

Prevalence and characteristics of ophthalmological extra-intestinal manifestations in Chinese patients with inflammatory bowel disease

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Received: 2016-05-22 Accepted: 2016-08-09

Abstract

• **AIM:** To investigate the prevalence of ophthalmological extra-intestinal manifestations (O-EIMs) in Chinese patients with inflammatory bowel disease (IBD) and to identify risk factors for the development of O-EIMs.

• **METHODS:** The study population consisted of Chinese patients with a definite diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) in a large teaching hospital between January 1995 and December 2014. Demographic and clinical characteristics of patients were extracted retrospectively.

• **RESULTS:** In this twenty-year cohort, 645 IBD patients (517 with UC, 128 with CD) were registered. Among them 122 (18.9%) exhibited at least one EIM. Of 13 patients (2.0%) developed O-EIMs, 7 of CD (5.5%) and 6 of UC (1.2%). Clinical ophthalmological manifestations included redness (76.9%), burning (61.5%), pain (38.5%), itching (15.4%) of eyes and vision change (7.7%). O-EIMs included episcleritis (7), uveitis (5) and dry eye (1). O-EIMs were more prevalent in female (odds ratio for male 0.61, 95% confidence interval 0.52–0.73, $P < 0.0001$), and patients who had IBD diagnosis at young age (odds ratio for patients aged >30 years 0.76, 95% confidence interval 0.65–0.88, $P < 0.0001$).

• **CONCLUSION:** The frequency of O-EIMs in Chinese patients with IBD is lower than the rates reported in the studies of European and American countries. Episcleritis

and uveitis are the most common O-EIMs. O-EIMs are more frequent in patients with CD and more prevalent in female and patients who have IBD diagnosis at young age.

• **KEYWORDS:** ophthalmological extraintestinal manifestations; inflammatory bowel disease; episcleritis; uveitis

DOI:10.18240/ijo.2016.10.18

Li YC, Li WZ, Wu CR, Feng Y, Ren L, Mi C, Li Y. Prevalence and characteristics of ophthalmological extra-intestinal manifestations in Chinese patients with inflammatory bowel disease. *Int J Ophthalmol* 2016;9(10):1476–1479

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory gastrointestinal disorder of unknown etiology and includes both ulcerative colitis (UC) and Crohn's disease (CD)^[1]. Patients with IBD may suffer one or more extra-intestinal manifestations (EIMs) during the course of their condition. The most frequent EIMs are arthritic, mucocutaneous, and ophthalmological. The overall prevalence of any EIMs in IBD patients ranges from 25%–40%^[2–4]. In most large studies of IBD, the prevalence of EIMs is higher in CD compared with UC^[3–5].

Episcleritis, scleritis, and anterior uveitis are the most common ophthalmological extra-intestinal manifestations (O-EIMs) in IBD. O-EIMs occur in 4%–10% of IBD patients in the previous studies^[6–9]. Data on epidemiology and risk factors of O-EIMs in Chinese patients with IBD are limited. The aims of this retrospective cohort study were to investigate the frequency of O-EIMs in a Chinese population of IBD patients and to identify risk factors for the development of the O-EIMs.

SUBJECTS AND METHODS

Data were extracted retrospectively from clinical files and electronic medical records of IBD patients in the First Affiliated Hospital of Xi'an Jiaotong University between January 1995 and December 2014. This study was conducted according to the Declaration of Helsinki and approved by the hospital's Ethics Committee. Diagnosis was based on the Lennard-Jones criteria^[10]. Only patients with a definite diagnosis of CD or UC were included. Demographic

characteristics, including age, gender, place of birth, residency, educational level, were registered in a standardized database. Patients provided informed consent to data processing.

Disease characteristics (age at IBD and EIMs diagnosis, number of different EIMs) were reviewed. The term EIMs was used to define IBD-associated disorders appearing in distant sites in regard to the digestive tract. Arthritic EIMs were diagnosed either by the treating physician or by a consulting rheumatologist. Mucocutaneous EIMs were diagnosed by an experienced dermatologist based on their clinical characteristics and skin biopsy where necessary.

The diagnosis of O-EIMs was made based on a previous diagnosis of episcleritis, scleritis, or uveitis and/or after evaluation by an ophthalmologist. Episcleritis is inflammation of the vascular layer directly beneath the conjunctiva that presents with acute redness of one or both eyes, with burning, itching, and pain to palpation. Scleritis is a more serious disorder, and is caused by inflammation of deeper scleral vessels; it presents with redness and pain, and may involve vision changes. Uveitis includes inflammation of the iris, vitreous, choroids, or retina. Patients typically present with acute redness, pain, and vision changes. Symptoms at O-EIMs diagnosis were recorded.

