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Alimentary Tract

Clinical, endoscopic, histological and radiological characteristics of Italian patients with eosinophilic oesophagitis

Edoardo Savarino[a,*], Salvatore Tolone[b], Roberta Caccaro[a], Ottavia Bartolo[a], Francesca Galeazzi[a], Loredana Nicoletti[c], Tiziana Morbin[c], Lisa Zanatta[c], Renato Salvador[c], Mario Costantini[c]

[a] Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy
[b] Division of General and Bariatric Surgery, Department of Surgery, Second University of Naples, Naples, Italy
[c] U.O. Clinica Chirurgica 3, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

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ABSTRACT

Background: Limited data are available on eosinophilic oesophagitis in Italy.
Aim: To evaluate typical features of eosinophilic oesophagitis patients in a tertiary centre.
Methods: 973 consecutive patients with dysphagia and/or bolus impaction were prospectively enrolled and underwent upper endoscopy for eosinophilic oesophagitis (≥15 eosinophils in at least one high-power field [hpf] and no response to acid suppressants). Demographic and multiple clinical factors were collected.
Results: 45 patients (80% males, mean age 35 ± 16) with incident eosinophilic oesophagitis (mean eosinophil peak count 57.2 ± 40.6/hpf) were enrolled. 32 patients complained of solids dysphagia (71%), and 29 of bolus impaction (64%). Endoscopy found rings in 20 (44%), furrows in 9 (20%), whitish exudates/plaques in 12 (27%), crêpe paper in 7 (13%) and normal findings in 14 patients (31%). Endoscopic and radiologic stenosis occurred in 20 (44%) and 23 (51%), respectively. Ten patients had proton pump inhibitor-oesophageal eosinophilia (22%). Topic fluticasone was effective in 28 of the remaining cases (62%), while 7 required additional treatments (16%).
Conclusion: Eosinophilic oesophagitis prevalence was 12% in patients with dysphagia and/or bolus impaction, emphasizing the importance of this disease in Italy. Despite different environmental factors and dietary habits, Italian patients with eosinophilic oesophagitis present similar characteristics to those of other Western counties.

1. Introduction

Eosinophilic oesophagitis (EoE) is a chronic immune/antigen-mediated disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation [1,2]. EoE seems to be more frequent in young adult males, even if it may affect individuals at any age, and may present with a wide range of symptoms; the most typical is intermittent dysphagia with food impaction; heartburn, chest pain, regurgitations, abdominal pain, nausea and vomiting are possible gastrointestinal symptoms of EoE [3,4]. Upper endoscopy with the evidence of at least 15 eosinophils per high power field (eosinophils/hpf) at oesophageal biopsies is mandatory for the diagnosis of EoE [1–4].

Recent studies have shown a progressive increase of its prevalence in Western countries, which is estimated around 43–55 cases per 100,000 inhabitants; this phenomenon seems to be related to a true increase of its incidence, rather than a better recognition of the disease by specialists [5–7]. Changes in environmental factors might explain this evolving epidemiology, especially in terms of antigen exposure [8]: there is strong evidence that EoE might be induced by exposure to ingested and/or inhaled allergens and EoE patients often present allergic disorders. Furthermore, geographic differences have been hypothesized to be involved in EoE pathogenesis [6,9].

According to these concepts, the characteristics of this chronic disease as well as those of the patients affected may differ from country to country and may reflect different environmental factors as well as dietary habits. Furthermore, despite the evidence of worldwide increase of EoE prevalence, very limited data are

* Corresponding author at: Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Via Giustiniani 2, 35128 Padova, Italy. Tel.: +39 0498217749; fax: +39 0498760820.
E-mail address: edoardo.savarino@unipd.it (E. Savarino).

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currently available on European countries other than Spain, the Netherlands and Switzerland [5,10,11]. Therefore, we aimed to evaluate the demographic and multiple clinical features of patients with EoE referring to one Italian tertiary referral centre as well as to compare these data with those reported in medical literature, to investigate potential differences that may improve our understanding of EoE pathogenesis and management.

2. Methods

2.1. Study population

This was a prospective cohort study conducted from 2008 to 2013 at the Gastroenterology and Surgery Units, Department of Surgery, Oncology and Gastroenterology, University of Padua, Italy. We enrolled all consecutive adult patients (>18 years) referred for symptoms suggestive of EoE (dysphagia and/or food impaction). Only incidence or newly diagnosed EoE cases were included. Patients with established diagnosis of EoE, history of thoracic or digestive surgery, gastrointestinal bleeding, oesophageal varices, actively anticoagulated, relevant medical instability/comorbidities were excluded, as well patients with previous or current malignancies and established diagnosis of achalasia, scleroderma or other connective tissue disorders. The identification of a prominent eosinophilic infiltrate in gastric and/or duodenal biopsies represented a further exclusion criterion. EoE was defined according to 2007 consensus guidelines by: (a) symptoms including but not restricted to food impaction and dysphagia; (b) presence of at least 15 eosinophils/hpf on oesophageal biopsies; (c) exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially gastroesophageal reflux disease (GERD) by means of high-dose proton pump inhibitor (PPI) treatment. Moreover, after 2011, patients have been also classified as PPI-responsive oesophageal eosinophilia (REE) when presenting symptoms of oesophageal dysfunction, having at least 15 eosinophils/hpf on oesophageal biopsies and achieving less than 15 eosinophils/hpf and a 50% decrease from baseline following at 8-week course of twice-daily PPI treatment [2]. However, for the purpose of this study EoE and PPI-REE were considered as a whole group.

