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Extra intestinal manifestations may increase the risk of synchronous and metachronous development of other extraintestinal manifestations in patients with Crohn's disease

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Although Crohn's disease (CD) affects the intestines, it is known to be a systemic disease rather than being limited to the intestines. Extra intestinal manifestations (EIMs) accompanying CD are reported at rates varying from 6 to 53%. While EIM negatively affects the quality of life of some patients, some EIMs, such as primary sclerosing cholangitis and thromboembolism, can be life-threatening. Although more than one EIM can occur simultaneously, the development of one EIM increases the probability of developing another EIM. There are few studies on how EIMs affect each other. The aim of this study was to examine the frequency of EIMs accompanying CD and their interactions with each other. This study included patients with CD who were under regular follow-up from March 1986 to October 2011. Accompanying EIMs and the time of development were recorded. The frequency of EIMs and their associations with each other were investigated. In total, 336 patients with CD (55.4% male) with a mean follow-up duration of 7.54 years (range, 6 months–25.4 years) were evaluated. At the time of CD diagnosis, 21.1% of the patients had at least one EIM, and at the end of the 25-year follow-up period, the prevalence of EIMs was 47.3%. The prevalence of multiple EIMs was 12.2% and 22.9% at the onset of CD and at the 25-year follow-up, respectively. Oral, joint 9.2%, respectively) were the most common EIMs. The development and skin involvement (32.4%, 24.7%, and of peripheral arthritis was significantly associated with axial spondiloarthropathy, skin involvement, ocular involvement, oral ulcers, and vascular thromboembolism ($p < 0.05$). There was a significant relationship between oral ulcers and peripheral arthritis, axial arthritis, skin involvement, ocular involvement, liver involvement and thromboembolism ($p < 0.05$). No significant relationship was detected between neurological involvement and any other EIMs. The development of EIMs in patients with CD may trigger the development of other EIMs during the course of the disease.

Keywords Crohn's disease, Extra intestinal manifestations, Interaction

Inflammatory bowel disease (IBD), which has two subtypes, Crohn's disease (CD) and ulcerative colitis (UC), is defined as chronic inflammation caused by a complex interaction between a dysfunctional host immune response and environmental trigger factors[1]. Although IBD primarily affects the intestines, it is not limited to the intestines; rather, it is a systemic disease. Although extra intestinal involvement, defined as an extraintestinal manifestation (EIM), is frequently observed, studies have shown varying results due to the evaluation of EIMs as different diseases[2,3]. In studies with different designs and criteria, the rate of EIMs has been reported to

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range from 6 to 53%[4–6]. EIMs are categorized as extra intestinal symptoms and extra intestinal complications. The joints, skin, hepatobiliary system, and oral and ocular systems are frequently affected in CD patients, and the lungs, heart, pancreas, and neurological and vascular systems are less commonly involved. Extraintestinal complications include pathological conditions resulting from the disease itself, such as malabsorption, micronutrient deficiencies, neuropathy, cholelithiasis, urolithiasis, osteoporosis, and the side effects of drugs used to treat CD[1,7,8].

While EIMs have a negative effect on quality of life in some patients, some EIMs, such as primary sclerosing cholangitis and thromboembolism, can be life-threatening[9]. Multiple EIMs can occur simultaneously, and the development of one EIM may also increase the likelihood of developing another manifestation. The probability of developing EIMs is associated with disease duration[1,4]. Studies have shown that 25% of EIMs are present at the time of diagnosis, whereas the other 75% occur after IBD is diagnosed[4,10]. It has also been reported that by the 30th year of disease, half of patients have developed at least one EIM, and multiple EIMs are seen in a quarter of patients[1,4,10].