Potential risk factors for the development of the O-EIMs (smoking status, IBD activity at O-EIMs diagnosis, familial IBD, IBD extend and location) were reviewed. Disease activity was clinically judged according to presence of related symptoms in combination with elevated inflammatory markers, mainly C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), despite appropriate treatment at the time of EIM diagnosis. Montreal classification was used for registering IBD location and behavior^[11].

Statistical Analysis All statistical analyses were performed with SPSS 20.0 software package (IBM SPSS Statistics, Armonk, NY, USA). Tests were two-sided and *P*-value <0.05 was considered statistically significant.

RESULTS

In total, 645 IBD patients (517 UC, 128 CD) were included (Table 1). Of those, 122 (18.9%) exhibited at least one EIM, while more than one EIMs co-existed in 7 patients (1.1%). Arthritic (peripheral arthritis) and mucocutaneous (aphthous stomatitis) EIMs were the most common manifestations. 2.0% patients exhibited IBD-related O-EIMs, and arthritic EIMs co-existed in 2 of those. Other IBD-related EIMs (primary sclerosing cholangitis, PSC) were found in 5 patients (0.8%).

IBD-related O-EIMs were diagnosed before, at the same time, or after the diagnosis of IBD. The median IBD duration until O-EIMs diagnosis was 2.2y. In 2 of those, ophthalmological manifestations appeared before IBD diagnosis. Clinical ophthalmological manifestations included

Table 1 Demographic and clinical characteristics of patients with IBD

| Parameters [®] | n (%) |
|-----------------------------------------------------|---------------------|
| Female/male | 269/376 (41.7/58.3) |
| CD/UC | 128/517 (19.8/80.2) |
| Median age at IBD diagnosis (a, IQR) | 41.1 (25.7-52.5) |
| IBD-related EIMs (at least one) | 122 (18.9) |
| IBD-related arthritic EIMs | 60 (9.3) |
| IBD-related mucocutaneous EIMs | 51 (7.9) |
| IBD-related O-EIMs | 13 (2.0) |
| Median IBD duration until O-EIMs diagnosis (a, IQR) | 2.2 (0.2-7.6) |

IQR: Interquartile range.

Table 2 Clinical manifestations of IBD-related O-EIMs n=13

| Clinical manifestations | No. of patient (%) |
|-------------------------|--------------------|
| Redness | 10 (76.9) |
| Burning | 8 (61.5) |
| Pain | 5 (38.5) |
| Itching | 2 (15.4) |
| Vision change | 1 (7.7) |
| No symptom | 2 (15.4) |

Table 3 Classification of O-EIMs in IBD patients according to gender and disease type

| O-EIMs | n | Female/male | CD/UC |
|------------------|----|-------------|-------|
| Episcleritis | 7 | 4/3 | 5/2 |
| Uveitis | 5 | 2/3 | 2/3 |
| Others (dry eye) | 1 | 1/0 | 0/1 |
| Total | 13 | 7/6 | 7/6 |

redness, burning, pain, itching of eyes and loss of visual acuity (Table 2). Two patients (15.4%) exhibited no symptom of O-EIMs and were diagnosed after examinations of eyes.

There were 13 patients with O-EIMs, 7 of 128 CD (5.5%) and 6 of 517 UC (1.2%). O-EIMs were more frequent in patients with CD (Table 3). Episcleritis and uveitis were more common among patients with IBD. No cases of scleritis, corneal involvement, or cataracts were observed in this cohort.

The clinical characteristics, potential risk factors for the development of the O-EIMs, were reviewed. The clinical characteristics included IBD disease activity, IBD diagnosis at young age (≤ 30 y), smokers, family history of IBD. Moreover, IBD extend and location were also reviewed. However, O-EIMs were more prevalent in female (odds ratio for male 0.61, 95% confidence interval 0.52-0.73, $P < 0.0001$) and patients who had IBD diagnosis at young age (odds ratio for patients aged > 30 years 0.76, 95% confidence interval 0.65-0.88, $P < 0.0001$).

