Autoimmune hepatitis with eosinophilic infiltration responsive to anti IL-5 Receptor treatment: a case report and literature review

Baglivo Ilaria[1], Ponziani Francesca Romana[1], Caruso Cristiano[1], Macagno Francesco[1], Gasbarrini Antonio[1], Santopaolo Francesco[1], Giustiniani Maria Cristina[1], Colantuono Stefania[1], and Pompili Maurizio[1]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS

January 30, 2024

Autoimmune hepatitis with eosinophilic infiltration responsive to anti IL-5 Receptor treatment: a case report and literature review

Ponziani Francesca Romana *[1], Caruso Cristiano*[2], Baglivo Ilaria[3°], Macagno Francesco[4], Gasbarrini Antonio[3], Santopaolo Francesco[1], Giustiniani Maria Cristina[5], Colantuono Stefania[2] and Pompili Maurizio[1]

1. Division of Internal Medicine and Gastroenterology, Hepatology Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
2. UOSD DH Internal Medicine and Gastroenterology, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
3. CEMAD Digestive Diseases Center, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
4. Complex Operational Unit of Pulmonology, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
5. Faculty of Medicine and Surgery, Institute of Pathological Anatomy, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.

* these authors equally contributed

° corresponding author

Keywords

Eosinophil; autoimmune hepatitis, severe eosinophilic asthma, interleukin-5, benralizumab.

Consent for publication

Informed consent was obtained from the patient to publish the case report along with all accompanying visual elements.

Conflict of interests

The authors declare that they have no conflict of interests.

Funding

No funding was obtained for this study.

Authors' contributions

FRP and MP made substantial contributions to the acquisition of data and analysis and interpretation of data and gave final approval for the version to be published. IB played a major role in the writing and design of the manuscript. CC, FM and FS analyzed and interpreted the immunological, pneumological and gastrointestinal data of the patient, respectively. MCG performed the histological examination of the liver. SC, AG and CC revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript, agree to be accountable for all aspects of the work, and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors' information

Francesca Romana Ponziani - email:*francesca.ponziani@gmail.com*

Cristiano Caruso - email:*carusocristiano1@gmail.com*

Ilaria Baglivo (corresponding author) - email:*ilaria.baglivo@outlook.it*; via Giuseppe Moscati, 31- 00168 Rome; Tel +39 329 4550061

Francesco Macagno - email:*francesco.macagno@policlinicogemelli.it*

Antonio Gasbarrini - email:*antonio.gasbarrini@policlinicogemelli.it*

Francesco Santopaolo - email:*francesco.santopaolo@policlinicogemelli.it*

Maria Cristina Giustiniani - email:*mariacristina.giustiniani@policlinicogemelli.it*

Stefania Colantuono - email:*stefania.colantuono@hotmail.it*

Maurizio Pompili - email:*maurizio.pompili@policlinicogemelli.it*

To the editor,

Inflammatory tissue damage plays a role in chronic autoimmune diseases (ADs): leaky intestinal barrier and gut dysbiosis contribute to disease onset, progression and exacerbation in diabetes, arthritis, ankylosing spondylitis, autoimmune hepatitis (AIH) and systemic lupus erythematosus (1).

AIH is a chronic immune-mediated inflammatory liver disease; the underlying pathogenetic mechanisms remain unclear, although it is known that both genetic and environmental factors are involved (2).

The continuous exposure of the liver to gut-derived antigens have an influence on both innate and adaptive immune responses. Moreover, the intestinal barrier disruption can trigger bacteria and bacterial products translocation with the activation of immune cells and the release of proinflammatory cytokines in the liver (3).

We describe the case of a 61-year-old woman with severe asthma in treatment with high doses of inhaled corticosteroids (ICS) and long-acting beta agonist (LABA), nasal polyposis, and chronic follicular gastritis who was admitted to our hospital because of acute abdominal pain 7 years ago.

Laboratory data revealed increased liver enzymes (ALT 465 UI/L), blood hypereosinophilia (3,320 cells/mmc), positive titer of antinuclear antibodies (ANA, 1:160) and anti-Liver-Kidney Microsomial antibodies (anti-LKM, 1:40); anti-neutrophil cytoplasmic antibodies (ANCA) were negative.

FIP1L1-PDGFRA fusion transcript was not found and parasitological infections were excluded.

The patient underwent liver biopsy which showed portal/periportal predominantly lymphohistiocytic infiltrate with associated Multiple Myeloma antigen 1 (MUM1) positive plasma cells, especially at the interface, with moderate eosinophilic granulocytosis, diffuse lymphocytic cholangitis, lobular hepatocytic pycnosis and necro-inflammatory foci (Fig.1).

