

RESEARCH ARTICLE

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Dermal Lesions and Skin Cancer in Patients with Inflammatory Bowel Disease Receiving Immunosuppressive Therapy

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Abstract

Background: Anti-TNF α medications represent the first effective biologic therapy for IBD that has largely revolutionized treatment. The aim of this study was to quantify the risk of MM and other skin cancers among patients from Northern Greece area with IBD who take immunosuppressive or biologic anti-TNF medications. **Methods:** The current study was conducted during a 3-year period (2014-2016). Clinical history and metabolic data of all patients were extracted from the IBD database that is kept since 1980. 101 patients with IBD from Northwestern Greece, were studied. **Results:** The mean age of enrolled patients was 44.2 \pm 15.9 years old ranging from 17 years to 77 years old. No sun burn was reported from the 44.6% of the patients, 53.5% presented mild reticular veins in the face, and lack of any elastosis was noticed in 60.4%. The occurrence of two cases with squamous and basal cell carcinoma is an important finding. The absence of any case with MM should not quiet down but should strengthen our efforts for further implementation of preventive measures. **Conclusions:** Furthermore, education of patients to avoid deleterious sun exposure may help decrease MM incidence.

Keywords: Skin cancer- IBD- anti-TNF α - malignant melanoma

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Introduction

Ulcerative Colitis (UC) and Crohn's Disease (CD) are the two main types of Inflammatory Bowel Diseases (IBD) and present several similarities but also major differences in their clinical presentation, as well as their therapeutic management. The exact etiology of the IBD is unknown, however various genetic, environmental, immunological, nutritional and psychological factors have been involved (Pierik et al., 2005). The incidence and prevalence of IBD, according to international registries, has been shown to increase throughout the world. It seems that the higher incidence of the disease occurs in Europe (24.3 per 100,000 person-years for UC and 12.7 per 100,000 person-years for CD). A lower incidence is observed in Northern America (19.2 per 100,000 person-years for UC and 20.2 per 100,000 person-years for CD) and even lower in Asia (6.3 per 100,000 person-years for UC and 5.0 per 100,000 person-years for CD) (Yulan et al., 2015; M'Koma, 2013).

The management of IBD includes various drug and surgical therapies. Drug therapy aims to reduce symptoms and relapses but also to delay or reverse the progress of the disease itself. The basic categories of

medicines that are provided in patients with IBD are the aminosalicylates, corticosteroids and immunosuppressives (Pierik et al., 2005). The pathogenesis of IBD disorders and other immune-mediated inflammatory diseases has led to the development of new and more specific biologic therapies that are proving more effective than traditional agents. Anti-TNF α medications, such as Infliximab (Remicade), are genetically engineered monoclonal antibodies that target the proinflammatory cytokine Tumor Necrosis Factor- α (TNF- α) and represent the first effective biologic therapy for IBD that has largely revolutionized treatment (Travassos and Cheifetz, 2005). Randomised clinical trials have shown the efficacy of infliximab in moderately to severely active luminal CD and also in CD with draining fistulas. Efficacy of infliximab has been reported in a population based IBD cohort comprising mainly of CD patients (Present et al., 1999; Ljung et al., 2004). Adalimumab (ADA) (Humira), is a subcutaneously administered, recombinant fully human IgG1 monoclonal antibody that binds with high affinity and specificity to human TNF- α , thus modulating its biologic functions and its proinflammatory effects. Available studies suggest

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that ADA has the potential to induce and maintain clinical response and remission in moderate-severe CD, both in anti-TNF-native patients and in subjects who lost their response and/or became intolerant to infliximab. ADA also seems effective in maintaining corticosteroid-free remission and obtaining complete fistula closure (Cassinotti et al., 2008).

IBD is a chronic autoimmune condition that is also associated with increased risk of development of skin cancer, especially when these patients are using these immunosuppressant medications. Proposed mechanisms predisposing IBD patients to skin cancer include chronic inflammation, cellular damage and underlying immune dysfunction, leading to altered tumor surveillance. Use of immunosuppressive medications and the effect of the IBD itself have been associated with a 4–7-fold increased risk of skin cancer (Singh et al., 2014; Long et al., 2012). Nonmelanoma Skin Cancer (NMSC) is the most common malignancy in humans and Basal Cell Carcinoma (BCC) is the most common NMSC outnumbering Squamous Cell Carcinomas (SCC) by a ratio of 4 to 1. Malignant Melanoma (MM) is the most fatal type of skin cancer; approximately 9,500 people died from melanoma in US in 2013 (American Cancer Society, 2013). The association of IBD and its treatment with a higher risk of MM and NMSC has been controversial (Kowalick et al., 2009; Khan et al., 2009). An increased risk of MM in patients with CD was shown in a study by Long et al. (2012), although the absolute risk of MM in patients with IBD remained quite low at 57/100,000 person-years. In the same study an increased risk of NMSC was driven by the use of thiopurines with an absolute risk of NMSC reaching 912/100,000 person-years (Long et al., 2012). This risk may be related to a combination of factors, including the immune dysfunction associated with IBD, the medications used in the therapy of IBD, or increased detection of MM in this population related to residual confounding from IBD-associated increased health care utilization. Other studies did not find an increased risk of MM in IBD patients. Nevertheless, defining the risk of MM and NMSC in patients with IBD is paramount, because preventive measures (such as sunscreen use) that have been shown to reduce the incidence of MM (Lund et al., 2011; Pedersen et al., 2010) may be of utmost importance in these patients.

