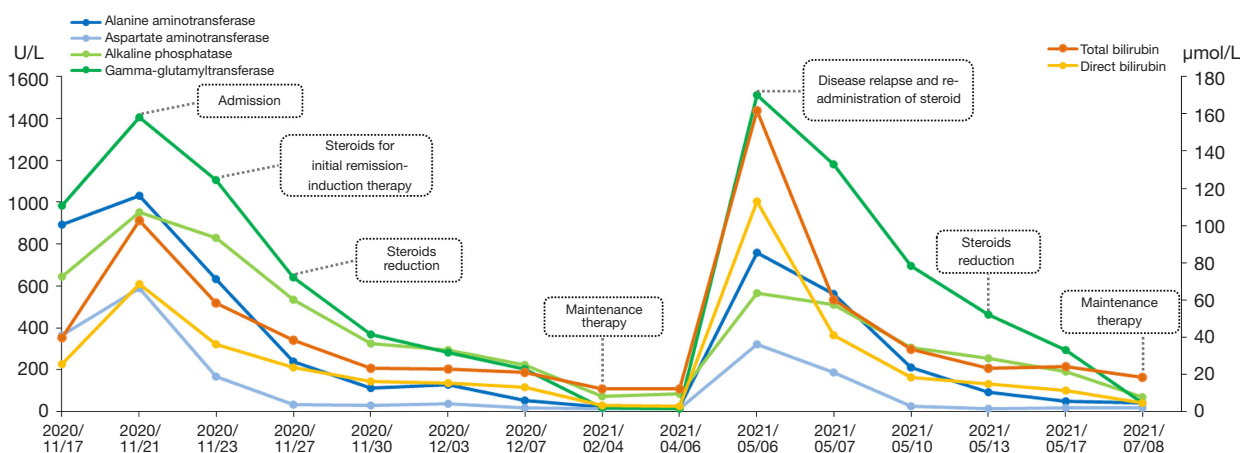


Figure 1 A timeline showing the disease course of this case.

by 5 mg every 1–2 weeks to the maintenance dosage by 2–3 months after imaging and serological improvement, and the recommended dosage of prednisolone is 5 mg per day for 3 years (5). However, the relapse of IgG4-SC is still a clinical challenge. It is reported that the relapse rate ranges from 24% to 59% in IgG4-RD patients treated with steroids alone (2,3,6-14). The international consensus (15) and Japanese practice guideline (5) recommend re-administration or up-dose of steroids, immunosuppressors, and rituximab for disease relapse. However, the standard protocol of steroids, including optimal starting dosage, adequate maintaining dosage, and withdrawal time, remain controversial (16). Herein, we reported a case of relapsing IgG4-SC, which was successfully treated by re-administration of steroids, and discussed the predictors and treatment strategy of disease relapse by reviewing the current evidence. We present the following case in accordance with the CARE reporting checklist (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-21-111/rc>).

Case presentation

On November 21, 2020, a 57-year-old male was admitted to our department due to abdominal distension and worsening liver function for 10 days. He had no underlying comorbidities. Physical examination revealed icteric sclera and skin without any tenderness or rebound pain in the abdomen. Laboratory tests on admission showed elevated levels of total bilirubin (102.7 μmol/L, reference range, 5.1–22.2 μmol/L) (Figure 1), direct bilirubin (68.4 μmol/L, reference range, 0–8.6 μmol/L), alkaline phosphatase (953.92 U/L, reference range, 45–125 U/L), gamma-

