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

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ABSTRACT

Inflammatory tissue damage plays a role in the onset, progression, and exacerbation of various chronic autoimmune and metabolic diseases such as autoimmune hepatitis. Here we present a case of autoimmune hepatitis with liver eosinophilic infiltrate in a severe eosinophilic asthma patient who failed conventional immunosuppressive treatment and showed improvement in gastrointestinal symptoms after anti-interleukin-5 receptor treatment. Our case highlights the potential role of eosinophils in initiating or worsening liver inflammation in autoimmune liver disease. The link between eosinophilic inflammation, barrier damage, and chronic autoimmune diseases should be considered in clinical practice.

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Introduction

Inflammatory tissue damage plays a role in chronic autoimmune and metabolic diseases: leaky intestinal barrier and gut dysbiosis contribute to disease onset, progression, and exacerbation in diabetes, obesity, arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune hepatitis, and systemic lupus erythematosus.[1]

Autoimmune hepatitis (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 has an influence on both innate and adaptive immune responses. Moreover, the intestinal barrier disruption can trigger bacteria and bacterial product translocation with the activation of immune cells and the release of proinflammatory cytokines and chemokines in the liver.[3]

Case report

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), a positive titer of antinuclear antibodies (ANA, 1:160) and anti-Liver-Kidney Microsomal antibodies (anti-LKM, 1:40); anti-neutrophil cytoplasmic antibodies were negative.

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

The patient underwent a liver biopsy which showed portal/periportal predominantly lymphohistiocytic infiltrate with associated multiple myeloma antigen 1 positive plasma cells, especially at the interface, with moderate eosinophilic granulocytosis, diffuse lymphocytic cholangitis, lobular hepatocytic pycnosis and necro-inflammatory foci (Figure 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 a 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 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 restarted (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. IL-5R is expressed by eosinophils and basophils. Benralizumab inhibits the growth, maturation, activation, and survival of eosinophils, promoting eosinophil apoptosis and it 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, the blood eosinophils count was not detectable already after three months of therapy.

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

In October 2022 the patient underwent a new liver biopsy which showed improvement in chronic autoimmune hepatitis 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 (Figure 2). Blood eosinophils were persistently undetectable and liver en-

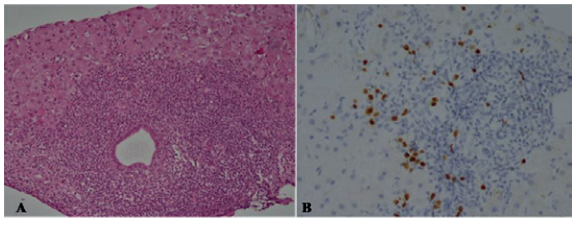

Figure 1. Pre-anti-interleukin-5 receptor liver biopsy. A) Hematoxylin-eosin 10´: A portal tract with a heavy infiltrate of lymphocytes, plasma cells, and eosinophils with interface hepatitis; B) Multiple myeloma antigen 1 20´: immunostain for multiple myeloma antigen 1 shows plasma cells in clusters at the interface region.

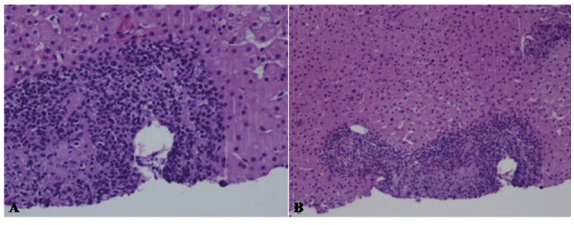

Figure 2. Post-anti-interleukin-5 receptor liver biopsy. A) Hematoxylin-eosin 10´: a portal tract with a mild infiltrate of lymphocytes and plasma cells; no eosinophils are present; B) Hematoxylin-eosin 20´: a portal tract with a mild infiltrate of lymphocytes and plasma cells; no eosinophils are present.

zymes were in the normal range during periodic monitoring blood tests.

Therapy with benralizumab allowed the complete withdrawal of immunosuppressive therapy with azathioprine with good control of autoimmune liver disease, which is currently in biochemical and histological remission. No further episodes of pericarditis were reported.

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

Discussion

Eosinophils have multiple homeostatic functions, but they also can contribute to tissue damage in autoimmune diseases by antibody-dependent cellular cytotoxicity, profibrotic action, and antigen presentation to T cells.[5]

Eosinophils can be detected in peripheral blood and also infiltrate tissues. This cellular type plays a central role in the pathogenesis of different inflammatory and autoimmune diseases rather than asthma, including 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 employment of benralizumab in eosinophilic asthma is extensive and evidence of efficacy is available in CRSwNP, EGPA, and HES, this is, to our knowledge, the first case of AIH that 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 are reported, presenting with peripheral blood eosinophilia usually associated with other autoimmune conditions, such as EGPA,[7] although cases of AIH with isolated peripheral blood eosinophilia are also described.[8]

The presence of an inflammatory eosinophilic liver infiltrate associated with peripheral blood eosinophilia is described in not many cases of both acute and chronic hepatitis,[9] while only one case concerning AIH in a patient with Crohn's disease has been described.[10]

The role of both peripheral and tissue eosinophils in the pathogenesis of AIH is still unclear; in eosinophil-related autoimmune diseases peripheral eosinophilia could precede the tissue infiltration; however, eosinophilic organ infiltration seems to characterize the early stage of the disease so, in advanced stages, eosinophils could be undetected at biopsy samples.[5]

In our case, the anti-IL-5R therapy proved to be effective in reducing liver inflammation, with improvement in both clinical and histological features. Our patient had shown a poor clinical response to conventional immunosuppressants while the use of benralizumab led to the depletion of the proportion of eosinophils infiltrating the liver which could have initiated, or worsened, liver inflammation.

Conclusions

Currently, although there is no evidence of the use of anti-eosinophilic drugs in autoimmune inflammatory diseases that appear to be not responsive to conventional immunosuppressive therapy, the response to anti-IL5R therapy observed in our case confirms that eosinophils could have a central role in AIH.

The link between eosinophilic inflammation, barrier damage, and the development or evolution of chronic autoimmune diseases 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.

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