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Crohn's disease and Takayasu's arteritis: are they associated?

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Abstract. – OBJECTIVE: Different types of vasculitis can occur in patients with inflammatory bowel disease [IBD], but large vessels vasculitis seems to be the most prevalent. Indeed, the presence of both Crohn's disease [CD] and Takayasu's arteritis [TAK] has previously been reported, with higher prevalence in young women between the second and the third decade of life. This article aims to provide clinicians with an accurate picture of the most common clinical features and current treatment strategy for patients with both CD and TAK.

PATIENTS AND METHODS: We described the coexistence of CD and TAK in three young women and also performed an extensive literature review about the association of these two immune-related disorders. Research on PubMed server was performed typing the terms "Takayasu's arteritis and inflammatory bowel disease", "Takayasu's arteritis and Crohn's disease", and "Takayasu's arteritis and Ulcerative colitis".

RESULTS: Although the association of CD with TAK is uncommon, due to the severity of both diseases, concomitance in the same patient may significantly complicate the diagnostic and therapeutic work-up. In addition, since TAK can compromise intestinal vasculature, it may possibly exacerbate the clinical course of patients with IBD. All patients we reported underwent surgery due to IBD complications and two of them started biological therapy with different outcomes.

CONCLUSIONS: Early detention of these conditions has a great importance for both gastroenterologists and immunologists, for ensuring a tailored multidisciplinary management, possibly in order to identify a common therapy for these two immune-related disorders.

Key Words:
Crohn's disease, Inflammatory bowel disease, Takayasu's arteritis, Tumour-necrosis factor-α, Ustekinumab.

Abbreviations

Crohn's disease [CD], Takayasu's arteritis [TAK], inflammatory bowel disease [IBD], gastrointestinal [GI], extraintestinal manifestations [EIMs], C-reactive protein [CRP], erythrocite sedimentation rate [ESR], ultrasonography [US], computed axial tomography [CT], magnetic resonance imaging [MRI], azathioprine [AZA], mercaptopurine [MP], methotrexate [MTX], infliximab [IFX], adalimumab [ADA], disease-modifying antirheumatic drugs [DMARDs], tumour-necrosis factor-α [TNF-α], interleukin [IL], acetylsalicylic acid [ASA], ulcerative colitis [UC], 5-aminosalicylic acid [5-ASA], , computed tomography angiography [CTA], 18-fluorodeoxyglucose (FDG) positron emission tomography/Computed Tomography [PET/CT].

Introduction

CD is an idiophatic chronic IBD, characterized by transmural inflammation, affecting the gastrointestinal [GI] tract, with three main phenotypes: inflammatory, stricturing and penetrating, with different therapeutic managements[1]. Pro-inflammatory cytokines seem to have a relevant role in the pathogenesis of CD, even though the exact trigger responsible of inflammatory process in IBD remains understood[2]. Hundreds of genetic loci have been identified as implicated in CD's susceptibility, such as NOD2, IL23R, and IL10[1,2], with a concordance between monozygotic tweens estimated from 20% to 50%[1]. In addition to genetics, CD could be initiated by environmental factors (for example smoking habits), or drugs, such as antibiotics, oral contraceptives or non-steroidal anti-inflammatory drugs[1-3]. Overexpression of pro-inflammatory cytokines, like TNF-α, IFN-γ or IL-12, drives immune dysregu-

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lation, with activation of Th cells and important implication in cell's proliferation and differentiation, regulation of signals through NF-kB and MAPK and increase of MHCII expression[2]. The pathway of cytokines plays an important role also as therapeutic target of biological therapy, like anti-tumour necrosis factor (TNF) monoclonal antibodies (infliximab [IFX] or adalimumab [ADA]), but also humanized monoclonal antibody to the α4β7-integrin (vedolizumab)[1,4,5].