The aim of this study was to quantify the risk of MM and other skin cancers like SCC and BCC among patients from Northern Greece area with IBD, who take immunosuppressive or biologic anti-TNF medications.

Materials and Methods

Study Population

Currently we enrolled patients with IBD from Northwestern Greece who were followed-up in the Gastroenterology Department of the University Hospital of Ioannina, the Gastroenterology Group of Northwestern Greece and the Ophthalmology outpatients' department of the University Hospital of Ioannina. Clinical history and metabolic data of all patients were extracted from the IBD database, that is kept since 1980. 101 patients with IBD were studied: 53 patients with UC and

48 patients with CD. Patients were taking either classical therapy with azathioprine and/or mesalazine (n=42, mean duration 7 years, ranging from 3-19 years) or biological factors including Infliximab (Remicade) (n=49) and Adalimumab (Humira) (n=10) (mean duration 6 years, ranging from 2-15 years). The current study was conducted during a 3-years period (2014-2016).

Documentation of IBD diagnosis

The diagnosis of IBD was based on clinical, radiographic, endoscopic and histological criteria. In the current study we enrolled exclusively patients with confirmed diagnostic criteria at least twice within 6 months. In patients diagnosed with UC the extent of disease was recorded at the time of the maximum intestinal involvement: pancolitis (involvement of the entire colon or proximal to the transverse colon), left-sided colitis (no involvement proximal to the splenic turn) or proctitis (no involvement proximal to the rectum or the last 15 cm of the colon).

To ensure a systematic report of patient's information, a specific platform was designed in order to record basic demographic characteristics such as age, gender, etc as well as the main type of disease (CD or UC). The report of skin/dermal characteristics included the skin colour, eyes' colour, the phototype of each patient (light/Fitzpatrick 1-2 -moderate/Fitzpatrick 3-4, and dark/Fitzpatrick 5-6) and the frequency of sunburns (Fitzpatrick et al., 2003). Also, several important risk factors for increased risk of skin cancer (e.g. professional sun exposure, smoking etc) were recorded. Finally, we recorded reticular veins, elastosis level, the number of pigmented moles and actinic keratosis (Grade 1-3). Grading of actinic keratosis was as follow: Grade 0: No actinic keratosis, Grade 1: 1-4 actinic keratoses, Grade 2: 5-9 actinic keratoses and Grade 3: ≥ 10 actinic keratoses.

Ethical Considerations

All patients gave their signed consent for their participation in the current study (IBD study cohort). Anonymity of all patients' data was preserved during the entire study period.

Statistical Analysis

Descriptive statistics were performed to present the sample responses. The results are presented in percentage distributions, mean values and standard deviations. Data analysis was performed using the statistical program SPSS 25 (statistical package for social sciences).

Results

The mean age of enrolled patients was 44.2 ± 15.9 years old, ranging from 17 years to 77 years old. The majority of our patients was males (59.4%), while 52.5% suffered from UC and the rest 47.5% from CD.

Most of our patients (48.5%) received Remicade as part of their therapy, while a small percentage (9.9%) received Humira. In 61.4% of our patients a moderate skin color level was observed and the majority had dark

Table 1. Demographics

	Number	%
Women	41	40.6
Men	60	59.4
Total	101	100.0
CD	48	47.5
UC	53	52.5
Total	101	100.0
Treatment		
Remicade	49	48.5
Humira	10	9.9
R->H	5	5.0
H->R	4	4.0
No Answer	33	32.7
Total	101	100.0
Skin Color		
Fair	19	18.8
Median	62	61.4
Dark	20	19.8
Total	101	100.0
Phototype		
Fair (Fitzpatrick 1-2)	37	36.6
Median (Fitzpatrick 3-4)	43	42.6
Dark (Fitzpatrick 5-6)	21	20.8
Total	101	100.0
Eye Color		
Fair	32	31.7
Dark	69	68.3
Total	101	100.0
Smoke		
Never	42	41.6
Past	47	46.5
Ongoing	12	11.9
Total	101	100.0
Professional Exposure		
Indoors	43	42.6
Indoors and outdoors	33	32.7
Outdoors	23	22.8
No Answer	2	2.0
Total	101	100.0

eyes color (68.3%). Phototype mostly belonged to the middle level according to Fitzpatrick scale (i.e. 3-4) in 42.6% of the patients. Past smoking history was evident in 46.5% of the study population, while of those currently smoking mean duration of smoking was 16.2 years. Patients who reported smoking presented a mean use of 20.4 (\pm 21.5) cigarettes per day. Finally, 42.6% of our population used to work inside and 22.8% in outer space (Table 1).