The study protocol was approved by the Internal Review Board and performed according to the Declaration of Helsinki Principles. All testing was done on a clinical basis. All patients gave written informed consent before the start of the study.

2.2. Clinical evaluation and EoE-related symptoms analysis

A complete clinical history was collected, including demographics, body mass index, history of atopy and allergy (allergic rhinitis, asthma, food allergies, and seasonal allergies), history of tobacco, alcohol and coffee consumption. Structured questionnaires on gastroesophageal reflux symptoms and functional dyspepsia symptoms were administered [12,13]. The onset and duration of EoE-related symptoms, as well as latency from diagnosis and response to medical treatment were collected. Laboratory, endoscopic, histological, and radiological findings were finally recorded.

2.3. Laboratory assessment

After the first clinical visit, all patients underwent peripheral blood sample collection at fasting. Elevated peripheral leucocytosis was identified when there was an absolute leucocyte count greater than 11.00×10^9/L, and a peripheral blood eosinophilia when there was an absolute eosinophil count greater than 0.50×10^9/L; elevated percentage of eosinophil count in total white blood lines was defined when greater than 2.0%. Total serum IgE at a value greater than 180 kU/L was considered abnormal in accordance with the Hospital of the University of Padua clinical laboratory reference range.

2.4. Upper endoscopy and histology

All patients underwent upper endoscopy at our Institution. All exams were performed by three experienced endoscopists (ES, TM, RS) and the endoscopic features EoE-related considered were: whitish exudates/plaques, rings, furrows, crepe paper and strictures [1,2]. Furthermore, presence of erosive oesophagitis or Barrett's oesophagus was evaluated. Multiple mucosal biopsies (at least two samples) were taken at three sites in the oesophagus (proximal, medio-thoracic, and distal body), in the stomach and duodenum. Additional clinical biopsies were taken as needed. The specimens were fixed in formalin, embedded in paraffin and then stained with haematoxylin and eosin for pathological diagnosis. Two experienced pathologists independently reviewed each specimen. The maximum count of eosinophils/hpf from all specimens was determined as the peak count. Patients with eosinophils $\geq$15/hpf in at least one hpf in the oesophageal specimen, without any gastric or duodenal involvement, were identified as having EoE [1,2]. In addition, the presence of degranulating eosinophils (defined as eosinophilic granules in the proximity of an eosinophil, but not in isolation), the presence of eosinophilic microabscesses (defined as clusters of 4 eosinophils), and the presence of spongiosis were noted [14]. Since 2011, an upper endoscopy after 8-weeks of PPI therapy was included in our protocol in order to identify PPI-REE patients [2].

2.5. Radiology

All patients underwent a structured oesophagogram as part of the diagnostic work-up of dysphagia established at our Centre and to verify the presence of oesophageal strictures. Radiologic examination with a 200 ml cup of barium swallow was performed by two expert local radiologists with the patient in standard orthostatic slightly left-lateral position. Reduction in oesophageal calibre was considered a radiological sign of stricture (a maximal oesophageal diameter of <21 mm and minimal diameter of <16 mm) [15]. The stricture site was classified as laying in proximal, medio-thoracic or distal oesophagus.

2.6. Allergy testing

All the patients underwent a skin prick test and radioallergosorbent test (RAST) test to evaluate their immediate sensitivity to foods and inhalants, whereas an atopy patch test was used to evaluate delayed sensitivities or sensitivities not measured using the IgE allergy test. Prick tests were performed with a commercial standardized series of aeroallergens. These tests were carried out following the recommendations of the EAACI and prick-to-prick tests were performed when trigger foods were implicated [16]. Histamine (10 mg/ml) and normal saline were used as the positive and negative controls. A wheal with an area 7 mm^2 larger or a diameter 3 mm larger than the negative control (saline solution) was considered positive. Reagents for patch test were the same commercial extract used for skin prick test, but they were prepared at a concentration of 5% in water and in petrolatum, with readings at 48 and 96 h. Skin prick and patch tests were performed by a team of experienced allergy specialists. Assessment of allergen specific IgE for food and aeroallergens was performed by RAST using Pharmacia ImmunoCAP 250 analyzer (Phadia, Uppsala, Sweden) in accordance with the recommendations of the manufacturers. Concentrations of specific IgE >0.35 kU/L was considered to be positive result with a moderate degree of sensitization.