Diarrhoea and abdominal pain are the most common GI symptoms, but frequent findings are also fever, weight loss, fatigue and anorexia[1]. Bowel obstruction, fistulas or abscesses are indicative of complicated CD, with necessity of surgical approach[1,6]. Extraintestinal manifestations [EIMs] are common features, affecting 25%-40% of patients and involving dermatological, musculoskeletal, hepatopancreatobiliary ore renal systems, whose management often requires a multidisciplinary team[3-5].

Laboratory evaluation in CD correlates with disease activity, with increased C-reactive protein level [CRP], erythrocyte sedimentation rate [ESR] and faecal calprotectin; anemia and thrombocytosis may be present during acute phases[1,7]. Endoscopy with biopsies plays fundamental role in IBD's diagnosis, the differentiation of CD and ulcerative colitis [UC], as well as excluding other diseases, showing mucosal alterations such as erythema, erosions, skip lesions and longitudinal ulcers[1,7]. Histology can evidence chronic inflammation, crypt irregularity and non-caseating granulomas (about 25% of cases)[1,7]. Trans-abdominal ultrasonography [US], computed axial tomography [CT], or magnetic resonance imaging [MRI] help clinicians to determine the extent of CD or identify complications, such as stenosis or fistulas[6,7]. The therapeutic aim is to achieve and maintain remission of this chronic pathology, with a strategy that includes a multidisciplinary team with surgeon, nutritionist, rheumatologist and dermatologist, and considers the characteristic of the disease (activity, localization, presence of EIMs or perianal fistulas), also predicting severe course of the disease[1,7]. In the last years, different molecules have been tested and approved, with the possibility of a treat-to-target therapy, not only to obtain a clinical and endoscopic remission, but also to evaluate adverse events of long-term therapies, and the quality of life of (most of the time) young patients. Aminosalicylates are used in ileal, ileo-colic or colonic CD, while steroids are effective in induction of remission, but they cannot be used in the mainteinance[1,7]. Immunosuppressants include also thiopurines (azathioprine [AZA] and mercaptopurine [MP]) and methotrexate [MTX][1,7]. Anti-TNFα agents such as IFX, a chimeric anti-TNFα antibody, and ADA], a humanized monoclonal antibody, are used in moderate-severe CD, also combined to other immunomodulator[1,4,7]. In the last years the use of other two biological therapy like vedolizumab, a humanized monoclonal antibody against α4β7-integrin, and ustekinumab, a monoclonal antibody to the p40 subunit of interleukin-12 [IL-12] and interleukin-23 [IL-23], have been approved in CD[1, 8]. Surgery is the therapeutic option in complicated CD and patients with stenosis, fistulas, or perianal disease require abdominal surgery[1]. Unfortunately, about 50% of patients will develop recurrence of disease, some of whom with necessity of multiple surgeries[1].

Previously published case reports and series suggest that IBD and vasculitis could coexist possibly more frequently than would be expected by chance[9]. Different types of vasculitis can occur in patients with IBD, but large vessels vasculitis seems to be the most prevalent[9]. Takayasu's arteritis [TAK] is a chronic large vessel vasculitis characterized by granulomatous inflammation, which affects the aorta, its major branches and pulmonary arteries. As observed in many studies, TAK usually affects female patients between the second and third decade of life[10-12], and it seems to be more common in Asians compared with Whites[12-15]. However, TAK cases have been reported in all ethnicities around the world[15].

TAK symptoms may vary from non-specific constitutional symptoms (e.g., fever, night sweats, malaise, anorexia, weight loss, myalgia or arthralgias) to more characteristic features resulting from vascular involvement (e.g., limb claudication, decreased or absent peripheral pulses, vascular bruits, hypertension, and reduction or discrepancies in blood pressure due to stenotic or occlusive lesions between arms)[12-14]. The hardening and narrowing of the blood vessels with subsequent ischemia of the vascular territories involved, may also cause severe complications such as acute cerebrovascular presentation, funduscopic alterations, renal artery stenosis, myocardial ischemia, and heart failure[12,16].

