CASE REPORT

Ascites in a patient with episodic angio-oedema and eosinophilia: thinking outside the box

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SUMMARY

Episodic angio-oedema with eosinophilia (EAE) or Gleich's syndrome is a rare condition characterised by recurrent episodes of oedema and eosinophilia, accompanied by urticaria, fever and weight gain. The presence of ascites has not been reported so far. We report a 21-year-old Caucasian woman who presented with marked ocular oedema and ascites. Laboratory evaluation revealed marked eosinophilia. During the last 3 months, three episodes of facial and neck oedema were reported, which resolved spontaneously over a period of 3–5 days. The diagnosis of EAE was established after exclusion of secondary causes (infections, allergic reactions, collagen diseases, neoplasms) and clonal disorders associated with marked eosinophilia. Low-dose steroids resulted in eosinophil decrease and complete resolution of symptoms, including ascites. This case highlights that ascites can be a very rare manifestation of EAE particularly if other more frequent causes of ascites have been excluded and the clinical and laboratory findings are supportive of EAE.

BACKGROUND

Episodic angio-oedema with eosinophilia (EAE), also known as Gleich's syndrome is a rare condition encompassing recurrent episodes of oedema and eosinophilia and is often associated with urticaria, fever and weight gain.¹ Characteristic features of the disease are oedema involving mainly the face and extremities, while rare manifestations have been described as part of this syndrome. To our knowledge, this is the first case of ascites reported so far among patients with EAE at least in Europe and the Americas. Distinction from other causes of hypereosinophilic syndromes (HES) is of outmost importance, since EAE does not affect usually vital organs, carries a good prognosis and has often a self-limiting course and a favourable response to steroid treatment.² However, long-term follow-up of these patients is recommended as endomyocardial involvement has been reported in a patient with EAE 16 years after the initial diagnosis,³ while some patients may develop clonal T cell populations that can progress to lymphocytic variant of HES.⁴

CASE PRESENTATION

A 21-year-old Caucasian woman was admitted to the Department of Medicine because of a 2-day history of marked bilateral, non-pitting ocular oedema with a tendency of spreading to the parotid area. The patient also presented with umbilical abdominal

pain and considerable abdominal distension. No skin lesions (erythematous papules, nodules or blistering areas) had been noticed. During the last 3 months, she reported three episodes of facial and neck oedema, which resolved spontaneously after 3–5 days. Her medical history was unremarkable apart from occasional episodes of allergic rhinitis and bronchial asthma. Nine months ago, she reported a severe attack of bronchial asthma, which required inhaled corticosteroids for few days. She had no history of alcohol or drug abuse. Her family history was unremarkable while the patient denied ever any travel to abroad. Physical examination on admission revealed the characteristic non-pitting, bilateral ocular oedema and abdominal distension without any other abnormal findings.

INVESTIGATIONS

The initial laboratory work-up (abnormal values) was as follows: white cell count (11x10⁹/L) with remarkable eosinophilia (absolute number of eosinophils: 3.3x10⁹/L), albumin 2.6 g/dL, fibrinogen 136 mg/dL and low C₃ and C₄ complement components (69 mg/dL and 5.5 mg/dL, respectively). The remaining haematological, microbiological, virological and biochemical parameters including liver function tests, blood, stools, urine and bone marrow cultures and investigation for viral hepatitis A, B and C and other viruses, tuberculosis, brucellosis, leptospirosis, leishmaniasis and other parasites including serological investigation for *Trichinella*, *Entamoeba* and *Echinococcus*, autoantibodies related to autoimmune rheumatic diseases including antineutrophil cytoplasmic antibodies, serum IgG, IgA, IgM, rheumatoid factors, erythrocyte sedimentation rate, C reactive protein, cryoglobulins and ferritin levels were within normal limits. Multiple stool samples were also negative for ova and parasites like *Enterobius vermicularis*, *Entamoeba histolytica*, *Cryptosporidium* and *Giardia* sp. Chest X-ray and echocardiogram were also unrevealing. However, abdominal ultrasound demonstrated the presence of ascites. Glomerular filtration rate was unaffected and protein determination after 24 hours urine collection was also normal (25 mg/24 hours).

During work-up, common causes of peripheral eosinophilia, including allergic reactions, infections, autoimmune rheumatic diseases and autoimmune cholestatic diseases like primary biliary cholangitis⁵ were appropriately ruled out. According to the patient history, there was no correlation between ingestion of a specific food or medication and the

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Figure 1 Bone marrow biopsy examination revealed hyperplastic marrow with eosinophilia and increased polymorphonuclear leucocytes.

appearance of symptoms. Taking into account the low C_4 serum levels, testing for the determination of serum C_{1q} , C_1 -esterase inhibitor and functional C_{1q} -esterase inhibitor was performed which was found within normal limits, excluding hereditary or acquired angio-oedema. CT of the neck, chest and abdomen showed no evidence of malignancy or enlarged lymph nodes. A bone marrow examination showed marked infiltration with mature eosinophils (figure 1). In order to investigate for primary (clonal) eosinophilia in the spectrum of HES, we proceeded to screening for the fusion gene *FIP1-like 1/platelet-derived growth factor receptor alpha* (*FIP1L-PDGFR*) by fluorescence in situ hybridisation (FISH), which was negative.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of marked eosinophilia ($>1.5 \times 10^9/L$) encompasses a wide spectrum of disease entities, including reactive causes (parasitic infections, allergic reactions, neoplasias, collagen vascular diseases) and primary (clonal) eosinophilia associated with molecular abnormalities. The assessment of these patients should be performed according to the appropriate clinical context. In our case, taking carefully into account the previous history of the patient, a diagnosis of EAE was made based on the typical presentation of the disease (recurrent episodes of angio-oedema on the face of self-limiting course) accompanied by eosinophilia, the absence of vital organ involvement and the absence of other causes of marked eosinophilia after a thorough investigation.

