Can ANCA differentiate eosinophilic granulomatosis with polyangiitis (Churg-Strauss) from idiopathic hypereosinophilic syndrome?

Sirs,

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) is a rare systemic vasculitis strongly associated with asthma and hypereosinophilia (1). Vasculitis can be proven by biopsy in roughly 25% of patients (2). Hence, clinical surrogates for vasculitis such as palpable purpura and alveolar haemorrhage are frequently used to diagnose EGPA. ANCA, especially targeting myeloperoxidase, may probably be accepted as an immunological surrogate marker for vasculitis in hypereosinophilic syndrome patients. However, a substantial diagnostic uncertainty remains especially when considering idiopathic hypereosinophilic syndrome (iHES) as differential diagnosis (3). We present here a case of a patient with iHES associated with ANCA without clinical or histological evidence of EGPA.

A 30 year old female patient was admitted to our hospital in April 2009. Eight months earlier, the patient suddenly developed recurrent pasty diarrhoea up to 4 times daily. Lactose and fructose intolerance, food allergy and parasitic infection had been excluded. The patient had a history of nasal polyposis in childhood, but no asthma. Four months earlier, the general practitioner recognised elevated liver enzymes. In addition to this, the patient noted recurrent joint pain in large and small joints without obvious swelling. One month before admission, a major increase in peripheral blood eosinophils was noted. A haematological consultation excluded clonal disorders after bone marrow biopsy and immune phenotyping of peripheral blood and the patient was referred to the rheumatology department for further evaluation.

The patient presented in good condition but reported fatigue and recurrent joint pain. Clinical examination revealed no swollen but 6 tender joints but was otherwise inconspicuous. Blood tests (Table I) revealed highly increased blood eosinophils (18560/µl), normal platelet count and mild normocytic anemia (haemoglobin 11,1 g/dl). Liver enzymes were highly elevated, with no indication of viral hepatitis in the serological tests. Total IgG levels were highly elevated, but IgG4 was not predominant. Autoantibody testing revealed positive rheumatoid factor, negative anti- nuclear antibodies and lack of autoantibodies associated with autoimmune hepatitis. However, ANCA testing showed positive perinuclear and cytoplasmic ANCA. ELISA testing to identify the responsible autoantigens revealed positive MPO-ANCA and PR3-ANCA, while autoantibodies to bactericidal/permability increasing protein, elastase, cathepsin G, lactoferrin were not detected. These results were confirmed by a reference laboratory (Euroimmun, Lübeck, Germany).

Colonoscopy with multiple biopsies was performed and revealed mild non-classifiable colitis with marked tissue eosinophilia but no vasculitic changes. Abdominal ultrasound and MR-cholangiography excluded bile stones and luminal changes in the large bile ducts. Liver biopsy showed lymphoplasmacellular portal tract inflammation with marked eosinophilic infiltration as well as portal and interstitial liver fibrosis and fibrosis surrounding the bile ducts. There were no vasculitic lesions observed. These findings were consistent with eosinophilic cholangiopathy (4). Considering the

Table I. Laboratory Data.

Variable	Reference range	At admission
Haemoglobin (g/dl)	12–16	11.1
White blood cell count (x 10^3/µl)	4–10	29
Differential count		
Neutrophils (%)	50–70	23
Lymphocytes (%)	25–40	9
Monocytes (%)	2–8	3
Eosinophils (%)	2–4	64
Platelet count (x 10^3/µl)	140–400	274
C-reactive protein (mg/l)	0–5	18
Creatinine (mg/dl)	- <1.00	0.66
Aspartate transaminase (U/L)	- <35	134
Alanine aminotransferase (U/L)	- <35	204
Alkaline phosphatase (U/L)	35–105	402
Gamma glutamyl transpeptidase (U/L)	- <40	275
Total bilirubin (mg/dl)	0–1.1	1.0
Immunoglobulin G (mg/dl)	751–1580	5030
Immunoglobulin E (U/ml)	0–100	1227
Anti-nuclear antibodies	Negative	Negative
c-ANCA IgG (IFT)	Negative	1:10
p-ANCA IgG (IFT)	Negative	1:1000
PR3-ANCA (U/ml)	0–6	11.1
MPO-ANCA (U/ml)	0–6	9