Since a reliable biomarker for TAK diagnosis is currently missing, and laboratory findings are often non-specific, imaging techniques are the most important diagnostic tool used in TAK diagnosis[15]. With a sensitivity and specificity of almost 100%, conventional angiography is the gold

standard for TAK diagnosis[17]. However, in clinical practice, angiography is frequently replaced by computed tomography angiography [CTA] or magnetic resonance angiography[15,18], that can identify stenosis, calcification, and occlusions of the involved arteries[15,18,19]. Less frequently, these investigations can detect vascular ectasias, aneurisms and aortic dissection[16,19]. Other important diagnostic tools are ultrasound, which is very sensitive in defining arterial wall thickening[15], and 18-fluorodeoxyglucose (FDG) positron emission tomography/Computed Tomography [PET/CT][19], which can be useful to assess disease activity[19]. Tissue biopsy is usually not performed in TAK patients, since arteries involved are usually difficult to reach in a safe and non-invasive manner and the histological sample are rarely diagnostic in the chronic phase[17].

The mainstay of TAK therapy remains glucocorticoids[14,20], but a specific steroid-sparing treatment is generally needed. In addition, it has been reported that approximately on-half of TAK patients develop glucocorticoids-resistant disease or steroid dependency[21,22]. So far good quality evidence regarding the use of disease-modifying antirheumatic drugs [DMARDs] is still lacking[16]. Throughout the years many therapeutic strategies have been performed, showing variable efficacy for MTX, mycophenolate mofetil, leflunomide and AZA[16]. Biologics such as ADA, IFX and tocilizumab (a monoclonal antibody that competitively inhibits the binding of interleukin-6 [IL-6] to its receptor [IL-6R])[23] have been used to treat refractory TAK, but their efficacy and safety have not been completely evaluated[21].

Patients and Methods

We performed a single-center retrospective data analysis of 3800 patients affected by IBD referred and/or managed within the Gastroenterology Unit, Department of Clinical Medicine and Surgery, Naples, Italy, starting from 1990. We reported 3 subjects (Table I) who presented with TAK, confirming that the concomitance of these two clinical entities in the same patient is rare, but possible.

Table I. Characteristics of 3 patients with inflammatory bowel disease and Takayasu's arteritis.

Patients' features	Patient 1	Patient 2	Patient 3
Gender (M/F)	F	F	F
IBD type	CD	CD	CD
Extraintestinal manifestations	Erythema nodosum	Metastatic CD	Erythema nodosum
TAK presentation symptoms	Headache Amaurosis fugax Paresthesia Hypothermia Muscular cramps Absent right radial pulse	NA	Pain on right arm Absent right radial and brachial pulse
Age at IBD diagnosis (years)	9	15	20
Age at TAK presentation (years)	23	NA	23
IBD complications	Entero-enteric fistula	Appendicitis Toxic megacolon Perianal fistula Ischiorectal abscess	Perianal fistula
Surgery	Subtotal colectomy Ileocecal resection Ileal resection	Appendicectomy Colectomy Fistulotomy	Fistulotomy Left proctocolectomy
Treatments	Glucocorticoids Sulfasalazine Acetylsalicylic acid	Glucocorticoids 5-ASA Infliximab	Mesalamine Adalimumab Glucocorticoids Vedolizumab Ustekinumab
Outcome	Clinical remission	Death	Clinical remission

IBD: inflammatory bowel disease; CD: Crohn's disease TAK: Takayasu's arteritis; NA: not applicable; ASA: acetylsalicylic acid; 5-ASA: 5-aminosalicylic acid.

We also performed a literature review about the association of these two immune-related disorders. Included in the review were all articles from September 2020 and earlier written in English, published in peer-reviewed and international journals which dealt with the association of TAK and IBD. We searched for original articles, case reports, and letters to editor reporting the association of TAK and IBD in a medical online database (PubMed). The keywords used for searching PubMed were "Takayasu's arteritis and inflammatory bowel disease", "Takayasu's arteritis and Crohn's disease", "Takayasu's arteritis and Ulcerative colitis".

