Idiopathic acute eosinophilic hepatitis : does it exists ?

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Abstract

Until now, "eosinophilic hepatitis" has not been recognized as a separate disease entity. We report a case of a middle-aged women with an acute febrile, severe cholestatic hepatitis accompanied with rash and quincke oedema, and an elevated serum IgE level. Liver biopsy showed lymphocytic inflammation with a remarkably high number of eosinophils. She responded rapidly to methylprednisolone treatment, which could be quickly tapered off and stopped without relapse. The term 'idiopathic acute eosinophilic hepatitis' seems to be the best fitting diagnostic term. (Acta gastroenterol. belg., **2015**, 78, **65-68**).

Key words : hepatitis, eosinophil, Ig E, rash, febrile, cholestatic, steroid.

Introduction

In recent years, there is an emerging interest in eosinophilic inflammation and resulting organ injury. Eosinophilic inflammation has been recognized as a real pathologic concern and a cause for disease in most organ systems : eosinophilic esophagitis, pneumonia (idiopathic acute and chronic), enteritis, colitis, gastritis, fasciitis and cystitis have been described. Only the liver seems to be spared of that type of eosinophilic inflammation, at least in medical literature. It is difficult to explain this phenomenon. We hypothesize that eosinophilic hepatitis does exist, but currently most patients are classified as autoimmune hepatitis and treated with long-term immunosuppression which may be unnecessary ; or are classified as drug induced liver injury (DILI) possibly leading to unnecessary cessation of important medication.

Case report

A 44-year- old woman was referred to our outpatient clinic in December 2011 due to nausea, vomiting and jaundice. She had been well until 7 days earlier, when she noticed an itching rash on her arms and chest, and a swollen lip (quincke oedema). At that moment, she was also febrile (> 39°C). There were no pain episodes.

She had a history of a surgical abdominal intervention in 2000 – presumably for diverticulitis. She was a schoolteacher. She was not known with allergic tendencies. Her sister suffered a congenital muscular disorder (fasciloscapulo humeral dystrophia). She took no medication or herbal medicine, besides paracetamol during the last few days (max 3 g a day) and onetime use of an antihistamine (levocetirisine) one week before presentation for the itching rash. Alcohol use was sporadic. She had a dog. She went on holiday to Senegal in 2006, and to the dominican republic in 2007 and 2008.

On examination the temperature was normal. The icterus was still present while the rash had totally disappeared. There were no adenopathy's. Abdominal examination was normal.

The laboratory values of the liver enzymes are summarized in table 1. PT (INR) and albumin were normal. There was a normal complete blood count and differentiation, normal renal function and electrolyte levels. Screening for known causes of hepatitis was negative (positive vaccination status for HAV/HBV, HCV-HEV-EBV-CMV-HSV were negative, ANCA negative, ANF-AMA-LKM-SMA negative, normal Ig G (12.34 g/l) and Ig G4, normal a1-antitrypsine and Cu/ceruloplasmine). Serum tryptase and C1-esterase inhibitor were normal. Serology for toxocara and strongyloides was negative. Abdominal ultrasound showed a moderately enlarged spleen (diameter 13 cm) while the liver parenchyma was normal (no biliary duct dilatation, normal portal and sushepatic flow, no ascites). MRCP showed a normal biliary tree.

During the following two weeks, liver enzyme tests continued to deteriorate (Table 1) and the patient noticed an itching rash, spontaneously resolving in a few hours (and never seen on consultation) on several occasions. PT (INR) remained stable and there were no signs of encephalopathy. Because of the deterioration and to rule out autoimmune hepatitis (repeat ANF was positive with a titer of 1/160) a percutaneous liver biopsy was performed (Fig. 1). The liver biopsy specimen was deemed adequate for diagnostic purposes. It showed an important portitis and interface hepatitis, the inflammation was lymphocytic with a few plasmocytes and a remarkable number of eosinophils (up to 10 eosinophilic granulocytes per portal tract).

The pathological conclusion was : "toxic or drug-induced hepatitis, with differential diagnosis of autoimmune hepatitis" Bone marrow examination (to exclude hypereosinophilic syndrome or lymphoma) was normal.

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Table 1. — **Laboratory data**

Weeks from presentation	W0	W2	Start steroids	W3	W4	W6	Reference range
Bilirubine (mg/dL)	3,6	30,7		16,5	6,5	2,4	< 0,9
GOT (U/L)	837	1356		342	105	25	< 31
GPT (U/L)	1082	1438		535	268	36	< 33
LDH (U/L)	444	439		281	307	341	< 480
gGT (U/L)	332	236		546	434	144	< 35
AF (U/L)	295	231		218	147	88	< 104 U/L