There are several theories that may explain the development of EIMs in patients with IBD. The most likely explanation is the hypothesis of shared epitopes between gastrointestinal luminal antigens, including the gut microbiota, that leak through the intestinal barrier and target tissues such as joints and skin[9,11]. Some EIMs can be associated with luminal disease activity, whereas others have been shown to be independent of the course of IBD. It has also been reported that some EIMs are completely independent of each other, whereas others are positively correlated[4,12,13]. The aim of this study was to evaluate the relationship between existing EIMs and the metachronous development of EIMs during long-term follow-up of patients with CD.

Materials and methods

Study design

This retrospective, single-center, cohort study initially screened a total of 336 patients with CD who were followed up between March 1986 and October 2011 in the Department of Gastroenterohepatology. The diagnosis of CD was made on the basis of clinical, endoscopic, histopathological and radiological examinations. Patients with CD who had a minimum of 6 months of follow-up after diagnosis were included in the study. Patients with CD accompanied by malignancy were excluded from the study. As the study covered a long period of time, only patients who regularly attended the gastroenterology clinic for continuous follow-up and treatment were included in the study to avoid errors in the data, and patients who neglected their follow-up over time were not included. After a physical examination by a gastroenterologist, the patients were evaluated by the relevant specialties, such as dermatology, rheumatology, neurology, and ophthalmology, for a diagnosis of EIMs.

Owing to the retrospective nature of the study, the need to obtain informed consent was waived by the ethics committee of the Istanbul University Faculty of Medicine, number 2011/831-577.

Extraintestinal manifestations

All the patients were evaluated in detail for screening of EIMs. Joint involvement, such as peripheral arthritis and spondyloarthropathy; skin involvement, such as erythema nodosum and pyoderma gangrenosum; eye involvement, such as uveitis and episcleritis; and liver involvement, such as primary sclerosing cholangitis (PSC), granulomatous liver disease, thromboembolism, neurological diseases, glomerulonephritis and aphthous ulcers, were considered EIMs. While those with effusion, pain and redness in a joint were considered to have arthritis, arthralgia alone was not considered an EIM. Patients with inflammatory low back pain and spondyloarthropathy on imaging were included in the study. Patients with mucocutaneous, eye and neurological symptoms were referred for dermatology, ophthalmology, and neurology evaluation. The findings were considered EIMs after other possible causes were excluded after the evaluations. Malnutrition, malabsorption, and drug-related pathologies were not evaluated as EIMs.

Granulomatous liver disease was diagnosed by liver biopsy in CD patients, and PSC was diagnosed by magnetic resonance cholangiopancreatography (MRCP) imaging in conjunction with elevated liver function tests. Liver biopsy was performed in some patients with suspected PSC with normal MRCP, and these findings were considered EIMs. Cholelithiasis, cholecystolithiasis, cirrhosis and focal nodular hyperplasia were not considered EIMs. Venous thromboembolism was considered an EIM. One patient with proteinuria who underwent kidney biopsy was also considered to have EIM due to the presence of glomerulonephritis and no other underlying cause. Diseases such as anemia, hypoalbuminemia, amyloidosis, nephrolithiasis, urolithiasis, and cholelithiasis, which occur as long-term complications of CD, were not considered EIMs. The rates of EIMs and their associations with each other were investigated.

Time-related frequency of extraintestinal manifestations

The rates of EIMs at diagnosis and in the 1st, 5th, 10th, 15th, 20th and 25th years were calculated. Similarly, the development rates of multiple EIMs (two or more) at diagnosis and in the 1st, 5th, 10th, 15th, 20th and 25th years were calculated.

Treatment

Medications, including aminosalicylates, antibiotics, budesonide or systemic corticosteroids, immunosuppressive drugs (6-mercaptopurine, azathioprine, and methotrexate) and biologics (infliximab or adalimumab), were administered according to individual treatment needs and indications. Treatment failure, perianal disease and uncontrolled extraintestinal manifestations were treated with biological agents after January 2003. Aminosalicylates were used in patients with mild forms of the disease. Systemic corticosteroids and budesonide were administered as the main treatments for remission induction and flare-up episodes. Immunosuppressive drugs (azathioprine 2–2.5 mg/kg, 6-mercaptopurine 1–1.5 mg/kg) were administered to maintain remission,

and intramuscular methotrexate (25 mg/week) was used as an alternative immunosuppressive agent in patients with intolerance to thiopurine therapy. Anti-TNF treatment was applied in patients whose disease activity continued despite standard immunosuppressive therapy.