Results

Case Report 1

A 19-year-old woman was referred to our Department in 1990, with 10-year history of severe ileo-colic CD and erythema nodosum treated with glucocorticoids, sulfasalazine, and sub-total colectomy with ceco-anal anastomosis. In September 1994, the patient was hospitalized due to exacerbation of CD and the unresponsiveness to medical therapies. This led to ileocecal resection with permanent ileostomy, with a subsequent laparotomic drainage of an abscess of the Douglas space. In the same year, the patient began to complain of headache, amaurosis fugax, paraesthesia and hypothermia of the right hand, nocturnal paraesthesia and cramps of the right leg. In addition, physical examination revealed absent right radial pulse. A duplex scan showed bilateral intima thickening of common carotids and right subclavian, with moderate stenosis. This pattern was coherent with diagnosis of TAK and therapy with acetylsalicylic acid [ASA] and low dose glucocorticoids was started. In 1995, she underwent oophorectomy due to a simple cystoma of left ovary. Two years later, because of recurrent subocclusive episodes, adhesiolysis with right annessiectomy was performed. In the following years, she continued gastroenterological and immunological follow-up. In February 2019 she referred abdominal pain with increased ileostomy output; abdominal US showed entero-enteric fistula, confirmed by MRI enterography. In April 2019, she was hospitalized in our Department and she underwent ileal resection with new ileostomy. In October 2020, the patient repeated ileoscopy, with evidence of active CD, so she is going to start therapy with ustekinumab.

Case Report 2

In 1984, a 15-year-old Italian woman affected by TAK, presented to the Emergency Department with acute right lower quadrant abdominal pain, diarrhoea, fever and anorexia. Hence, given the presumed diagnosis of acute appendicitis she underwent an appendectomy. Some months later, due to the worsening of GI symptoms, she was admitted to the Surgical Department where she was diagnosed with ulcerative colitis [UC] complicated by toxic megacolon and she underwent an urgent colectomy with ileorectal anastomosis.

In 1987, the patient developed a perianal fistula, so fistulotomy and drainage of ischiorectal abscess was performed. Rectoscopy and rectal biopsies were compatible with diagnosis of CD; consequently, the diagnosis changed from UC to CD and she started a therapy with 5-aminosalicylic acid [5-ASA] and glucocorticoids. In 1999, after evaluation of TAK activity in another Hospital, the patient was referred to our Department because of persistence of diarrhoea and occurrence of large perineal erosions and a large ulcer in the intergluteal sulcus. Endoscopy showed active CD and rectal biopsies revealed inflammatory cell infiltration, cryptitis, and vasculitis. Physical examination of perineum showed cutaneous erosions with purulent serum exudate, genital edema and multiple pedunculated polypoid growths on the external genitalia. A skin biopsy led to the diagnosis of metastatic CD. In June 2000, she started anti-TNF-α therapy with IFX, with clinical and biochemical benefits. During the second administration of IFX, she had a severe adverse reaction with laryngospasm, hypotension and cutaneous rash leading to therapy discontinuation. Unfortunately, one year later, the patient died from an ischemic stroke.

Case Report 3

A 20-year-old female patient presented to our Department in December 2013 with diarrhoea, low-grade fever, oral ulcers, and erythema nodosum. Ileocolonoscopy with biopsies was performed, and she was diagnosed with ileo-colic CD. Hence, a therapy with mesalamine and ADA was started. Eight months later, she temporarily discontinued biological therapy because of HPV infection, which was successfully treated. In December 2014, after the reintroduction of ADA, she attended our unit complaining fever (until 38° C), anal pain and rectal bleeding, which required hospitalization. Laboratory findings showed CRP increase (2.04 mg/dl) and anaemia (haemoglobin:

