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Brief Clinical Observation

Eosinophilic esophagitis is a component of the anticonvulsant hypersensitivity syndrome: Description of two cases

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Abstract

Anticonvulsant hypersensitivity syndrome is a rare syndrome caused by a specific, severe unusual reaction to antiepileptic agents; anticonvulsant hypersensitivity syndrome develops 1 week to 3 months after the introduction of the drug and most frequently consists of a multisystemic and multiorgan involvement. Drug withdrawal usually leads to rapid improvement of symptoms. Up to now no oesophageal damage has been described. We present two cases of carbamazepine hypersensitivity syndrome with concomitant development of eosinophilic oesophagitis that resolved after drug withdrawal.

Keywords: Anticonvulsant hypersensitivity syndrome; Carbamazepine; Eosinophilic esophagitis

1. Introduction

Anticonvulsant hypersensitivity syndrome (AHS) usually consists of a triad of fever, skin rash and internal organ involvement [1] that can vary from mild to severe. Carbamazepine, phenytoin and phenobarbital are commonly responsible of such reaction, and cross-sensitivity among these drugs is common [2]. AHS occurs in 1/1000 to 1/10,000 exposures and is most frequently encountered among elderly black males [3]. As far as gastrointrointestinal involvement is concerned, hepatitis is the most frequently encountered complication, figuring in 50–60% of cases, with manifestations that vary from mild increase in transaminase levels to rare cases of fulminant hepatitis. Splenomegaly and colitis [4,5] have also been observed while only one report of oesophageal involvement has been concisely published [6].

Eosinophilic esophagitis is a disorder characterised by a dense esophageal eosinophilic infiltration. Adults typically present with disphagia, food impaction [7,8], vomiting and chest pain [9] and men are more frequently affected [10]. The vast majority of eosinophilic oesophagitis is considered primary or idiopathic and is defined as a chronic inflammatory disorder in an atopic, non-atopic and familial form [11], that is probably caused by food allergies [12]. Secondary eosinophilic oesophagitis are associated with various eosinophilic or non-eosinophilic disorders such as connectivitis, vasculitis, eosinophilic gastroenteritis, parasitic infections, GERD and drug-induced reactions [13].

The increasing interest for this disorder, that can also be seen by the exponential raise of the publications on this issue in the last few years, seems to be due to extended awareness and a probable increase of its incidence [14,15].

2. Case reports

2.1. Case 1

A 61-year-old man was admitted to our Internal Medicine Unit for high fever ($T^{\circ} = 39\,^{\circ}C$), lasting 5 days, resistant to conventional antibiotics. The patient had been on therapy with carbamazepine for a month because of a pain at the

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left lower limb which was attributed to neuralgia. He had a history of multiple sclerosis with spastic paraparesis, chronic hepatitis C, autoimmune thyroiditis, hypertension and prostatic hypertrophy and he had no personal or family history of allergic diseases. The patient had been treated with lisinopril, oxybutynin an baclofen for years.

His physical examination was normal except for body temperature (38.5 °C) and slight consequent tachycardia (105 bpm). Laboratory data and, in particular, acute phase reactants such as E.S.R, C-PR and fibrinogen, as well as white blood cell count $6.56 \times 10^3/\mu L$ (4.07×10^3 neutrophils, 1.98×10^3 lymphocytes, 0.11×10^3 eosinophils, 0.38×10^3 monocytes) were repeatedly within normal limits. Cultures of blood and urine were negative. Abdominal ultrasound, abdominal and chest X rays, cranial TC, cardiac echo Doppler and transthoracic echocardiography were normal. Starting at admission ciprofloxacin and piperacillin/tazobactam were administered. Immunological evaluation of IgM anti-CMV, TOXO, EBV, HSV-1, HSV-2, HIV, HHV-6, Vidal Wright, Rickettsiae, VDRL were negative.

Two days after admission fever persisted and the patient developed pruritic erythematous non-papular eruption in the interscapular space, thorax and arms and became symptomatic for dysphagia, epigastric pain, nausea and vomiting. At endoscopy, starting from the cervical oesophagus the mucosa was reddened, fragile, partly detached, covered with whitish, partially removable membranes (Fig. 1). Stomach and duodenum were normal. This picture was potentially attributed to an infective oesophagitis but biopsies were also taken for histological examination. Oesophageal brushing excluded the presence of CMV or a fungal infection and oesophageal histology revealed a significant mucosal eosinophilic infiltration with a range of 15–61 and a concentration of 32.5 ± 2.4 eosinophils/HPF (mean ± S.D., Zeiss Axioskop 2, ocular magnification 10, lens magnification 40); mucosal eosinophilia was absent in gastric and duodenal tissues.