glutamyltransferase (1,407.5 U/L, reference range, 10–60 U/L), alanine aminotransferase (1,030.07 U/L, reference range, 9–50 U/L), aspartate aminotransferase (589.62 U/L, reference range, 15–40 U/L), serum amylase (192.00 U/L, reference range, 30–110 U/L), serum lipase (2,956.0 U/L, reference range, 23–300 U/L), and IgG4 (499 mg/dL, reference range, 1.2–201 mg/dL). He had negative immunoglobulin A, G, and M, autoantibodies (i.e., anti-nuclear antibody, anti-mitochondrial antibody, and anti-smooth muscle antibody), hepatitis virus A, B, C, and E, and tumor markers (i.e., alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen-199, 50, 24-2, 125, and 153). Contrast-enhanced magnetic resonance imaging (MRI) showed diffuse enlargement of pancreas with its delayed enhancement (Figure 2). Additionally, the inner and outer layers of the bile duct were smooth. Magnetic resonance cholangiopancreatography (MRCP) showed pancreatic duct stricture, intrahepatic bile duct and upper middle segment of common bile duct dilatation, and lower common bile duct stricture with slight wall thickness (Figure 3). A diagnosis of primary sclerosing cholangitis was excluded due to the presence of elevated serum IgG4 level and the absence of short strictures and beaded appearance of biliary trees on MRCP. A diagnosis of cholangiocarcinoma was also excluded due to the absence of a two-layer bile duct wall at the arterial phase of contrast-enhanced MRI scans. Finally, a diagnosis of type 1 autoimmune pancreatitis (AIP) combined with IgG4-SC was established. Since November 23, steroid therapy was started with methylprednisolone sodium succinate at 40 mg/day for 4 days, and then adjusted to oral methylprednisolone tablets at 36 mg/day. Serum IgG4 level decreased to

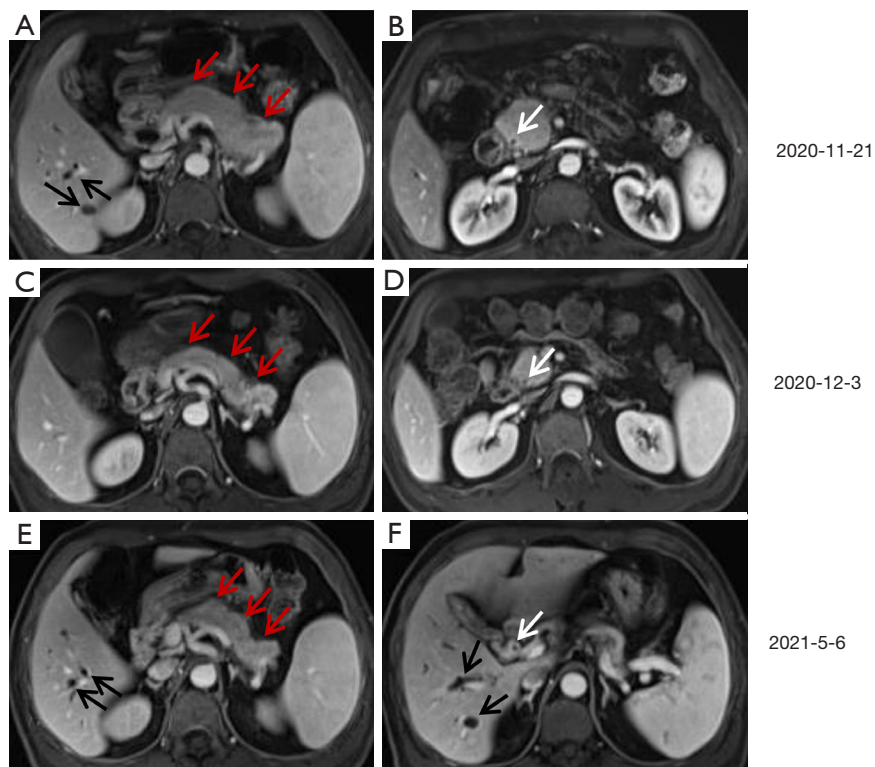


Figure 2 MRI findings at the time of first attack and disease relapse in this patient. (A,B) Images before steroid therapy at the first attack. (A) Diffuse enlargement of pancreas with delayed enhancement (red arrows) and rim-like enhancement; dilated intrahepatic bile duct (black arrows). (B) Circular-symmetrical wall thickening in the lower common bile duct (white arrow). (C,D) Images after steroid therapy at the first attack. (C) Mild enlargement of pancreas with delayed enhancement (red arrows). (D) Thickened lower common bile duct wall with no significant change compared to previous images (white arrow). (E,F) Images before steroid therapy at the disease relapse. (E) Swollen pancreas morphology with no significant change compared to the previous images (red arrows), dilated intrahepatic bile duct (black arrows). (F) Thickened upper segment of common bile duct wall (white arrow), dilated intrahepatic bile duct (black arrows). MRI, magnetic resonance imaging.