No sun burn was reported from the 44.6% of the patients, 53.5% presented mild reticular veins in the face and lack of any elastosis was noticed in 60.4%.

Table 2. Skin Characteristics

	Number	%
Sun Burn		
None	45	44.6
1-4	35	34.7
5-9	8	7.9
>10	13	12.9
Total	101	100.0
Telangiectasia		
None	27	26.7
Light	54	53.5
Median	17	16.8
Heavy	3	3.0
Total	101	100.0
Solar Elastosis		
None	61	60.4
Light	32	31.7
Median	7	6.9
Heavy	1	1.0
Total	101	100.0
Actinic Scabs		
None	37	36.6
Light	54	53.5
Median	9	8.9
Heavy	1	1.0
Total	101	100.0
Number of Nevi		
None	9	8.9
1-4	35	34.7
5-9	26	25.7
>10	31	30.7
Total	101	100.0
Actinic Keratoses		
None	84	83.2
1-4	15	14.9
5-9	2	2.0
Total	101	100.0
Grade		
0 (0)	90	89.1
1 (1-4)	1	1.0
2 (5-9)	9	8.9
3 (\geq 10)	0	0.0
No Answer	1	1.0
Total	101	100.0
Skin Cancer		
No Answer	99	98.0
Squamous Cell Carcinoma (SCC)	1	1.0
Basal Cell Carcinoma (BCC)	1	1.0
Total	101	100.0

Actinic scabs was observed in 53.5% of the patients while 30.7% reported having more than 10 moles.

The majority of our patients did not report any

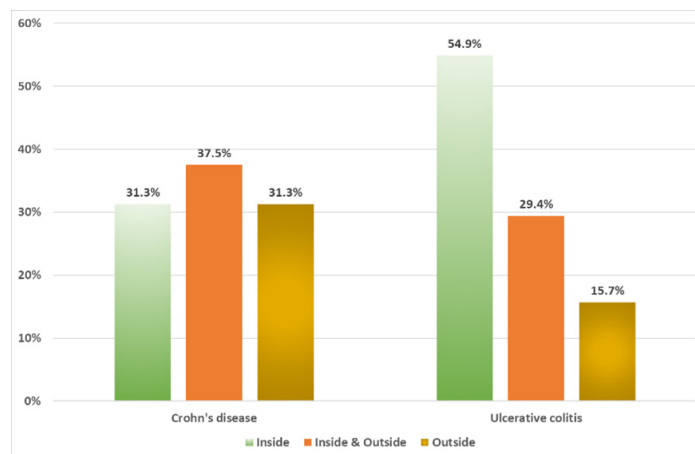


Figure 1. Disease Compared to Occupational Exposure

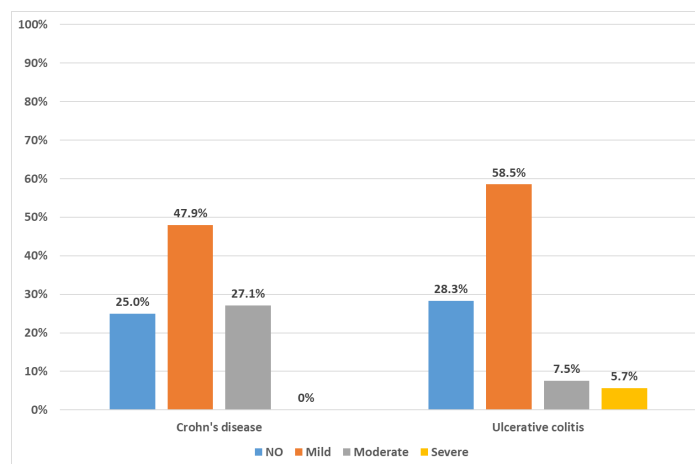


Figure 2. Disease Compared to Spider Veins

actinic keratosis (83.2%) while only 2 patients had been diagnosed with skin cancer: one with basal cell carcinoma and one with SCC (Table 2).

Men were more likely to have been diagnosed with CD (64.6% vs 35.4%) and UC (54.7% vs 45.3%) compared to women. CD is diagnosed more frequently in younger ages compared to UC (Mean values: 45.0±17.0 vs 43.7±15.0 respectively).