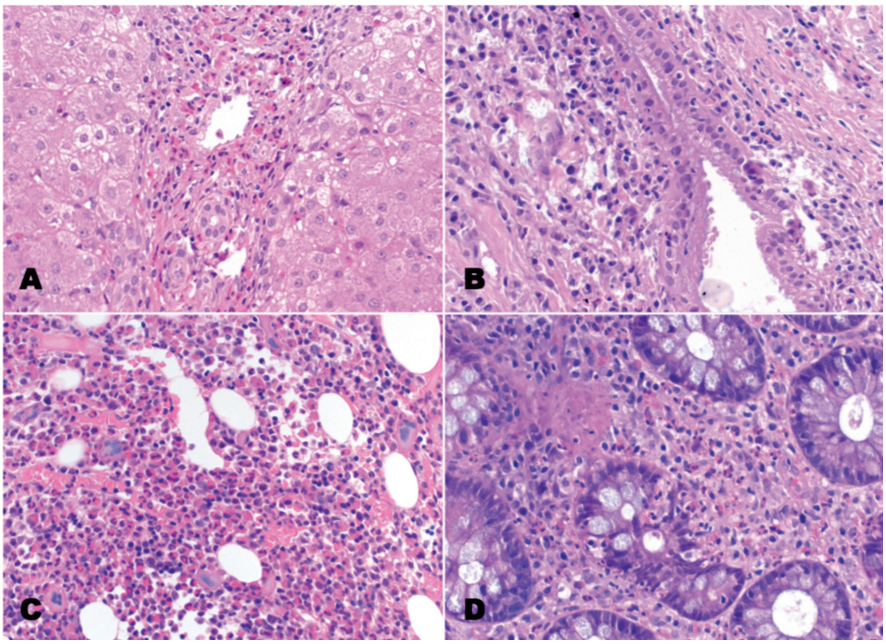

Fig. 1. Histologic findings in an idiopathic hypereosinophilic syndrome (HES) patient with positive ANCA. (**A**, **B**) Liver biopsy with dense portal tract infiltration by eosinophils. Small bile ducts show reactive changes (**A**) and a larger bile duct presents with intraepithelial infiltration by eosinophils (**B**) consistent with eosinophilic cholangiopathy (HE stain, 400x). (**C**) Bone marrow biopsy with marked eosinophilia (HE stain 400x). (**D**) Colonic biopsies with markedly increased numbers of eosinophils in the mucosa and focal intraepithelial infiltration (HE stain, 400x).

clinical presentation, organ manifestations and histologic changes we diagnosed iHES and started prednisone therapy (60mg/day). The patient responded well but soon relapsed when prednisone was tapered below 20mg per day. Following the addition of azathioprine (200mg/d) and after a switch from prednisone to budesonide (9mg/d), the patient remains now in clinical remission three years after diagnosis. ANCA were detectable for several months but became negative during longer follow-up.

ANCA, mainly targeting myeloperoxidase, are found in about one third of EGPA patients (5-8). The presence of ANCA is therefore often used as additional surrogate for EGPA but its value for differential diagnosis is not proven. In fact, we could not identify a single study on the prevalence of ANCA in iHES. We present here a case that is typical for iHES. The absence of asthma, sinusitis and the lack of vasculitis in multiple biopsies make EGPA extremely unlikely in this patient. However, the patient clearly had detectable ANCA targeting myeloperoxidase and proteinase-3. Dual ANCA positivity, although rare, may occur in systemic vasculitides as well as infectious diseases (9, 10). Overall, it remains questionable whether ANCA can indeed differentiate between EGPA and iHES.

Current treatments options are largely overlapping in EGPA and HES. Nevertheless, correct classification is important as (i) uncertainty in diagnosis is sometimes difficult to handle for patients and referring physicians, (ii) disease course in HES may differ substantially from EGPA and (iii) future treatment may change for both subsets of hypereosinophilic disorders (11). Systematic studies such as the ongoing DCVAS study are warranted to clarify this clinically relevant question (12).

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