10.9 g/dl). Pelvic-MR showed a perianal fistula, and in February 2015, she underwent lay open fistulotomy. In August 2016, she experienced pain on right arm, exacerbated by movements, so she was again admitted to our Department. Physical examination revealed that the right radial and brachial pulses were markedly reduced; the left radial and brachial pulses were normal, as the other peripheral pulsations; there was no systolic bruit in either the carotid or other arteries. Power Doppler examination showed wall thickening and sub-occlusive stenosis of right subclavian and humeral arteries, with normal carotid arteries. Similar findings were obtained with CTA and PET/CT. These observations taken together were in accordance with diagnosis of TAK. Hence, she was discharged from the hospital in November 2016 with glucocorticoids treatment. In April 2017, she reintroduced ADA in combination with glucocorticoids. After 2 months from the beginning of biological therapy the patient presented with mycotic and herpetic infections. Hence, ADA was discontinued, and after a one-month washout, we switched to vedolizumab in association with low dose of glucocorticoids. In April 2018, despite the biological therapy, the patient showed worsening symptoms, malnutrition and severe endoscopic activity of CD, therefore she underwent left proctocolectomy with temporary ileostomy. One month later, she presented with rectal bleeding, so she was hospitalized again in our Department, and endoscopic re-evaluation showed active CD with colonic involvement. After multidisciplinary evaluation with immunologists, she started therapy with ustekinumab. At the time of writing, she is on the same biological treatment associated with low dose steroids, with good clinical response.

Discussion

CD is an IBD that can affect people of any age; its incidence and prevalence are increasing worldwide, in particular in developed countries[1,3,5,7]. Diarrhoea and abdominal pain are the most common GI symptoms; fever, weight loss, fatigue and anorexia are typical findings in CD[1,7]. Up to 40% of patients can experience EIMs, involving dermatological, musculoskeletal, hepatopancreatobiliary ore renal systems, whose management often requires a multidisciplinary team[3-6].

TAK is an idiopathic granulomatous vasculitis, involving the aorta and its major branches[10,11]. Vessel inflammation, with thickening of the wall and intense perivascular infiltrates, can lead to fibrosis, stenosis and thrombus formation[14,20]. Different types of vasculitis can occur in patients with IBD, including cutaneous vasculitis and ANCA associated vasculitis, but large vessels vasculitis (mainly TAK) seems to be the most prevalent[9]. Indeed, the presence of both CD and TAK has previously been described, with higher prevalence in young women between the second and the third decade of life[1,9,14,24]. In 1976, Yassinger et al[25] described for the first time a case of 15-year-old patient affected by IBD and large vessel lesions, compatible with TAK. Later in 1991, Wakefield et al[26] observed granulomatous vasculitis in 15 of 24 patients who underwent bowel resection because of CD. Vasculitis was an evidence found in colonic biopsies of our second patient. A review of literature by Kusunoki et al[24] identified 37 patients affected by both CD and TAK: in 78% of them, CD's diagnosis preceded or was simultaneous to TAK's diagnosis; most patients had therapy with prednisolone (alone or associated to other immunosuppressants) and 4 of them underwent surgery because of CD. In a French study, Reny et al[27] described 44 patients with TAK; 4 of them were also affected by CD (9%): this group included younger people and with more systemic symptoms than the patients with TAK alone[27]. The prevalence of CD was high as 6% in a study of 32 North American patients with TAK[28]. However, the exact frequency of this association could not be determined, because a multicenter study with a broad IBD cohort is currently missing. In addition, both TAK and CD are rare diseases and the likelihood of their coexistence in the same patient remains very low. These patients can be particularly challenging for physicians, since TAK may present with gastrointestinal bleeding due to the involvement of the aorta and its vasculature (mesenteric arterial involvement occurs in 11 to 28% cases[29]). Despite isolated GI vasculitis without systemic symptoms is a rare condition, patients with TAK may experience abdominal pain, nausea, vomiting, weight loss, and melena[30, 31], but these symptoms could be referred to the underlying GI disorder[32]. Intestinal ischemia as the first manifestation of TAK has been rarely reported in the literature[33]. However, in a recent study Mirouse et al[34] indicated mesenteric ischemia as one of the main causes of death (25%) in a cohort of 318 patients with TAK. For this reason, gastroenterologists should be aware of TAK as a rare cause

of gastrointestinal vasculitis in young adults, and that TAK can exacerbate the clinical course of patients with IBD[13,32].