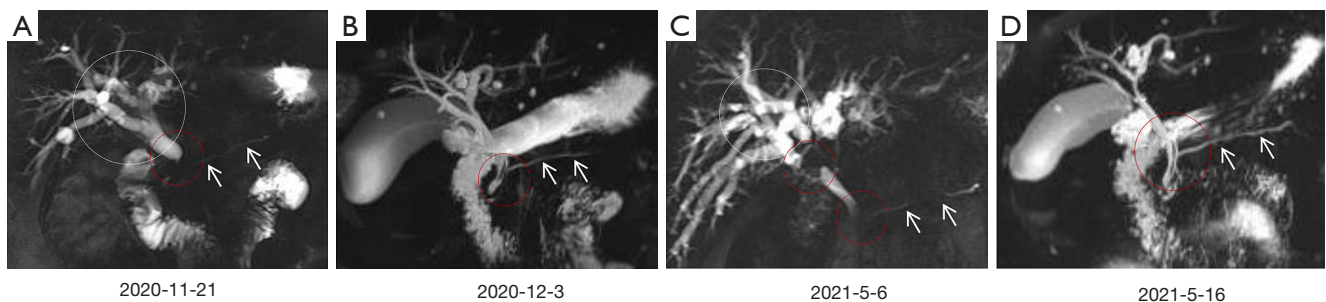


Figure 3 MRCP findings at the first attack and disease relapse in this patient. (A,B) Images before (A) and after (B) steroid therapy at the first attack. (A) Dilated intrahepatic bile duct and common bile duct (white frame) with an inner diameter of about 1.3 cm, narrowed lower common bile duct (red frame), and obscure pancreatic duct (white arrows). (B) Improvement of dilated intrahepatic bile duct and common bile duct with a diameter of about 0.9 cm, improvement of narrowed low common bile duct (red frame), and clear pancreatic duct (white arrows). (C,D) Images before (C) and after (D) steroid therapy at the disease relapse. (C) Dilated intrahepatic bile duct (white frame), narrowed hilar bile duct and lower common bile duct (red frames) with a diameter of about 0.7 cm, and obscure pancreatic duct (white arrows). (D) Significant improvement of narrowed hilar bile duct and lower common bile duct (red frame), and clear pancreatic duct (white arrows). MRCP, magnetic resonance cholangiopancreatography.

394 mg/dL on the 11th day of steroid treatment. MRI and MRCP also showed the improvement of pancreatic enlargement and biliary stricture on December 3, 2020 (Figures 2,3). Subsequently, methylprednisolone tablets were regularly reduced by 4 mg per week within 2 months and finally maintained at 2 mg/day. Serum IgG4 level and liver function markers gradually recovered during follow-up (Figure 1).