Ethical approval

Approval for this study was obtained from the Ethics Committee of Istanbul University, Faculty of Medicine (No: 2011/831–577). All the applied procedures complied with the ethical standards of the Human Testing Committee of our institution and the *Helsinki Declaration*.

Statistical analysis

The data obtained in the study were analyzed using the Statistical Package for Social Sciences vn. 19.0 software (IBM Corpn., SPSS, Armonk, NY, USA). Categorical data were examined using the chi-square test, and the results are presented as frequencies and percentages (n, %). The frequency of development of EIMs and associations with other subsequent EIMs were evaluated using logistic regression models. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A value of $p < 0.05$ was considered statistically significant.

Results

Evaluations were made of 336 patients with CD who were followed up for a total of 2535 patient-years, with an average of 7.54 years (range: 6 months–25.4 years). The patients included 55.4% (n = 186) men and 150 (44.6%) women, with a mean age at diagnosis of CD of 30.6 years (10.3–68.2 years). According to the Montreal classification, at the time of diagnosis, no complications were detected in 79.7% (n: 268) of the 336 patients (inflammatory type), stenosing complications were detected in 17 patients (5.1%), and penetrating complications were detected in 51 patients (15.2%). At the end of the follow-up period, no complications were detected in 155 patients (46.1%) (inflammatory type), stenosing complications were detected in 63 patients (18.8%), and penetrating complications were detected in 118 patients (35.1%). At the time of diagnosis, EIM was detected in 68 (28.4%) inflammatory type patients, 2 (11.8%) stenosing type patients, and 9 (17.6%) penetrating type patients ($p = 0.468$). At the end of the follow-up period, EIM was detected in 87 (56.1%) inflammatory-type patients, 23 (36.5%) stenosing-type patients, and 49 (41.5%) penetrating-type patients ($p = 0.009$).

Frequency of extraintestinal manifestations

At least one EIM was detected in 159 (47.3%) patients, and multiple EIMs were found in 77 (22.9%) patients. Only one EIM was identified in 82 (24.4%) patients, two in 51 (15.1%) patients, three in 16 (4.8%) patients, four in 8 (2.4%) patients and five in 2 (0.6%) patients (Fig. 1). The distribution of EIMs was as follows: oral involvement in 109 (32.4%) patients, joint involvement in 83 (24.7%), skin involvement in 31 (9.2%), ocular involvement in 14 (4.2%), hepatobiliary involvement in 8 (2.4%), neurological involvement in 8 (2.4%), thromboembolism in 7 (2.1%), and glomerulonephritis in 1 (0.3%) (Table 1). At the time of diagnosis, EIMs were identified in 71 patients, and 265 patients did not have EIMs. During the follow-up period, 88 of the 265 patients with no EIM at the time of diagnosis developed a new EIM. Among the 71 patients with EIM at the time of diagnosis, additional EIM development was detected in 21.

Time-related frequency of extraintestinal manifestations

EIMs were detected at the onset of CD in 21.1% of patients. The frequency of EIMs was 28% in the 1st year, 38.7% in the 5th year, 44.6% in the 10th year, 46.7% in the 15th year, and 47.3% in the 20th and 25th years of the disease (Fig. 2). Multiple (two or more) EIMs were diagnosed at the time of CD onset in 12.2% of patients. The frequency of multiple EIMs was 15.8% in the 1st year, 20.2% in the 5th year, 22% in the 10th year, 22.3% in the 15th year, and 22.9% in the 20th and 25th years of the disease (Fig. 3).