According to Seyahi et al[15] patients who have both TAK and CD seems to share such common features as an earlier onset of TAK and predominant constitutional and vascular symptoms. In addition, IBD diagnosis usually precedes that of TAK. The review published in 2016 by Sy et al[9], including 12 patients with TAK associated to IBD, showed that most patients were women (82%), came from Asia, had systemic symptoms, and had therapy with 5-ASA, corticosteroids, other immunosuppressant, including biological drugs (such as anti-TNFα), with clinical benefits and tapering of steroids. Moreover, IBD's diagnosis preceded TAK's and was inactive when vasculitis was confirmed in most cases. Differently, two out of three patients had active CD when TAK was diagnosed. In another study, Kusunoki et al[24] reported that in 78% of 32 patients, CD diagnosis preceded or was simultaneous to TAK diagnosis. Most of these patients were treated with prednisolone (taken alone or in combination with other immunosuppressants) and 4 of them underwent surgery due to CD complications[24]. Similarly, in our case reports, 2 out of 3 patients were diagnosed with CD before TAK diagnosis, they had therapy with glucocorticoids or biologics, and all of them underwent surgery due to IBD.

Patients affected by IBD have a risk three times higher than patients without IBD to develop venous thromboembolism, in particular during phases of active disease. In the course of hospitalization this risk has been evaluated even higher than non-hospitalized people, so in patients with moderate-severe IBD and no evidence of GI bleeding, thromboprophylaxis with anticoagulant is raccomanded[35]. The higher risk may be related to hypercoagulable state due to inflammation, in particular when other risk factors (such as immobilization, smoke, use of oral contraceptive) are presents[36]. Gastroenterologists should be aware of these potential complications and of the higher possibility of ischemic stroke, in particular when other cardiovascular risks factors are concomitant[37]. Although the pathogenesis of both diseases remains unknown, several factors have been implicated, including hereditary and infectious factors, a specific inflammatory pattern and a dysregulation of immune system[38]. Several evidence indicate that T cells-mediated immune responses play a pivotal role by inducing the release of pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-12[39,40]. In particular, TNF-α has a relevant role in the development of granulomas and, for this reason anti-TNF-α monoclonal antibodies have been considered as a therapeutic option for both granulomatous disorders[39,40]. Minami et al[41] reported a review of 9 patients (including 8 women) affected by both IBD and TAK, not responsive to conventional therapy thereby treated with anti-TNF-α therapy that resulted in improved symptoms, and tapering of steroids. Indeed, in last few years several biological drugs have been used in patients with both CD and TAK, especially to treat those patients who developed steroid dependency or adverse drug reaction to conventional DMARDs (Table II)[3,39,41-49].

The onset of vasculitis during treatment with biological therapies and vasculitis has been previously described. Ramos-Casals et al[50] reported that among 132 patients treated with TNF-α-targeting agents, including IFX, approximately 72% of them showed involvement of vasculatures localized to the skin, but there was no case of TAK. On the other hand, the onset or worsening of TAK during IFX administration in patients with concomitant IBD has been previously described by many other authors, though IFX has been considered a therapeutic option in refractory TAK[20,39,51]. The pathogenetic mechanisms involved are unknown, however an immune-related process or adverse event related to low dose of IFX may be implicated[20,39]. Similarly, in a recent review, Sy et al[9] described some patients who developed TAK during anti-TNF-α therapy. The temporal link between anti-TNF-α administration and TAK onset is pivotal for assessing a possible pathogenetic connection, especially considering that suppression of TNF-α is more likely to show good therapeutic effects in both TAK and CD, in which inflammation is at least in part dependent on this cytokine[52]. Moreover, a common inflammatory pathway mediated by the same cytokines could exist between TAK and CD as they are both Th1-predominant[52,53].