Based on clinical, laboratory and histopathological data, the patient was diagnosed with type I autoimmune liver disease.

Immunosuppressive therapy with oral corticosteroid (OCS) prednisone 37.5 mg/day was started and, when biochemical response was obtained, therapy with azathioprine 100 mg/day was added. OCS therapy was tapered until discontinuation, and azathioprine was progressively reduced to 50 mg/day in the absence of episodes of biochemical reactivation. However, during the course of immunosuppressive therapy, the patient reported several episodes per year of abdominal pain.

In February 2021 the patient presented an episode of chest pain, so she was hospitalized and diagnosed with acute pericarditis. Infectious or autoimmune etiologies were excluded and the patient was successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs).

The administration of NSAIDs to treat pericarditis worsened asthma symptoms, so OCS therapy was re-started (prednisone 25 mg/day) and the patient needed more OCS pulses per year to reach the asthma symptoms control.

Taking into account the high rate of circulating and tissue eosinophils and the frequent asthma exacerbations which required OCS therapy, treatment with the monoclonal anti-interleukin-5 receptor (IL-5R) antibody benralizumab was started in September 2021 according to asthma schedule. Benralizumab is an IL-5R alpha-directed cytolytic monoclonal antibody which inhibits the maturation, activation, and survival of eosinophils, promoting eosinophil apoptosis. Benralizumab is indicated for the treatment of severe eosinophilic asthma uncontrolled with high doses of ICS/LABA, requiring OCS in add-on.

No consensus exists on how to reduce OCS after the initiation of biologics in severe asthma. The reduction of OCS dosages by 5 mg every 4 weeks, maintaining asthma control and adrenal function status, is suggested by recent evidence (4). A similar scheme was used in this case.

One year after starting benralizumab both respiratory and gastrointestinal symptoms were still well controlled.

In particular, from the first month of therapy, the patient presented improvement in dyspnea and reduction in wheezing episodes; no new asthma exacerbations occurred, no OCS therapy was required during the one-year period and the patient also reduced inhalation therapy without any worsening of asthma. Moreover, during the period of treatment with benralizumab, no new episodes of abdominal pain occurred. As expected, blood eosinophils were not detectable already after three months of therapy.

Forced expiratory volume in the first second (FEV1) value improved from 56% (pre-therapy) to 102% in September 2022; the fractional exhaled nitric oxide (FeNO) value was 18 ppb versus 47 ppb pre-therapy.

In October 2022 a new liver biopsy showed improvement in chronic AIH, compared to the previous biopsy. Although moderate lymphocytic inflammatory infiltrate in the portal spaces and focal interface hepatitis with mild fibrosis were present, no eosinophilic granulocytes and granulomas were detected (Fig.2).

Blood eosinophils were persistently undetectable and liver enzymes were in the normal range during periodic monitoring blood tests.

Therapy with benralizumab allowed the complete withdrawal of azathioprine with good control of autoimmune liver disease, which is currently in biochemical and histological remission.

No further episodes of pericarditis were reported.

Eosinophils have multiple homeostatic functions but they also can contribute to the tissue damage in ADs through different cellular mechanisms (5), playing a central role in the pathogenesis of asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic esophagitis, atopic dermatitis, eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES). More of these diseases are characterized by epithelial barrier damage: eosinophils secrete several cationic proteins that induce a decrease in the number of desmosomes and a loss of epithelial cells (6).

Although the benralizumab is extensively employed in eosinophilic asthma, this is, to our knowledge, the first case of AIH which has shown improvement after benralizumab treatment. The inhibition of the IL-5R

allows the decrease of both circulating and tissue eosinophils, for this reason, in this case, benralizumab was our therapeutic choice.

Currently, few cases of AIH presenting with peripheral blood eosinophilia isolated (7) or associated with other AD, such as EGPA (8), are reported.

The presence of inflammatory eosinophilic liver infiltrate associate with peripheral blood eosinophilia is described in sporadic cases of both acute and chronic hepatitis (9) and only in one other case of AIH (10).

In our case, the anti IL-5R therapy proved to reduce liver inflammation, with both clinical and histological improvement, in a patient with a poor clinical response to conventional immunosuppressants, confirming that eosinophils could have a central role in some cases of AIH.

The link between eosinophilic inflammation, barrier damage and development, or evolution, of chronic ADs is suggested by increasing clinical evidence and should be considered in clinical practice. In this context, the employment of anti-eosinophilic drugs could improve the clinical management and outcome of non-canonical type 2 diseases.