Associations of extraintestinal findings with each other

The associations between EIMs were analyzed, and details are provided in Table 2. There was a significant relationship between the development of peripheral arthritis and axial arthropathy, skin involvement, ocular involvement, oral ulcers and thromboembolism ($p < 0.05$). Among the 51 patients who developed peripheral arthritis, 13 had axial arthropathy (OR: 2.7, CI 95%: 1.304–5.608, $p = 0.006$), 15 had skin involvement (OR: 7.0, CI 95%: 3.195–15.368, $p < 0.001$), 7 had ocular involvement (OR: 6.3, CI 95%: 2.114–18.883, $p = 0.001$), 30 had oral ulcers (OR: 3.7, CI 95%: 2.014–6.890, $p < 0.001$), and 4 had thromboembolism (OR: 8.0, CI 95%:

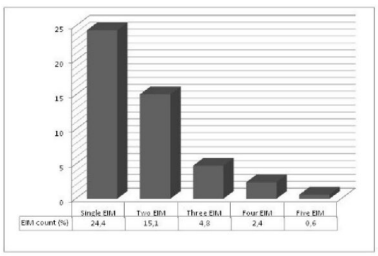


Fig. 1. Number of extraintestinal manifestations.

All patients with EIM	N (%)
Total patients	159 (47.3)
Oral involvement	109 (32.4)
Joint involvement	83 (24.7)
Peripheral arthritis	51 (15.2)
Axial arthropathy	45 (13.4)
Skin involvement	31 (9.2)
Erythema nodosum	12 (3.6)
Pyoderma gangrenosum	12 (3.6)
Psoriasis	2 (0.6)
Dermatitis	2 (0.6)
Erythema multiforme	1 (0.3)
Erythema bullosa	1 (0.3)
Neurological involvement	8(2.4)
Ocular involvement	14 (4.2)
Uveitis	11 (3.3)
Conjunctivitis	2 (0.6)
Episcleritis	2 (0.6)
Thromboembolism	7 (2.1)
Cranial thrombosis	3 (0.9)
Deep vein thrombosis	3 (0.9)
Brachial vein thrombosis	1 (0.3)
Hepatobiliary involvement	8 (2.4)
Primary sclerosing cholangitis	5 (1.5)
Granulomatous liver disease	3 (0.9)
Glomerulonephritis	1 (0.3)

Table 1. Extraintestinal manifestations in patients with Crohn's disease. *EIM* extraintestinal manifestations; *N* number of patients.

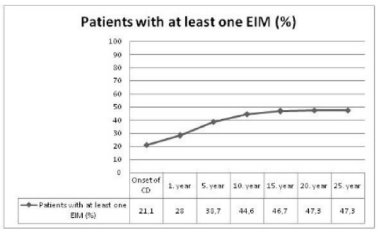


Fig. 2. Patients with at least one extraintestinal manifestation.

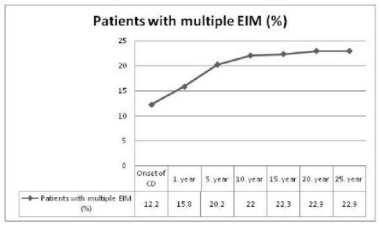


Fig. 3. Patients with multiple extraintestinal manifestations.

1.735–36.889, $p = 0.002$). Although hepatic involvement was 3.50-fold greater in patients with peripheral arthritis, the association was not significant ($p = 0.075$). A statistically significant association was detected between axial arthropathy and oral ulcers and peripheral arthritis ($p < 0.05$), but no significant associations were detected with other EIMs. Among the 45 patients who developed axial arthropathy, 24 developed oral ulcers (OR: 2.7, CI 95%: 1.464–5.241, $p = 0.001$), and 13 developed peripheral arthritis (OR: 2.7, CI 95%: 1.304–5.608,