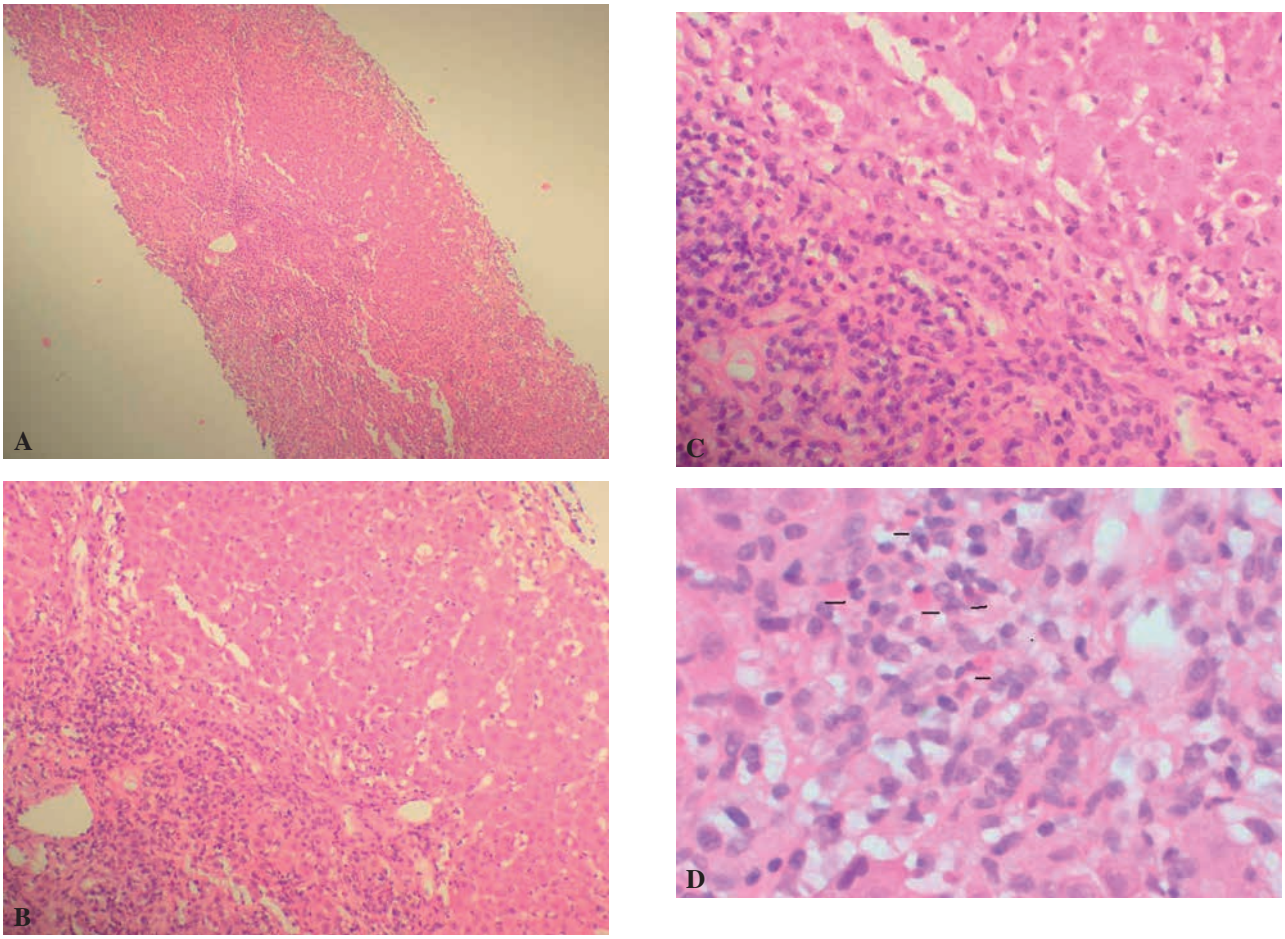

Fig. 1. — Liverbiopsy. Hematoxylin and eosin. [A] original magnification : 40×. Preserved architecture with in the middle an enlarged portal tract. [B] original magnification 100×. At the edge of the portal tract, a dense inflammatory infiltrate obscuring the interface. [C and D] original magnification : 400×. This infiltrate is mixed with lymphocytes, neutrophils and several scattered eosinophils (black lines). There is also a moderate number of plasmocytes, a few of them with positive Ig G4 -staining.

Oral treatment with methylprednisolone 32 mg a day was started on day 19, leading to a dramatic improvement in symptoms and lab results (Table 1). Steroids were tapered and stopped on week 12 after presentation. Bilirubin normalised and the transaminases remained normal (last follow-up consultation on week 50). Ig G level after resolution of the hepatitis, remained a normal value (9.76 g/l). The following years, her physician monitored the liver enzymes without new events (making the follow-up almost 3 years). Two years after the hepatitis event, she took again levocetirisine for itching (without rash), under close monitoring of the liver enzymes which remained normal.

