EJCRIM
European Journal
of Case Reports
in Internal Medicine

PECULIARITY OF AUTOIMMUNE HEPATITIS TRIGGERED BY SARS-COV-2 INFECTION

Antonella Gallo[1], Francesca Ibba[2], Maria Grazia Massaro[2], Fiammetta Rognoni[2], Maria Cristina Giustiniani[1], Francesca Romana Ponziani[1], Massimo Montalto[1,2]

[1] Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[2] Università Cattolica del Sacro Cuore, Rome, Italy

Corresponding author: Antonella Gallo **e-mail:** antonella.gallo@policlinicogemelli.it

Received: 09/11/2023 **Accepted:** 13/11/2023 **Published:** 29/11/2023

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient signed an informed consent and cannot be identified in the text or images.

How to cite this article: Gallo A, Ibba F, Massaro MG, Rognoni F, Giustiniani MC, Ponziani FR, Montalto M. Peculiarity of autoimmune hepatitis triggered by SARS-CoV-2 infection. *EJCRIM* 2023;**10**:doi:10.12890/2023_004195.

ABSTRACT

Introduction: Recently, medical interest has been growing in SARS-CoV-2 infection and its multiorgan involvement, including the liver. Up until now, a few reports have described autoimmune hepatitis (AIH) triggered by SARS-CoV-2 infection, but no data are available about the specific liver inflammatory infiltrate and cluster of differentiation. We report a case of AIH triggered by SARS-CoV-2 infection, with a particular focus on its histological and mainly immunohistochemical features.

Case description: A 60-year-old man, with a history of paucisymptomatic SARS-CoV-2 infection that occurred one month earlier, was admitted for alterations of hepatocellular necrosis and cholestasis indexes. He completed vaccination for SARS-CoV-2 a year earlier. The serologies for hepatotropic viruses were negative. The anti- smooth muscle antibodies (ASMA) and antinuclear antibodies (ANA) results were positive. Anti-liver kidney microsome (anti-LKM) antibodies and antimitochondrial (AMA) were negative. By liver biopsy, haematoxylin-eosin staining highlighted severe portal inflammation with a rich CD38+ plasma cell component, while immunohistochemical staining showed low cell CD4+ count and prevalence of CD8+ and CD3+. After biopsy, the patient started an immunosuppressant regimen, with benefit.

Discussion: We can conclude that the patient developed a type 1 AIH triggered by SARS-CoV-2 infection. The presence of CD8 T-cells at immunohistochemical examination suggests different mechanisms from classic AIH. Similar cases are described after AIH triggered by SARS-CoV-2 vaccination.

Conclusion: The AIH after SARS-CoV-2 infection developed by the patient showed a histological picture similar to a classic AIH for the abundant presence of plasma cells, and immunohistochemical features similar to those described after SARS-CoV-2-vaccination.

KEYWORDS

Acute hepatitis, COVID-19, autoimmunity

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Recently, medical interest has been growing in SARS-CoV-2 infection and its multiorgan involvement, including the liver. Underlying mechanisms are not still clear, more likely consisting of an inflammatory and immune mediated process rather than a direct cytopathic damage.
- Our report describes a rare case of type 1 AIH triggered by SARS-CoV-2 infection, showing a peculiar histological pattern, different from classic AIH, conversely similar to AIH triggered by SARS-CoV-2 vaccination.
- The mechanisms underlying liver involvement in SARS-CoV-2 infection are still under investigation. Further studies should be encouraged to improve understanding on this focus and to support physicians in its management.

INTRODUCTION

Recently, medical interest has been growing on SARS-CoV-2 infection and its multiorgan involvement, including the liver. Underlying mechanism are not still clear, more likely consisting of an inflammatory and immune mediated process rather than a direct cytopathic damage.

Up until now, only a few reports have described autoimmune hepatitis (AIH) triggeredby SARS-CoV-2 infection, but no data are available about the specific liver inflammatory infiltrate and cluster of differentiation. We report a case of AIH triggered by SARS-CoV-2 infection, with a particular focus on its peculiar histological and mainly immunohistochemical features.