DISCUSSION

Patients with IBD often develop one or more EIMs during the course of disease. The most frequent EIMs are arthritic, mucocutaneous, and ophthalmological. EIMs are present in approximately one third of IBD patients, and O-EIMs occur in 4% to 10% of patients with IBD in previous studies^[6-9,12]. The prevalence of EIMs associated with IBD varies wildly in

different retrospective national studies; 40.6% in an Italian^[13], 38.1% in a Swiss^[14], 21.3% in a Hungarian^[4], and 36% in a Canadian^[6] cohort. These variations could be attributed to differences in definitions, specific characteristics of the populations studied, spectrum of EIMs included in each study, accuracy of diagnosis, recall bias, and previous medical treatment. In this retrospective study investigating the prevalence and characteristics of the O-EIMs in a twenty-year cohort of Chinese patients with IBD, the frequencies of EIMs (18.9%) and O-EIMs (2.0%) in our population were lower than the rates reported in the studies of European and American countries. The major type of IBD is UC in China, and the proportion of UC in this study was 80.2%, while the EIMs are more frequent in CD compared with UC^[3-5]. This was one of the reasons causing the lower frequencies of EIMs in present study. Second, some common abnormal conditions not strictly related to IBD, for example nonalcoholic fatty liver disease (NAFLD), cholelithiasis and anaemia, were not included as classic EIMs in this study. Third, there may also be racial differences in prevalence. For example, blacks have a higher risk for eye and joint manifestations, and Hispanics have a higher risk for skin manifestations compared with whites^[15]. Moreover, Chinese clinicians didn't pay enough attention to the O-EIMs of IBD, and most of the patients with IBD didn't receive any ophthalmological examination.

EIMs of IBD can occur prior to, in conjunction with, or subsequent to active bowel disease. In this study, the median IBD duration until O-EIMs diagnosis was 2.2y, but O-EIMs appeared before IBD diagnosis in 2 patients. Moreover, complaints of O-EIMs are often nonspecific. O-EIMs of IBD should be considered in patients presenting with redness, burning, pain, itching of eyes and loss of visual acuity. Clinical relevance may not be appreciated by patient or physician and, thus, be misdiagnosed. Evaluation of the eye should be a routine component in the care of patients with IBD. Clinicians must be aware of the spectrum of ocular symptoms and know that these complaints may precede a diagnosis of UC or CD^[9,16].

The ocular system is a major organ system that can be affected in IBD. Episcleritis, scleritis, and uveitis are the most common O-EIMs in IBD, and other less common eye manifestations with reported associations to IBD include retinal vasculitis, papillitis, corneal infiltrates, myositis, scleromalacia perforans, and optic neuritis^[17]. In present study, episcleritis and uveitis were the most common O-EIMs and no cases of scleritis were observed. Episcleritis typically presents as painless hyperemia of the conjunctiva and sclera without visual changes. It typically parallels disease course, with onset during flares and resolution with effective treatment. Conversely, uveitis can occur independent of disease activity. It is defined as inflammation

of the middle chamber of the eye. Anterior uveitis is also referred to as iritis. It typically presents as redness, pain, and vision changes. Diagnosis is confirmed by slit lamp examination. These conditions usually respond well to treatment of the underlying bowel disease. Patients with episcleritis may also respond to topical steroids. Scleritis and uveitis are more likely to respond to systemic treatment and should be managed in conjunction with treatment by a specialist^[9]. Dry eye, a rare extra-intestinal manifestation, was found in one female patient with UC.

Pathogenesis of O-EIMs is largely unknown, but there is evidence that environmental^[18], autoimmune^[19-20] and genetic^[21-23] factors are implicated. In this study, development of O-EIMs was associated with demographic parameters such as female gender and young age. We identified higher prevalence of O-EIMs in women, consistent with previous studies. Moreover, O-EIMs were more prevalent in patients who had IBD diagnosis at young age ($\leq 30y$).

In conclusion, the frequencies of EIMs and O-EIMs in Chinese patients with IBD are lower than the rates reported in the studies of European and American countries. Episcleritis and uveitis are the most common O-EIMs. O-EIMs are more frequent in patients with CD and more prevalent in female and patients who have IBD diagnosis at young age. IBD patients who present with the symptoms described above should be suspected of having O-EIMs. Clinicians have to raise increased awareness for the identification of IBD-related O-EIMs and for the early diagnosis of IBD, in order to offer the appropriate treatment and to avoid long-term complications.

ACKNOWLEDGEMENTS

Conflicts of Interest: Li YC, None; Li WZ, None; Wu CR, None; Feng Y, None; Ren L, None; Mi C, None; Li Y, None.

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