	Axial arthropathy			Skin involvement			Ocular involvement			Hepatobiliary involvement			Oral involvement			Thromboembolism			Neurological involvement		
	−	+	OR (95% CI)	−	+	OR (95% CI)	−	+	OR (95% CI)	−	+	OR (95% CI)	−	+	OR (95% CI)	−	+	OR (95% CI)	−	+	OR (95% CI)
Peripheral arthritis			2.705 (1.304–5.608)			7.005 (3.195–15.368)			6.318 (2.114–18.883)			3.500 (0.810–15.127)			3.725 (2.014–6.890)			8.000 (1.735–36.889)			NA
−	253	32		269	16		278	7		280	5		206	79		282	3		277	8	
+	38	13		36	15		44	7		48	3		21	30		47	4		50	0	
Axial arthropathy						2.049 (0.827–5.081)			2.741 (0.822–9.147)			NA			2.770 (1.464–5.241)			NA			1.085 (0.130–9.028)
−				267	24		281	10		283	8		206	85		284	7		284	7	
+				38	7		41	4		45	0		21	24		45	0		44	1	
Skin involvement									2.864 (0.754–10.873)			3.437 (0.663–17.807)			6.125 (2.713–13.829)			4.138 (0.768–22.281)			1.419 (0.169–11.925)
−							294	11		299	6		218	87		300	5		298	7	
+							28	3		29	2		9	22		29	2		30	1	
Ocular involvement												3.462 (0.396–30.241)			13.918 (3.057–63.365)			21.682 (4.320–108.809)			NA
−										315	7		225	97		318	4		314	8	
+										13	1		2	12		11	3		14	0	
Hepatobiliary involvement															6.553 (1.301–33.022)			NA			NA
−													225	103		321	7		320	8	
+													2	6		8	0		8	0	
Oral involvement																		13.165 (1.565–110.759)			1.452 (0.288–7.317)
−																226	1		221	6	
+																103	6		107	2	
Thromboembolism																					NA
−																			321	8	
+																			7	0	

Table 2. Interactions of extraintestinal manifestations with each other.

$p = 0.006$). There was a significant association between skin involvement and both oral ulcers and peripheral arthritis ($p < 0.05$). Among the 31 patients with skin involvement, 22 developed oral ulcers (OR: 6.1, CI 95%: 2.713–13.829, $p < 0.001$), and 15 developed peripheral arthritis (OR: 7.0, CI 95%: 3.195–15.368, $p < 0.001$). The associations between ocular involvement and oral ulcers, thromboembolism and peripheral arthritis ($p < 0.05$) were also significant. Among the 14 patients with ocular involvement, 12 developed oral ulcers (OR: 13.9, CI 95%: 3.057–63.365, $p < 0.001$), 3 developed thromboembolism (OR: 21.6, CI 95%: 4.320–108.809, $p < 0.001$), and 7 developed peripheral arthritis (OR: 6.3, CI 95%: 2.114–18.883, $p = 0.001$). There was a significant association between liver involvement and oral ulcers ($p < 0.05$). Oral ulcers (OR: 6.5, CI 95%: 1.301–33.022, $p = 0.009$) were observed in 6 of the 8 patients with liver involvement. Significant associations were detected between oral ulcers and peripheral arthritis, axial arthropathy, skin involvement, ocular involvement, liver involvement and thromboembolism ($p < 0.05$). Among the 109 patients who developed oral ulcers, 30 had peripheral arthritis (OR: 3.7, CI 95%: 2.014–6.890, $p < 0.001$), 24 had axial arthropathy (OR: 2.7, CI 95%: 1.464–5.241, $p = 0.001$), 22 had skin involvement (OR: 6.1, CI 95%: 2.713–13.829, $p < 0.001$), 12 had ocular involvement (OR: 13.9, CI 95%: 3.057–63.365, $p < 0.001$), 6 had liver involvement (OR: 6.5, CI 95%: 1.301–33.022, $p = 0.009$) and 6 had thromboembolism (OR: 13.1, CI 95%: 1.565–110.759, $p = 0.002$). A significant association was detected between thromboembolism and peripheral arthritis, ocular involvement, and oral ulcers ($p < 0.05$). Among the 8 patients who developed thromboembolism, 4 developed peripheral arthritis (OR: 8.0, CI 95%: 1.735–36.889, $p = 0.002$), 3 developed ocular involvement (OR: 21.6, CI 95%: 4.320–108.809, $p < 0.001$), and 6 developed oral ulcers (OR: 13.1, CI 95%: 1.565–110.759, $p = 0.002$). No associations were found between neurological involvement and other EIMs (Table 2).