CASE DESCRIPTION

A 60-year-old man was admitted to our Emergency Department for asthenia and alterations of hepatocellular necrosis and cholestasis indexes. He did not report any chronic diseases or medications. A month earlier he experienced a paucisymptomatic SARS-CoV-2 infection lasting for 10 days and was treated at home with amoxicillin/clavulanate and ibuprofen for 7 days, according to his general practitioner's advice. He was vaccinated for SARS-CoV-2 a year earlier. The patient denied taking additional medications or dietary supplements. He reported intake of four alcohol units (wine) every day from youth, but he denied a recent increase in habitual alcohol intake. Family history was negative for autoimmune or liver diseases. Laboratory examinations confirmed an increase of serum bilirubin (3.1 mg/dl), alanine aminotransferase (1,390 IU/l) and aspartate transaminase (1,348 IU/l), alkaline phosphatase (317 IU/l) and gamma-glutamyltransferase (353 IU/l). Serum protein electrophoresis documented polyclonal hypergammaglobulinemia and an increase of immunoglobulin G (35 g/l). The international normalised ratio and blood counts were within normal limits.

As differential diagnosis of acute hepatitis, serologies for hepatotropic viruses (varicella zoster virus, parvovirus, herpes simplex virus 1 and 2, hepatitis E, hepatitis B, hepatitis A, hepatitis C, cytomegalovirus and Epstein-Barr) and for HIV were performed; all results were negative for acute infection. Instead, investigating an autoimmune aetiology, the anti-smooth muscle antibodies (ASMA) and antinuclear antibody (ANA) results were positive (1:40 and 1:640, respectively), while anti-liver kidney microsomal (anti-LKM) antibodies and antimitochondrial antibody (AMA) results were negative. An ultrasound of the abdomen ruled out signs of advanced liver fibrosis disease. An abdominal magnetic resonance imaging documented diffuse oedema of the periportal-biliary spaces associated with periportal fluid and pericholecystic levels. Finally, for the persistent high hepatocellular necrosis and cholestasis indexes, a liver biopsy was performed. Haematoxylin-eosin staining highlighted severe portal inflammation with a rich CD38+ plasma cell component and interface hepatitis *(Fig. 1A)*. Immunohistochemical staining also showed low cell CD4+ T-cell count *(Fig. 1B)* and prevalence of CD8+ T-cells *(Fig. 1C)* and CD3+ T-cells *(Fig. 1D)* throughout the whole lobule. The CD38+ plasma cells were concentrated in the portal space *(Fig. 1E)* with a shortage in the whole lobule *(Fig. 1F)*. After biopsy, the patient started a corticosteroid therapy, with a progressive improvement in liver function indexes. This allowed a steroid tapering and starting of azathioprine therapy, with progressive improvement since resolution of serum alterations within few weeks.

DISCUSSION

Napodano et al. recently suggested that liver injury in COVID-19 disease more likely consists of an inflammatory and immune mediated process rather than direct cytopathic damage. This is mainly due to the relevant cytokine release in the acute phase of disease, representing one of the major determining mechanisms for COVID-19 progression[1].

Based on laboratory, radiological and histological findings, we concluded that our patient was affected by a type 1 autoimmune hepatitis triggered by a SARS-CoV-2 infection. However, conversely to the classic forms of autoimmune hepatitis, usually characterised by a prevalent CD4 T-cells immune mediated response[2], different mechanisms seem to be involved in this specific case, due to the predominant presence of CD8 T-cells at immunohistochemical examination.

While similar data on AIH triggered by SARS-COV-2 infection are lacking, however, our finding partially replicated the previous reports regarding the forms of AIH after SARS-CoV-2 vaccination[1,3].