On May 6, 2021, he was re-admitted to our department for icteric sclera and skin after a 3-month maintenance treatment of methylprednisolone tablets at a dosage of 2 mg/day. Except for an elevated serum IgG4 level of 388 mg/dL, laboratory tests revealed significantly elevated levels of total bilirubin (161.8 $\mu\text{mol/L}$, reference range, 5.1–22.2 $\mu\text{mol/L}$), direct bilirubin (112.9 $\mu\text{mol/L}$, reference range, 0–8.6 $\mu\text{mol/L}$), alkaline phosphatase (566.75 U/L, reference range, 45–125 U/L), gamma-glutamyltransferase (1,510.32 U/L, reference range, 10–60 U/L), alanine aminotransferase (758.53 U/L, reference range, 9–50 U/L), aspartate aminotransferase (321.94 U/L, reference range, 15–40 U/L) (Figure 1). MRI showed a slightly swollen pancreas, which was not significantly deteriorated compared to the previous images (Figure 2). MRCP showed intrahepatic bile duct dilatation as well as hilar bile duct and lower common bile duct stricture with wall thickness (Figure 3). A relapse of IgG4-SC was considered. Methylprednisolone sodium succinate was given at 40 mg/day for 1 week. His liver dysfunction and jaundice gradually improved. Then, it was adjusted to oral methylprednisolone tablets at 36 mg/day for 1 week. On the 10th day of steroid therapy, MRCP showed a significant improvement of bile duct stricture (Figure 3). After induction of remission, methylprednisolone tablets were reduced by 4 mg per week to a maintenance dosage of 4 mg/day. IgG4 level and liver function normalized after a 1.5-month steroid therapy (Figure 1). At the last follow-up in December 2021, he was still stable with methylprednisolone tablets at 4 mg/day.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

IgG4-RD relapse may increase the risk of sclerosis and

permanent damage of organs affected (17). It is very necessary to recognize the management and predictors of disease relapse. Most previous studies focused on the management of relapse of IgG4-RD or type 1 AIP, but few studies on IgG4-SC. Currently, a relapse of IgG4-SC is often defined as the recurrence of symptomatic, serologic, radiologic, and/or histological abnormality after complete or partial remission of this disease, but not all of these abnormalities may appear at the same time (18). After IgG4-SC remission, our patient developed recurrent obstructive jaundice, elevated serum IgG4 level, and more aggressive biliary stricture as compared to the imaging presentations at the first onset of his diseases. This suggests that clinical symptoms, serum IgG4 level, and imaging should be closely screened in such patients to catch relapsing flames in time.

Among the Asian population with AIP or IgG4-RD, the relapse rate after steroid therapy alone ranges between 24% and 47.8% (3,6–12,19–23). By comparison, a few studies from Western countries show a higher relapse rate of 50–59% (2,13,14,24,25). Such a heterogeneity in relapse rate may be related to the difference in dosage and duration of steroids and follow-up duration. Maintenance treatment can reduce the relapse rate. A large retrospective study of 459 patients with type 1 AIP showed that the relapse rate was significantly lower in patients receiving the maintenance steroid therapy than those with drug withdrawal (23% *vs.* 34%, $P=0.048$) (3). In addition, it seems that a longer duration of steroid therapy leads to a lower relapse rate. A retrospective study by Kubota *et al.* (8) showed that the relapse rates were 80% (12/15) and 25.9% (7/27) in AIP patients who had received steroids for less and more than 12 months, respectively ($P<0.01$). Long-term follow-up is required to monitor the patients' conditions and assess the disease relapse because there is an increasing trend of relapse rate over time (Figure 4) (3,10).

Except for drug withdrawal, there are some other predictors of disease relapse. First, serum IgG4 level is a predictor of IgG4-SC relapse. Tsang *et al.* (26) found a significant correlation between a raised serum IgG4 level (greater than twice the normal upper limit) at the time of first diagnosis and disease relapse. Similarly, our patient's serum IgG4 level at the time of initial onset was greater than two times the upper limit of reference range, which suggests a higher risk of IgG4-SC relapse. In addition, a more rapid rate of decrease in serum IgG4 level during steroid therapy correlated with a lower risk of relapse after steroid therapy (27). Re-elevation of serum IgG4 level