Discussion

We report a case of a middle-aged women with an acute febrile, severe cholestatic hepatitis accompanied with rash, quincke oedema, and splenomegaly. There were no biliary abnormalities. Liver biopsy showed lymphocytic inflammation with a high number of eosinophils. After having ruled out viral hepatitis, we performed

a bone marrow examination to exclude myeloproliferative disorders. Hypereosinophilic syndrome (HES) – defined as a hypereosinophilic state (a persistent peripheral eosinophil count exceeding 1.5 x 10^9/L blood) associated with HE-induced organ damage (1) – was another possibility. In our patient, the criteria for HES were not met. The association of hepatitis and allergic-like symptoms, raised the possibility of systemic mastocytosis, which was ruled out by the normal serum tryptase and bone marrow examination. Drug hypersensitivity was also a differential diagnosis. Our patient took no medications or herbal preparations previously associated with drug- induced liver injury (DILI) besides onetime use of an antihistamine (levocetirisine) one week before presentation for the itching rash, probably a symptom of her disease. In addition, a re-challenge two years later was uneventful. Parasitic infection of the liver parenchyma (without biliary involvement) was another concern, in particular toxocara (visceral larva migrans) – having a dog as pet – and strongyloides – having travelled to (sub)tropical regions. Serology for toxocara and strongyloides was negative. The most important differential diagnosis is autoimmune hepatitis, since liver biopsy in patients with autoimmune hepatitis can also reveal eosinophils (2). The Revised Scoring System of the International Autoimmune Hepatitis Group gives a value of 17 pre-treatment (> 15 : definite diagnosis) and 19 post treatment (> 17 : definite diagnosis) (3). Because of the suspicion of autoimmune hepatitis, we started treatment with oral methylprednisolon 32 mg a day as a diagnostic tool, with rapid response. Nevertheless we doubted the diagnosis of AIH on the basis of normal Ig G levels and no other autoimmune parameters, so we chose to taper and to stop steroid treatment very quickly. No relapse was seen, which is an argument against classical auto-immune hepatitis. Indeed, relapse is the signature of autoimmune hepatitis, even after prolonged immunosuppressive therapy (4). The Ig G level did not change significantly after treatment ; as normal values of Ig G in autoimmune hepatitis can still fall to what is the normal low level of a particular patient.

For most organs, there is a recognised description of 'eosinophilic …-itis' : eosinophilic esophagitis, pneumonia (idiopathic acute and chronic), enteritis, colitis, gastritis, fasciitis, meningitis, cystitis... It is striking that 'Eosinophilic hepatitis' as such, has never been described. Could we classify this case as eosinophilic hepatitis ?

In general, the definition of 'eosinophilic …-itis' contains three components : symptomatic disease, presence of an abnormally high amount of eosinophils in tissue biopsies and absence of other known causes of eosinophilia. In our case, the first two requirements were fulfilled : there was symptomatic disease and liver biopsy showed lymphocytic inflammation with an unusually high number of eosinophils. The eosinophils were not as abundantly present as described in some other types of eosinophilic inflammation, for instance eosinophilic esophagitis. It is important to realise that eosinophils are nonspecific amplifiers and effectors of a specific immune response. Infiltrates in other types of eosinophilic -itis are typically composed of different types of immune cells and injury results from all of these cells, rather than from the eosinophils alone.

As discussed, all efforts were made to exclude other known causes of eosinophilia.

This case shares many similarities with "immune-mediated DILI" characterized by (possibly) eosinophilia and rash, good response to steroids and maintained remission after successful withdrawal of steroids (5). One hypothesis of this immune mechanism is the hapten hypothesis. Drugs or their metabolites can act as haptens and covalently bind to liver proteins, such as cytochrome P450 (CYP) enzymes, to form drug-protein products, which can elicit an immune response (or overcome immune tolerance, which is the dominant type of immune response in the liver) (6). It seems plausible that other molecules than drug or herbs can illicit this reaction. However, the pathological diagnosis of 'toxic or drug-induced liver injury' has only the 'drug-induced liver injury' as clinical correlate. The reaction of the immune system to normally harmless substances in the environment, is in fact an allergic reaction by definition. This mechanism may offer an explanation for the physiopathology of eosinophilic hepatitis.

So the patient's condition seems to fulfil the three requirements to fit a possible definition of eosinophilic hepatitis. This term was already proposed by Omata *et al*. in the description of a case of a patient with known asthma, drug allergy and eosinophilia. In this case, there was a course of relapses when the steroids were tapered and 6-mercaptopurine had to be given as maintenance therapy (7) – unlike in our case.

The case described in this paper fits a definition of 'idiopathic acute eosinophilic hepatitis', with febrile disease at onset, rash and rapidly evolving hepatitis, without underlying conditions or known atopy. It shares many similarities with idiopathic acute eosinophilic pneumonia which is defined be a rapid onset with febrile disease, severe disease with hypoxemic respiratory failure, a high number of eosinophils in the BAL fluid, the possibility of absence of peripheral eosinophilia, and the absence of relapse after a short course of steroid treatment (8). As stated above, an allergic aetiology, similar to immune-mediated DILI, may begin to explain the pathogenesis.

It is important to consider this diagnosis and to differentiate it from classical autoimmune hepatitis, which requires chronic immunosuppression. It seems also very difficult to distinguish this entity from DILI, if a patient has taken medication or herbs and if there is no close time-frame.

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