Boettler et al. recently described a case of overlap syndrome, with both ANA and AMA positivity, occurring 2–3 weeks after

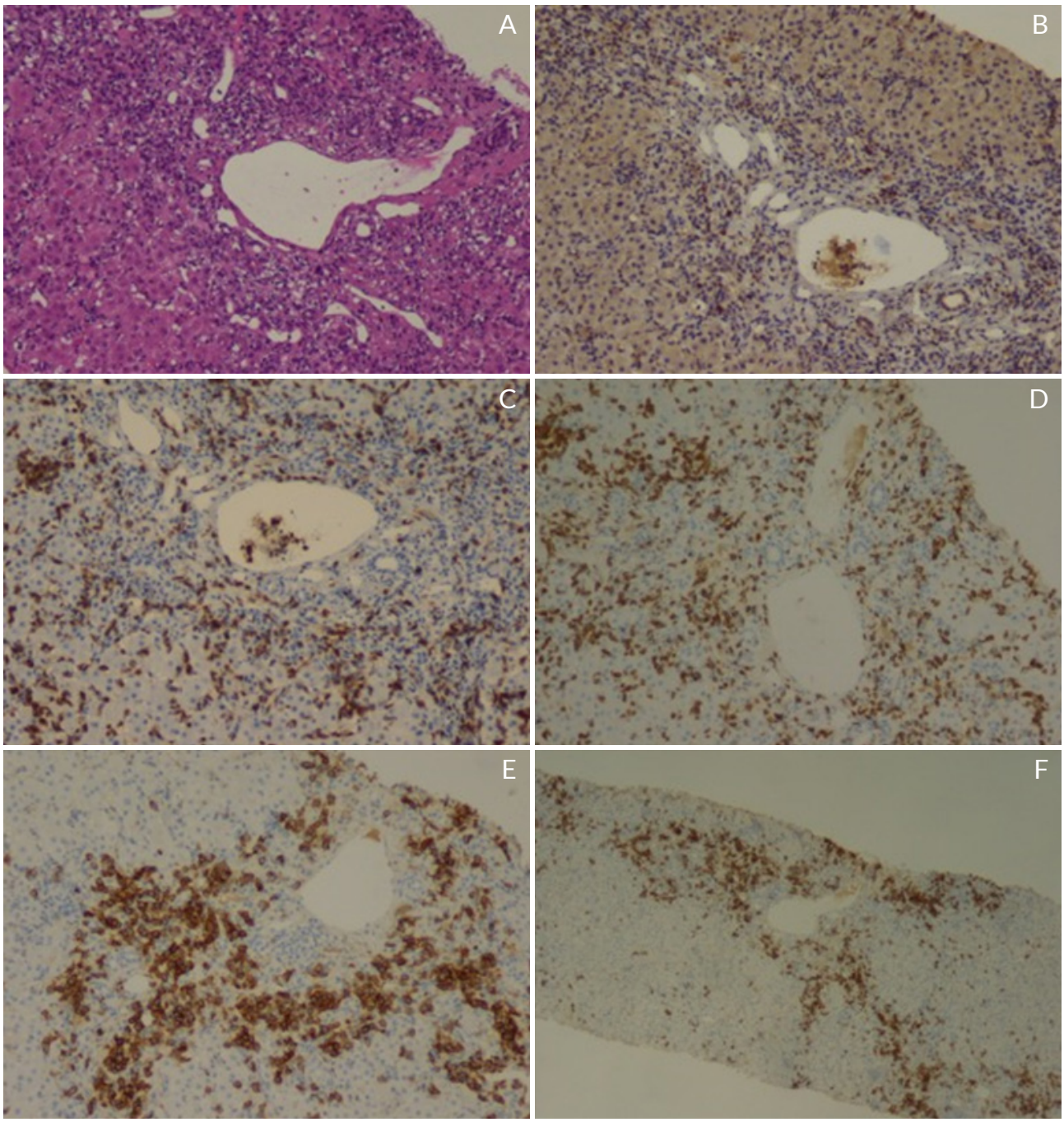

Figure 1. Liver biopsy. Haematoxylin-eosin staining highlights severe portal inflammation with a rich plasma cell component and interface hepatitis (A 20×). Immunohistochemical staining shows slow CD4+ cells (B 20×) and prevalence of CD8+ (C 20×) and CD3+ cells (D 10×) throughout the whole lobule; CD38+ plasma cells concentration in the portal space (E 20×) with a lack in the whole lobule (F 4×).

