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Review

Eosinophilic gastrointestinal disorders associated with autoimmune connective tissue disease

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ABSTRACT

Objectives: To determine the clinical and pathological characteristics of eosinophilic gastrointestinal disease (EGID) associated with autoimmune connective tissue disease (CTD).
Methods: Systematic literature review.
Results: Twenty cases of CTD associated with EGID were identified. Systemic lupus erythematosus was the main EGID-associated CTD (35%), followed by rheumatoid arthritis (20%), systemic sclerosis or inflammatory myopathies (15%, each), and Sjögren's syndrome, scleromyositis or other overlapping connective tissue disease (5%, each). No patient had a history of atopy. In contrast with classical EGID among which eosinophilic esophagitis is the most frequent type, eosinophilic gastritis and/or enteritis represented 95% of cases. Gastrointestinal symptoms were often unspecific. Peripheral eosinophilia was found in 67% of cases. Upper and lower gastrointestinal endoscopy showed abnormal findings in only 40% and 30% of cases, respectively. EGID was confirmed by evidence of digestive eosinophilic infiltration, mainly in mucosal or submucosal layer. In all but one patient, the CTD was diagnosed prior to the occurrence of the EGID. In total, 95% of EGID had a favorable outcome, with corticosteroids being used in almost all cases.
Conclusion: Clinicians should consider EGID as a possible diagnosis and perform gastrointestinal tract biopsies in patients with CTD presenting with gastrointestinal symptoms and unexplained eosinophilia. Conversely, more rarely extra-digestive features during follow-up in patients with EGID may lead to a diagnosis of an associated CTD. More research is needed to better understand the underlying pathophysiological processes leading to eosinophilic gastrointestinal infiltration in patients with CTD.
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1. Introduction

Eosinophils are key effector cells of the innate immune system which, at physiological state, sparsely populate the entire gastrointestinal tract except the esophagus. Pathological eosinophilic infiltration of the gastrointestinal tract is observed in a variety of conditions, including parasitic infections, malignancies and drug use. Although gastrointestinal eosinophils have long been considered as protective cells against helminthic infections, the role of these multifunctional leucocytes seems to be wider [1]. In particular, increasing evidence suggests that gastrointestinal eosinophils may act as modulators of gastrointestinal immune response, as recently reviewed [2].

Eosinophilic gastrointestinal diseases (EGIDs) are characterized by an inappropriate accumulation of eosinophils within the gastrointestinal tract, after excluding other causes of eosinophilia [3]. EGID include eosinophilic esophagitis (EoE), the most frequent subtype for which updated consensus recommendations have been published [4], eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC). During the last decade, EGID (and EoE in particular) have been recognized as clinically relevant diseases and described with increasing incidence [5]. This heterogeneous group of diseases has no specific presentation, as clinical symptoms may vary depending on both the location and the depth of bowel wall involvement. Diagnosis is mainly based on upper and lower endoscopies, with microscopic evaluation of biopsies samples. In 1990, Talley et al. suggested the following criteria for EGE [6]:

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- presence of gastrointestinal symptoms;
- biopsies showing eosinophilic infiltration of one or more areas of the gastrointestinal tract from esophagus to colon or characteristic radiologic findings with peripheral eosinophilia;
- no evidence of parasite or extra-intestinal eosinophilic disease.

EGIDs are often classified as either being primary (i.e. idiopathic, including atopic, non-atopic and familial variants) or secondary (e.g. the consequence of an inflammatory, infectious or hypersensitivity disease) [1,7]. Besides eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) in which diffuse eosinophilic infiltration is a key finding, systemic sclerosis is the only autoimmune connective tissue disease (CTD) classically recognized as being associated with EGID. However, several cases of EGID associated with other CTD, in particular systemic lupus erythematosus (SLE), have been reported.

Hereafter, we review the literature with the aim of determining the clinical and pathological characteristics of EGID associated with autoimmune CTD (EGID-CTD).

2. Methods

We present a systematic review of literature of EGID-CTD with no time limit. EGPA and inherited connective tissue diseases were not included. Pediatrics and adults published cases of EGID-CTD were identified by a computerized Medline search. The key words used were eosinophilic gastroenteritis/enterocolitis/enteritis/oesophagitis/eosinophilic gastrointestinal disease/connective tissue disease/autoimmune disease/systemic lupus erythematosus. References of the reports were also used to identify additional articles. According to Talley's criteria and updated consensus recommendations on EoE, cases of asymptomatic patients, and post-mortem diagnoses of EGID were excluded [4,6]. A case of Satoyoshi syndrome was excluded because of absence of consensus on disease diagnosis criteria and pathogenesis.