TREATMENT

After the diagnosis of EAE (Gleich's syndrome) was established, prednisolone was administered orally (initial dose: 0.5 mg/body weight/day). It is worthy to state here that no antiparasitic treatment like ivermectin has been administered to the patient empirically as first, Greece is a country of extremely low incidence

of specific parasitic infections (eg, ascariasis, strongyloides and schistosoma) and second, the presence of other parasites had been appropriately excluded.

OUTCOME AND FOLLOW-UP

During the first 8 days of treatment, the patient showed a remarkable response demonstrating a sharp decrease of eosinophil levels (from $3.3 \times 10^9/L$ on admission to $1.7 \times 10^9/L$) and complete resolution of oedema with a 5 kg weight loss. Also the concentrations of C_3 and C_4 complement components were normalised. At this point, a repeat ultrasound of the abdomen failed to demonstrate the presence of ascites. She was discharged in a very good health with the instruction of prednisolone tapering by 5 mg every 15 days. One month later, eosinophil count was normal ($0.2 \times 10^9/L$). However, 2 months later from her discharge, she was readmitted to our department due to a new episode of neck oedema. Her body weight was increased again by 4.5 kg since her discharge and eosinophil count was again increased ($2 \times 10^9/L$). In this second admission, C_3 and C_4 complement components were within normal limits. Prednisolone was initiated at the same dose (25 mg/day) and she discharged 4 days later with considerable improvement of oedema (weight loss of 2.6 kg) and decrease of peripheral eosinophilia ($1.2 \times 10^9/L$). A slower tapering schedule of prednisolone was now advised (2.5 mg every 15 days). So far, 1 year after discontinuation of steroids, the patient remains asymptomatic with normal eosinophil count.

DISCUSSION

The following major point has been raised from the present case: ascites can be a very rare component of EAE. To our knowledge, this is the first reported case of EAE accompanied by ascites in the PubMed literature so far. Therefore, clinicians should be aware and should be keeping in mind this extremely rare EAE component in particular when numerous other more frequent

causes of ascites have been excluded. Hereditary or acquired angio-oedema could also be presented with abdominal cell wall thickening or ascites as a consequence of fluid accumulation.⁶ However, determination of serum C_{1q} , C_1 -esterase inhibitor and functional C_{1q} -esterase inhibitor usually distinguishes quite easily hereditary or acquired angio-oedema from EAE especially when C_4 complement component is low as in our case since low complement concentrations are not usually expected in EAE.¹

EAE was first described in 1984, and even though it is often classified in the broad category of idiopathic HES, it is considered a separate entity, mainly based on the absence of systemic involvement and particularly of cardiac disease in most of cases so far.⁷ Since then, several cases of EAE have been reported.

The manifestation of this entity is quite homogenous, pointing towards a common aetiology in affected patients. Even though the pathogenesis of EAE is not clear, it is considered a cell cycling disorder. Recently, it was demonstrated that apart from eosinophils, multiple lineage cycling, including lymphocytes and neutrophils are involved and may contribute to disease pathogenesis. Several studies have shown an aberrant CD3-CD4+ T cell population with clonal rearrangement in some of these patients. A peak of T helper 2 serum cytokines like interleukin 5⁸ has been detected prior to the onset of symptoms and eosinophil cycling that correspond to intracellular cytokines inside CD3+CD4+CD154+ T cells.⁹

Most cases of angio-oedema associated with eosinophilia up to now have been reported in Japan and Southeast Asia and have been classified as non-episodic angio-oedema with eosinophilia (NEAE), based on the transient appearance of symptoms.^{10 11} Even though NEAE was regarded as distinct disease, similarities in the clinical presentation and response to corticosteroids suggest rather a milder form of EAE, with often absence of constitutional symptoms and normal IgM levels.¹²

In conclusion, EAE is a rare entity, usually presenting with typical symptoms. However, our case highlights that ascites can be a very rare manifestation of EAE suggesting that EAE might be included in its differential diagnosis in particular if other more frequent causes of ascites have been appropriately excluded and the clinical and laboratory findings are supportive of EAE.

Contributors GND and EIR had the original idea, designed the study and wrote the first draft of the manuscript. GND and GP were the principal treating physicians of the patient. EIR, GP and GND collected and summarised the published literature and data of the patient. MI made the pathological analysis and diagnosis. GND made the final critical revision of the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Learning points

- Episodic angio-oedema with eosinophilia (EAE), even though classified in the broad category of idiopathic hypereosinophilic syndrome, is considered a separate entity based on the absence of systemic involvement and the excellent response to steroid treatment.
- EAE presents with typical features including recurrent episodes of oedema and eosinophilia, often accompanied by urticaria, fever and weight gain.
- Our case highlights that physicians must keep in mind that ascites can be a very rare component of EAE in particular when other numerous more frequent causes of ascites have been excluded and the underlying clinical signs and symptoms along with the haematological investigations are typical of EAE.

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