SARS-CoV-2 vaccination[3]. They demonstrated, performing a cytometry on liver biopsy tissue, the presence of a highly activated cytotoxic CD8 T-cell infiltrate with a SARS-CoV-2 specificity (spike-specific CD8 T-cells). They also showed that the peripheral activation state of these spike-specific CD8 T-cells correlated with hepatitis severity and the clinical course after introduction of immunosuppressive therapy[3].

The precise mechanism underlying infiltration of spike-specific CD8 T-cells into the liver still remains unclear. Also, Lee et al. described another case of overlap syndrome after SARS-CoV-2 vaccination[4]. The percutaneous liver biopsy revealed a moderate portal inflammation with CD3 T-cell dominant infiltration along with CD38 cells suggesting plasma cells. Although virus-specific CD8 T-cells were not identified, it is conceivable that most of the infiltrated T-cells might be SARS-CoV-2 specific CD8 T-cells, according to the results of Boettler et al.[3].

In both these reports, ANA and AMA results were positive. It is well known that CD8 T-cells are directly involved in the pathogenesis of primary biliary cholangitis, and that a consistent infiltration of CD4 and CD8 T-cells in the portal tracts represents a typical finding in this disease[5]. Therefore, it is likely that the immunohistochemical pattern described in these cases may be partially justified by a concomitant overlap syndrome. Instead, in our patient the AMA result was negative, while ANA and ASMA results were positive,

suggesting a final diagnosis of type 1 autoimmune hepatitis, without overlap. Otherwise, also in our case, the consistent presence of CD8 T-cells, not typical in a classic autoimmune hepatitis, may support the hypothesis that the SARS-CoV-2 virus triggers a specific CD8 T-cell immune response.

Although all pathophysiologic mechanisms of AIH are not fully understood, there is growing evidence that a genetic predisposition, molecular mimicry and an imbalance between effector and regulatory immunity in a particular autoimmune ecosystem are key pathologic factors for disease development.

Different viral agents have been identified as potential triggers for AIH[2]. However, data on specific liver inflammatory infiltrate in the case of AIH triggered by other viral infections are still lacking, so we are not able to perform a comparison with our case. Moreover, it is known that the association of autoimmune hepatitis with a viral aetiology is mostly prominent in autoimmune hepatitis type 2, usually characterised by anti-LKM-1 positivity[6], conversely to our patient.

CONCLUSION

In conclusion, we suggest that AIH triggered by SARS-CoV-2 infection may have a typical immune behaviour, quite similar to that described after COVID-19 vaccination, and differently from classical autoimmune forms.

We hope that further studies on large populations could better clarify the pathogenetic mechanisms underlying liver involvement in COVID disease, with a particular focus on immune reactions.

REFERENCES

1. Napodano C, Pocino K, Stefanile A, Marino M, Miele L, Gulli F et al. COVID-19 and hepatic involvement: the liver as a main actor of the pandemic novel. *Scand J Immunol* 2021;**93**:e12977.
2. Sucher E, Sucher R, Gradistanac T, Brandacher G, Schneeberger S, Berg T. Autoimmune hepatitis-immunologically triggered liver pathogenesis-diagnostic and therapeutic strategies. *J Immunol Res* 2019;**2019**:9437043.
3. Boettler T, Csernalabics B, Salié H, Luxenburger H, Wischer L, Salimi Alizei E, et al. SARS-CoV-2 vaccination can elicit a CD8 T-cell dominant hepatitis. *J Hepatol* 2022;**77**:653–659.
4. Lee SK, Kwon JH, Yoon N, Lee SH, Sung PS. Immune-mediated liver injury represented as overlap syndrome after SARS-CoV-2 vaccination. *J Hepatol* 2022;**77**:1209–1211.
5. Li H, Guan Y, Han C, Zhang Y, Liu Q, Wei W, et al. The pathogenesis, models and therapeutic advances of primary biliary cholangitis. *Biomed Pharmacother* 2021;**140**:111754.
6. Manns MP. Viruses and autoimmune liver disease. *Intervirology* 1993;**35**:108–115.