3. Literature review

A literature review found 19 published [8–21] and one submitted cases (Lecouffe-Desprets et al.: eosinophilic gastrointestinal disorders preceding Sjögren's syndrome: submitted) of EGID-CTD. Reported cases are shown in Table 1 and the main clinical, laboratory and pathological findings of the patients in Table 2. Patients were mostly female (80%), with a median age of 47 years (range 10–71). Digestive clinical features were nonspecific, mainly abdominal pain (85%), nausea and/or vomiting (55%) and diarrhea (45%). Interestingly, 3 patients had clinical signs of intestinal obstruction. In another patient, EGID was complicated by presumed intestinal perforation. Eosinophilic ascites was found in 3 patients (15%). In 4 cases [9,15,17,20], patients had intermittent episodes of digestive symptoms before EGID diagnosis. Peripheral eosinophilia was specified in 15 cases (75%) and was elevated ($> 500/mm^3$) in the majority of patients (67%). Most patients had upper gastrointestinal endoscopy, which was abnormal in 40% of cases, while only half of them had colonoscopy, which showed abnormal findings in only 30% of cases. All patients but one had histological confirmation of EGID with digestive eosinophilic infiltration, mainly in mucosal or submucosal layer (70%). Eosinophilic infiltration of muscularis propria and serosa or subserosa was less frequent (41% and 21%, respectively).

Reported autoimmune CTD associated with EGID were mainly SLE (35%), rheumatoid arthritis (20%), systemic sclerosis (15%), and inflammatory myositis (15%). Two patients were affected by overlap autoimmune disease with features of SLE and systemic sclerosis in one case and of systemic sclerosis and polymyositis in the second.

Digestive signs occurred after the diagnosis of CTD in 9 cases (45%), the time between the 2 diagnoses having being reported up to 11 years. In 9 cases (45%), diagnosis of CTD and EGID were concomitant, with clinical and/or biological of active autoimmune disease in all patients. Only one case presented with clinical signs of primary Sjögen syndrome (SS) years after the onset of EGID (Lecouffe-Desprets et al.: eosinophilic gastrointestinal disorders preceding Sjögren's syndrome: submitted).

Therapeutic management was recorded in 13 cases (65%). Corticosteroids were used in almost all cases (92%), often starting with intravenous pulses (67%). Immunosuppressants were added in 2 cases and intravenous immunoglobulins were used in 3 cases. Finally, one patient showed full resolution of symptoms with only a symptomatic treatment.

Follow-up time ranged from 1 month to 5 years. Resolution of the digestive signs and symptoms was most frequently reported (11/13 cases, 85%). Relapse was observed in a single patient.

4. Discussion

4.1. EGID associated with autoimmune connective tissue disease

To our knowledge, there is currently no study available focusing on the association of EGID and autoimmune CTD. Systemic sclerosis is usually the only autoimmune CTD mentioned as belonging to the subgroup of secondary EGID [3]. In our literature review, we found that EGID-CTD has mainly been reported during SLE (35% of reported cases of EGID-CTD), followed by rheumatoid arthritis (20%). This over-representation of SLE and rheumatoid arthritis compared to systemic sclerosis in EGID-associated CTD may be due to the most frequent prevalence of these two diseases. However, since EGID diagnosis is often difficult to establish (endoscopic examination can be unrevealing, and histologic features of EoE are not pathognomonic) [22], clinicians should be aware that several autoimmune diseases other than systemic sclerosis may be associated with EGID. In this literature review, only one third of patients with EGID-CTD had abnormal findings at upper and/or lower endoscopies. Thus, systematic biopsies should be performed whenever EGID is suspected, regardless of the macroscopic aspect of the endoscopy. Last, since eosinophilic infiltration often has a patchy distribution, normal biopsies do not necessarily rule out the diagnosis [3].

4.2. Patients characteristics and clinical features

EoE is the most common EGID, with a rising incidence partly due to increased recognition by physicians [1]. Interestingly, in this literature review we found that isolated EoE represented only one case of EGID-CTD, whereas eosinophilic gastritis and/or enteritis (EGE) represented 95% of cases. Eosinophilic colitis was described in a single case of EGID-CTD, associated with EGE. This distinctive repartition suggests a close link between CTD and eosinophilic gastritis and/or enteritis.

A non-surprising predominance of female was found in this literature review focusing on autoimmune diseases (sex ratio male/female, 4/16), although there is a classically slight male predominance in EGID, mostly in EoE (sex ratio 3/1) [1]. Approximately 75% of patients with EGID are atopic [3], but in our review a history of atopy was specified only for 5 patients and was always negative. The link between atopy and EGID in CTD patients warrants further studies. Nonspecific gastrointestinal symptoms were concordant with the general clinical presentation of EGE during the mucosal form, which usually represents slightly more than 50% of EGE cases [6] and was found in 79% of patients with CTD. Interestingly, 3 patients with EGID-CTD (15%) presented with intestinal

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