Some authors suggested a genetic link between TAK and IL-12B locus, which codifies for p40, a common subunit of IL-12 and IL-23[54-56]. IL-12B locus has been identified as a susceptibility gene for TAK and Terao et al[55,57] demonstrated that its single nucleotide polymorphism is linked to disease activity. The administration of ustekinumab in patients affected by TAK resulted in decreased levels of inflammatory markers, but no change in vascular wall enhancement was noticed[55]. A very recent

Table II. Case reports of TAK associated with IBD treated with biological drugs.

Treatment	References	IBD Type (CD/UC)	Patients (number)	Sex (M/F)	Age (years)	Other treatment	Adverse drugs reactions	Surgery	Final outcome
Infliximab	Domenech et al, 2005[42]	CD	1	F	27	Glucocorticoids	NR	NO	Clinical remission
						Azathioprine	Acute pancreatitis		
						6-Mercaptopurine			
						Mesalazine	Granulomatous hepatitis		
						Methotrexate	NR		
						Granulocytapheresis	NR		
	Kellermayer et al, 2008[43]	CD	1	F	17	Glucocorticoids	NR	NO	Clinical remission
						Mesalazine	NR		
						6-Mercaptopurine	NR		
	Katoh et al, 2010[39]	CD	1	F	20	Glucocorticoids	NR	NO	TAK developed during the infliximab therapy for CD*
						5-amimosalicylic acid	NR		
						Azathioprine	NR		
	Tung Chen et al, 2013[44]	CD	1	F	25	Glucocorticoids	NR	Subtotal colectomy with end ileostomy	Lack of response to infliximab. Switch to adalimumab with good clinical control
						5-amimosalicylic acid	NR		
						Azathioprine	GI intolerance		
						6-Mercaptopurine	GI intolerance		
						Methotrexate	NR		
	Minami et al, 2013[41]	CD	2	F	42	Glucocorticoids	NR	NO	Clinical remission
						6-Mercaptopurine	NR		
				F	34	Glucocorticoids	NR	NO	Clinical remission
						Azathioprine	NR		
	Sy et al, 2016[9]	CD	6	1/M 5/F	16 (median age)	Glucocorticoids	NR	NA	4/Clinical remission 2/NA
						Azathioprine	NR		
						5-amimosalicylic acid	NR		
							Methotrexate	NR	
							Abatacept	NR	
							Adalimumab	NR	

Continued

Table II *(Continued)*. Case reports of TAK associated with IBD treated with biological drugs.

Treatment	References	IBD Type (CD/UC)	Patients (number)	Sex (M/F)	Age (years)	Other treatment	Adverse drugs reactions	Surgery	Final outcome
Adalimumab	Yilmaz et al, 2012[45]	CD	1	F	24	Glucocorticoids Sulfasalazine Methotrexate Azathioprine Cyclophosphamide Leflunomide Etanercept	NR NR NR NR NR NR NR	NO	Clinical remission
	Kiyohara et al, 2015[46]	CD	1	F	23	Glucocorticoids Mesalazine	NR Drug-induced liver dysfunction	NO	Adalimumab induced aortitis*
	Singh et al, 2014[47]	CD	1	F	26	Glucocorticoids Azathioprine	NR NR	NO	Clinical remission
	Sy et al, 2016[9]	CD	3	F	14 (median age)	Glucocorticoids Azathioprine Methotrexate Infliximab Abatacept	NR NR NR NR NR	1/Subtotal colectomy with end ileostomy	1/Clinical remission 1/NA 1/Recurrent flares
		UC	1	F	16	Glucocorticoids 5-amimosalicylic acid 6-Mercaptopurine	NR NR NR	NO	Active disease on glucocorticoids and adalimumab
	Scheicht et al, 2019[48]	CD	1	F	21	Glucocorticoids Mesalazine Methotrexate	NR NR NR	Perineal abscess/ fistula repair	Clinical remission
Abatacept	Sy et al, 2016[9]	CD	1	F	8	Glucocorticoids Azathioprine Methotrexate Leflunomide Rituximab Adalimumab Infliximab	NR NR NR NR NR NR NR	Ileostomy Subtotal colectomy Aortic stent	Recurrent flares