Discussion

CD is a multifactorial polygenic disease with genetic heterogeneity. In genetically predisposed people, the disease develops as a result of dysregulation of the immune system secondary to stimuli such as enteric antigens and disruption of the mucosal barrier[13,14]. CD predominantly affects the intestines but is also associated with many EIMs[15]. Previous studies have reported highly variable rates of EIMs in patients with CD. A study by Bernstein et al. conducted on a Canadian population that included only a limited number of EIMs reported a prevalence of 6.2%[5]. A Korean review of 13,925 patients with CD from 17 studies reported a 22.9% rate of EIMs, with musculoskeletal, ocular, and skin manifestations frequently observed among these patients[10]. A study of a Greek population that included 1001 patients with CD reported that the rate of EIMs was approximately 44%, with a single EIM accounting for 24% of the patients and two or more EIMs accounting for 20%. In that study, joint and mucocutaneous manifestations were the most common findings[16]. A study from Switzerland of 580 patients with CD reported that the rate of EIMs was 42.9%, with a single EIM in 27.6% and two or more EIMs in 15.3%, most commonly arthritis, aphthous stomatitis, erythema nodosum and uveitis[4]. In the present study, 47.3% of the patients developed EIMs, 24.4% developed a single EIM, and 22.9% developed two or more EIMs. Unlike in other studies, in this study, the most common EIMs were found to involve the mouth, followed by joint and skin involvement.

The different results of these studies are due to differences in genetic and geographical characteristics and the different definitions of an EIM[18–20]. The fact that oral aphthae were significantly more common in the current study than in other studies is the most important reason for the high rate of EIM in this study. In another study conducted in a Turkish population, aphthous ulcers were reported in 33% of CD patients[17].

Although EIMs frequently accompany CD, it is still unclear whether EIMs are a direct result of the inflammatory process in the intestines or whether there is a common genetic background that causes a dysfunctional immune response to environmental stimuli[21]. Epidemiological and genome-wide related studies have emphasized the importance of the role of genetics in the development of EIMs. The effect of genetic factors on the development of EIM first came to prominence after studies showing that EIM development was observed in 70% of parent-child pairs and 84% of sibling pairs[22]. Similarly, humoral immunity has been shown to play an important role, and EIMs that develop due to high levels of autoantibodies, such as in p-ANCA-associated primary sclerosing cholangitis, have been shown to develop much less often in the Asian population than in the Western population[23]. In addition, NOD2, a well-known genetic mutation in Crohn's disease, has been reported to be a risk factor for the development of sacroiliitis and uveitis[21,24]. The greater prevalence of autoimmune diseases in women than in men and the presence of hormonal differences suggest that the development of EIMs may also be related to sex[25].