Legend to the Figures

Fig. 1. Pre anti IL-5R liver biopsy. (A) Hematoxylin-eosin 10X: A portal tract with heavy infiltrate of lymphocytes, plasma cells and eosinophils with interface hepatitis. (B) MUM1 20X: immunostain for MUM1 shows plasma cells in clusters at the interface region.

Fig. 2 . Post anti IL-5R liver biopsy. (A) Hematoxylin-eosin 10X: A portal tract with mild infiltrate of lymphocytes and plasma cells; no eosinophils are present. (B) Hematoxylin-eosin 20X: A portal tract with mild infiltrate of lymphocytes and plasma cells; no eosinophils are present.

List of abbreviations

Autoimmune diseases (ADs); autoimmune hepatitis (AIH); inhaled corticosteroids (ICS); long-acting beta agonist (LABA), antinuclear antibodies (ANA); anti-Liver-Kidney Microsomial antibodies (anti-LKM); anti-neutrophil cytoplasmic antibodies (ANCA); Multiple Myeloma antigen 1 (MUM1); oral corticosteroid (OCS); non-steroidal anti-inflammatory drugs (NSAIDs); interleukin-5 receptor (IL-5R); forced expiratory volume in the first second (FEV1); exhaled nitric oxide (FeNO); chronic rhinosinusitis with nasal polyps (CRSwNP); eosinophilic granulomatosis with polyangiitis (EGPA); hypereosinophilic syndrome (HES).

References

1. Mu Q, Kirby J, Reilly CM, Luo XM. Leaky Gut As a Danger Signal for Autoimmune Diseases. Front Immunol. 2017 May 23;8:598. doi: 10.3389/fimmu.2017.00598. PMID: 28588585; PMCID: PMC5440529. 2. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the study of liver diseases. Hepatology (2020) 72:671–722. doi: 10.1002/hep.31065. 3. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut (2019) 68:1516–26. doi: 10.1136/gutjnl-2019-318427. 4. Menzies-Gow A, Corren J, Bel EH, Maspero J, Heaney LG, Gurnell M, Wessman P, Martin UJ, Siddiqui S, Garcia Gil E. Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. ERJ Open Res. 2019 Sep 25;5(3):00009-2019. doi: 10.1183/23120541.00009-2019. PMID: 31579676; PMCID: PMC6759576. 5. Diny NL, Rose NR, Čiháková D. Eosinophils in Autoimmune Diseases. Front Immunol. 2017 Apr 27;8:484. doi: 10.3389/fimmu.2017.00484. PMID: 28496445; PMCID: PMC5406413. 6. Caruso C, Colantuono S, Ciasca G, Basile U, Di Santo R, Bagnasco D, Passalacqua G, Caminati M, Michele S, Senna G, Heffler E, Canonica GW, Crimi N, Intravaia R, De Corso E, Firinu D, Gasbarrini A, Del Giacco SR. Different aspects of severe asthma in real life: Role of Staphylococcus aureus enterotoxins and correlation to comorbidities and disease severity. Allergy. 2022 Aug 3. doi: 10.1111/all.15466. Epub ahead of print. PMID: 35922152. 7. Nardelli MJ, Cançado GGL, Naves GNT, Vidigal PVT, Couto CA. Autoimmune hepatitis presenting with peripheral eosinophilia: Case report and literature review. Transpl Immunol. 2022 Oct;74:101671. doi: 10.1016/j.trim.2022.101671. Epub 2022 Jul 13. PMID: 35842079. 8. S. Lohani, S.

Nazir, N. Tachamo, P. Pagolu, Autoimmune hepatitis and eosinophilic granulomatosis with polyangiitis: a rare association, BMJ Case Rep. 2017 (2017), https://doi.org/10.1136/bcr-2016-218385 bcr2016218385. 9. L. Van Overbeke, H. Van Dijck, Idiopathic acute eosinophilic hepatitis : does it exists ? Acta Gastroenterol. Belg. 78 (2015) 65–68. 10. Garrido I, Lopes S, Fonseca E, Carneiro F, Macedo G. Autoimmune hepatitis and eosinophilia: A rare case report. World J Hepatol. 2023 Feb 27;15(2):311-317. doi: 10.4254/wjh.v15.i2.311. PMID: 36926232; PMCID: PMC10011904.

Hosted file

`figure_1.pptx` available at https://authorea.com/users/723977/articles/708227-autoimmune-hepatitis-with-eosinophilic-infiltration-responsive-to-anti-il-5-receptor-treatment-a-case-report-and-literature-review

Hosted file

`figure_2.pptx` available at https://authorea.com/users/723977/articles/708227-autoimmune-hepatitis-with-eosinophilic-infiltration-responsive-to-anti-il-5-receptor-treatment-a-case-report-and-literature-review