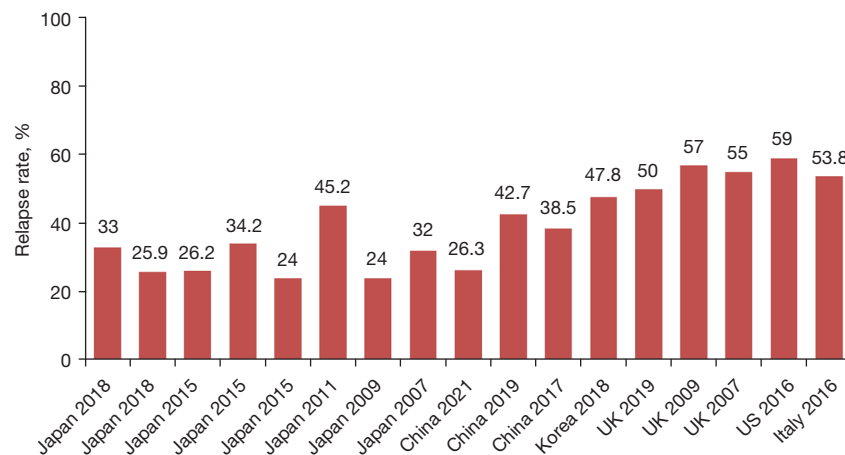


Figure 4 An overview of disease relapse rates in IgG4-RD patients after steroid therapy alone. IgG4-RD, immunoglobulin G4-related disease.

during steroid therapy is also a useful predictor of disease relapse (6,19). Second, the degree of bile duct involvement during the initial attack is also related to IgG4-SC relapse. Multiple bile duct strictures and thicker bile duct walls can increase the risk of disease relapse (5,12,28). Third, a long duration from first diagnosis to initiation of treatment and history of allergy are risk factors for disease relapse (10). Fourth, serum tumor necrosis factor- α (TNF- α) ≥ 13 pg/mL and soluble interleukin-2 receptor (sIL-2R) $\geq 1,010$ U/mL are the independent risk factors for IgG4-SC relapse (29).

There is no standard treatment regimen for IgG4-SC relapse. First, steroids are appropriate for the treatment of disease relapse. Accordingly, our patient's condition improved significantly after re-administration of methylprednisolone tablets. However, during long-term follow-up, we cannot ignore the side effects of steroids, such as osteoporosis and diabetes (3). Second, immunosuppressors have also been used for relapsing IgG4-SC. It was reported that seven patients with relapsing IgG4-SC were treated with azathioprine at 2.0–2.5 mg/kg/day or mycophenolate mofetil at 750 mg twice daily at the Mayo Clinic. During a median follow-up period of 6 months (range, 2–19 months), they all achieved remission (30). In a retrospective single-center study in China, 17 patients with relapsing or refractory IgG4-RD were treated with igitatimod at 25 mg twice daily, of whom 16 patients responded well without any serious drug related side effect (31). Third, rituximab, an antiCD20 antibody, is an appropriate alternative when some relapsing cases are resistant or intolerant to immunosuppressors or steroids. Among 12 relapsing AIP cases who were intolerant

or resistant to steroids or immunosuppressors at Mayo Clinic, the complete remission rate was 83% after rituximab treatment (375 mg/m² intravenously per week for 4 weeks, and then repeat infusions every 2–3 months for 24 months), and side effects related to rituximab were uncommon (32).

In conclusion, based on the case report and current evidence reviewed, IgG4-SC is likely to relapse after steroid treatment, especially in patients who have high serum IgG4 level at initial onset and receive low-dose steroids as a maintenance treatment. In addition, steroids interruption, more severe bile duct stricture, long duration from diagnosis to treatment, history of allergy, and high serum TNF- α and sIL-2R levels are the predictors of disease relapse. Re-administration or up-dose of steroids and initiation of immunosuppressors and rituximab are useful for the treatment of relapsing disease. In the future, more large-scale cohort studies are needed to clarify the optimal treatment strategy and long-term outcomes of IgG4-RD.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tgh.amegroups.com/article/view/10.21037/tgh-21-111/rc>

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-21-111/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/tgh-21-111

Cite this article as: Zhu M, Li H, Zhou W, Wang W, Yin Y, Xu S, Yu K, Qi X. Relapsing immunoglobulin G4-related sclerosing cholangitis during maintenance treatment with low-dose steroids: a case report. *Transl Gastroenterol Hepatol* 2023;8:22.