Continued

Table II *(Continued)*. Case reports of TAK associated with IBD treated with biological drugs.

Treatment	References	IBD Type (CD/UC)	Patients (number)	Sex (M/F)	Age (years)	Other treatment	Adverse drugs reactions	Surgery	Final outcome
Tocilizumab	Nishimoto et al, 2008[49]	UC	1	F	20	Glucocorticoids Cyclophosphamide Cyclosporin A Leukapheresis Azathioprine Mycophenolate mofetil	NR NR NR NR NR NR	NO	Clinical remission
Ustekinumab	Present case	CD	1	F	20	Glucocorticoids Mesalamine Adalimumab Vedolizumab	NR HPV infection NR	Fistulotomy Left procto-colectomy	Clinical remission

CD: Crohn's disease; UC: ulcerative colitis; TAK: Takayasu's arteritis; GI: gastrointestinal; NR: not reported. *Patients developed TAK during biological therapy for CD.

study[21] demonstrated ustekinumab as a promising therapeutic approach for treating refractory TAK. Even in our third case report, the patient has been treated with ustekinumab for 1 year, with benefits on both TAK and CD, confirming the abovementioned data. Long-term observation is necessary to evaluate the use of ustekinumab as a therapeutic option for TAK, while it is a well-known therapeutic option in CD[58].

Conclusions

We report three patients affected by CD associated to TAK: they are Caucasian women with onset of both diseases before 30 years old. All of them showed EIMs (two of them had erythema nodosum and one was diagnosed with metastatic CD), required multiple surgeries because of worsened or complicated CD; moreover, two of them underwent surgery because of perianal localization of CD. At the time of writing, one of them is on biological therapy, with benefits in CD and TAK. Due to the severity of both CD and TAK, their concomitance in the same patient can significantly complicate the diagnostic and therapeutic work-up. Early detection of these diseases has a great importance in order to provide a tailored multidisciplinary management, and possibly to identify a common therapeutic strategy for these two immune-related disorders. For this reason, large-scale clinical investigations should be performed to better understand the possible pathophysiological link between these granulomatous inflammatory disorders and to obtain further evidence on the efficacy and safety of the long-term use of immunosuppressant and biological therapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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ALL authors approved the final version of the article, including the authorship list. The manuscript is submitted on behalf of all authors and they have all participated in the work to be published. The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration elsewhere.

Authorship Statement

Guarantor of article: Prof. Fabiana Castiglione; Specific author contributions: Alessia Dalila Guarino: planning the study, drafting the article, analysis and interpretation of data; Anna Testa: planning the study, drafting the article, analysis and interpretation of data, final approval of the article; Ilaria Mormile: drafting the article, analysis and interpretation of data; Nicola Imperatore: drafting the article, analysis and interpretation of data, critical revision of the article for important intellectual content, final approval of the article; Francescopaolo Granata: drafting the article, analysis and interpretation of data; Antonio Rispo: critical revision of the article for important intellectual content, final approval of the article; Amato De Paulis: critical revision of the article for important intellectual content, final approval of the article; Fabiana Castiglione: planning the study, drafting the article, critical revision of the article for important intellectual content, final approval of the article..

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