The organs most affected by EIMs are the joints, skin and eyes. Although the underlying cause is not fully understood, the high incidence in these organs suggests a common pathophysiological mechanism[21]. In addition, while erythema nodosum, episcleritis, oral aphthous ulcers and peripheral arthritis have been associated with intestinal activity, spondyloarthropathy and PSC are not associated with intestinal activity, and the relationships between intestinal activity and pyoderma gangrenosum and uveitis are not clear[26,27]. In a study by Vavricka, in which the relationships of EIM findings with each other were investigated, there was a significant relationship between peripheral arthritis and ankylosing spondlitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, and uveitis. There was also a significant relationship between uveitis and peripheral arthritis, ankylosing spondlit, erythema nodosum, pyoderma gangrenosum and aphthous stomatitis. However, it has been reported that there is no relationship between psoriasis and primary sclerosing cholangitis or other EIMs[4]. Other studies have reported a significant relationship between the development of peripheral arthritis and erythema nodosum, pyoderma gangrenosum and aphthous stomatitis[28,29]. In the present study, a significant relationship was detected between the development of peripheral arthritis and axial arthropathy, skin involvement, ocular involvement, oral aphthous stomatitis and thromboembolism. Moreover, there was a significant relationship between oral aphthous stomatitis and peripheral arthritis, axial arthropathy, skin involvement, ocular involvement, liver involvement and thromboembolism. The relationships between

thromboembolism and peripheral arthritis, ocular involvement, and oral aphthous stomatitis were significant, but no significant relationships were detected between neurological involvement and other EIMs.

The pathophysiological mechanisms underlying the development of EIMs in patients with CD are not yet fully understood. However, genetic factors and immunity are known to play important roles[30–32]. The diseased gastrointestinal mucosa may trigger an immune response in the extraintestinal tract because of common shared epitopes such as intestinal bacteria and synovia. In particular, the positive relationships among the joint, skin, ocular and biliary systems suggest that a common pathological mechanism triggers existing EIMs. It has been shown that joint, skin and biliary damage is associated with immune reactions against bacteria that contain a common epitope that leaks from the damaged and dysfunctional intestinal barrier[29,33].

A previous study revealed an autoimmune reaction to the isoform of tropomyosin (tropomyosin-associated peptide) expressed in the eyes (nonpigmented ciliary epithelium), skin (keratinocytes), joints (chondrocytes), bile epithelium and intestine[34]. It is also known that the development of EIMs in IBD is associated with histocompatibility complex loci. While EIMs are more common in CD patients with positive HLA-A2, HLA-DR1 and HLA-DQw5, EIM is more likely to occur in UC patients when the HLA-DR103 genotype is present. Specific HLA complexes are also associated with specific EIMs. While HLA-B8/DR3 is associated with an increased risk of PSC in UC patients, HLA-DRB1*0103, HLA-B*27 and HLA-B*58 are associated with EIMs of the joints, skin and eyes, respectively[35,36].

This study has several limitations that may impact the interpretability of the results. First, the data may not reflect the general Turkish population, as they were only collected from a single tertiary-level referral center. Second, it should be considered that some findings may have been overlooked due to the retrospective screening of patient files. In addition, as the data were collected from patients who were followed up for 25 years, the documentation of some EIM diagnoses prior to digital recording systems may not have been available. Another limitation of our study was that patients lost to follow-up were not included in the final analysis because complete longitudinal data were required to assess primary outcomes. However, the structured characterization of EIMs, analyses of the relationship between the development of different EIMs, and long-term follow-up of a large number of patients can be considered strengths of this study.

In conclusion, the results of this study demonstrated that at least one EIM develops in approximately 50% of CD patients and that two or more EIMs develop in 25% of patients during long-term follow-up. EIMs are highly variable, ranging from mucocutaneous and joint involvement, which only impairs quality of life, to life-threatening vascular complications and liver injury. Moreover, one EIM can contribute to the development of another, and there is a relationship between EIMs. Therefore, a multidisciplinary approach should be provided to patients with CD. When the prevalence of EIMs and their relationships with each other are well known, improvements in terms of timely diagnosis and appropriate management of EIMs can be made. Physicians who are responsible for the management of patients with CD should question systemic manifestations that may develop during the course of the disease and ensure early diagnosis to prevent morbidity and mortality.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

Data collection was performed by YK. Statistical analysis was performed by GK, RD and AO. ACO ,FA, KD and GK conducted the literature search, writing of the article and confirm the authenticity of all the raw data. YK, BB, FB and SK analyzed the results and contributed to the final manuscript. The original draft was written by YK, AO. All authors read and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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