At this point the occurrence of an AHS was hypothesized and treatment with carbamazepine was withdrawn. Treatment

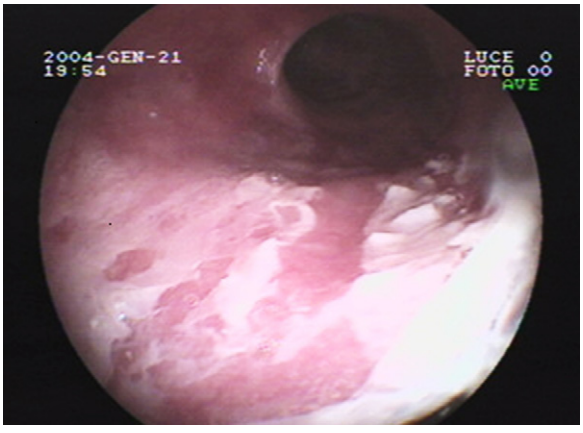

Fig. 1. Case 1: at endoscopy the oesophageal mucosa appeared diffusely reddened and covered with whitish membranes.

with prednisolone 40 mg i.v. and loratadine 10 mg p.o. daily was started and gradually removed within 10 days; during this period the patient was also given 20 mg of omeprazole p.o. In the first 48 h fever subsided and shortly skin rash and dysphagia disappeared.

To confirm the diagnosis a provocation test was performed, with gradual oral administration of carbamazepine starting from 50 mg up to 400 mg that in 4 h time determined fever and pruritic eruption and therefore was immediately interrupted.

Four weeks after carbamazepine withdrawal, endoscopy revealed complete healing of the oesophageal mucosa, with presence of esophageal rings. Histology documented a decrease of the number of eosinophils per field with a range of 5–16 and an average of 11 ± 0.7 eosinophils/HPF. White blood cell count ($6.99 \times 10^3/\mu L$), and in particular eosinophils ($0.41 \times 10^3/\mu L$) remained within normal limits.

At the same time a skin patch test was performed and showed reactions to carbamazepine at four different concentrations of the drug (0.1%, 0.5%, 1%, 10%).

Three months after hospital discharge the patient had no symptoms, there was no evidence of skin lesions or esophagitis recrudescence at upper endoscopy and at histology the range of eosinophils/HPF in the esophageal mucosa was 0–1.

2.2. Case 2

A 40-year-old woman was referred for recent appearance of dysphagia and chest pain; 3 days before admission she had developed an exanthema and intermittent high-grade fever ($T^\circ = 39.4$ °C).

She had neither history of allergy, nor of other medical or surgical conditions apart from recent occurrence of left trigeminal neuralgia treated with carbamazepine for 10 days.

At admission, physical examination of the patient showed a maculo-papular eruption on the face, spreading to the upper trunk. Body temperature was $T^\circ = 39$ °C. She had normal heart and respiratory rate (82 bpm, 16 cpm) and blood pressure (135/70 mmHg). No lymphnodes enlargement or hepatosplenomegaly were present.

Blood biochemistry was normal except for a slight leucocytosis $10.58/\mu L$ (7.3×10^3 neutrophils, 2.5×10^3 lymphocytes, 0.45×10^3 eosinophils, 0.27×10^3 monocytes), and a mild increase of transaminase values (ALT 70 U/L, AST 96 U/L, γGT 130 U/L). Blood and urine cultures were negative.

ECG, chest X-rays and abdominal ultrasound did not show abnormalities. Serum and immunological evaluation for infective hepatitis, or other infective diseases and rheumatic reaction were also negative.

At upper endoscopy we observed a diffuse oesophageal mucosal granularity and the presence of whitish exudates (Fig. 2). Histology demonstrated a severe eosinophilic mucosal infiltration of the oesophagus with a concentration of 27 ± 2 eosinophils/HPF (mean ± S.D., range 17–45), while such aspect was not present in gastroduodenal biopsies taken.