Most participants had a medium coloured skin both in CD and UC (60.4% and 62.3% respectively), while a light

colour was observed more often in CD vs UC patients (20.8% vs 17.0% respectively) and a dark coloured skin was more prominent in UC vs CD (20.8% vs 18.8% respectively). Most participants with either CD (72.9%) or UC (64.2%) had dark coloured eyes.

The phototype of participants was calculated based on Fitzpatrick scale 1-6. Phototype 3-4 (medium) was more often in CD (41.7%) and UC (43.4%) patients while phototype 5-6 was less frequent in both CD (22.9%) and UC (18.9%) patients.

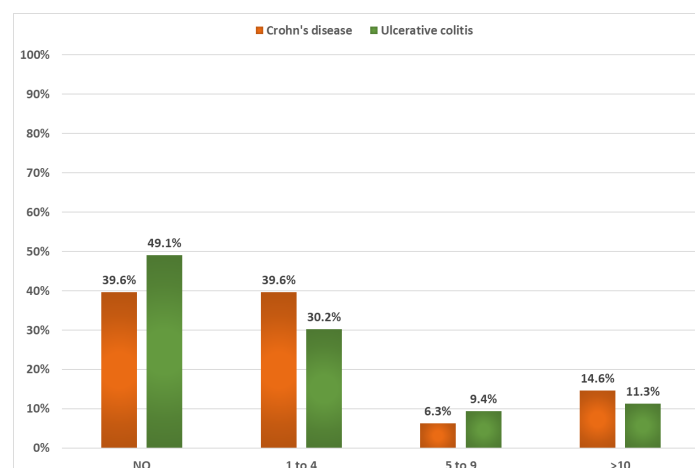


Figure 3. Disease Compared to Sunburn

Table 3. Skin Characteristics Compared to Disease

		Solar Elastosis			
		None	Light	Median	Heavy
CD	Number	28	15	5	0
	%	58.3%	31.3%	10.4%	0.0%
UC	Number	33	17	2	1
	%	62.3%	32.1%	3.8%	1.9%
		Solar Lentiginosities			
		None	Light	Median	Heavy
CD	Number	16	26	5	1
	%	33.3%	54.2%	10.4%	2.1%
UC	Number	21	28	4	0
	%	39.6%	52.8%	7.5%	0.0%
		Number of Nevi			
		None	1-4	5-9	>10
CD	Number	3	14	14	17
	%	6.3%	29.2%	29.2%	35.4%
UC	Number	6	21	12	14
	%	11.3%	39.6%	22.6%	26.4%
		Actinic Keratoses			
		None	1-4	5-9	>10
CD	Number	38	9	1	1
	%	79.2%	18.8%	2.1%	0.0%
UC	Number	46	6	1	1
	%	86.8%	11.3%	1.9%	0.0%

Patients with UC were greatly affected by an inner professional working space (54.9%) and had more spider veins, while similar sunburn rates were observed in the two groups (Figures 1-3).

Regarding elastosis, both patients with CD (58.3%) and UC (62.3%) did not have any spider veins at all. Similarly, mild forms of actinic scabs were observed in CD (54.2%) and UC (52.8%). The number of moles was highly variable, but a large number of moles (i.e. >10) was evident in a significant percentage of both CD (35.4%) and UC (26.4%) patients. Finally, low prevalence of actinic keratosis was observed in CD (2.1%) and UC (1.9%) patients (Table 3).

Discussion

Skin cancer, either MM or NMSC, has been previously shown to appear more often in immunocompromised patients (Yu et al., 2014). Patients that had undergone a transplantation had a greater risk of skin cancer (Jensen et al., 2010). The use of immunosuppressive medications has been associated with a high risk of skin cancer. Several studies have reported that medications such as calcineurin inhibitors, tacrolimus and cyclosporine have been related to an increase in skin cancer incidence by 66% (Dantal et al., 1998; Euvrard et al., 2012; Wimmer et al., 2013).

Patients with IBD are a special group of patients who may be treated with specific immunosuppressive medications. These patients may triple the risk for NMSC

due to the use of long-term immunosuppressive medications and if this risk is added to the exposition of patients to Ultraviolet Radiation (UVR) without preventive measures then the danger is clearly very high (Bahi et al., 2017).

The long-term use of Humira has been associated with an increased risk for NMSC (0.2/100 PYs) as shown by many international studies. Similarly, an increased incidence of MM is also observed in patients treated with Humira (Chakravarty et al., 2005; Burmester et al., 2009; Burmester et al., 2013; Vajdic et al., 2006). On the contrary, the study by Cleynen et al (2005) reported that the long-term administration of Anti-TNF factors did not increase the risk for (Cleynen et al., 2015).

Currently, this is an original study of a single center in patients with IBD treated with long-term immunosuppressive medications either classical immunotherapy or novel biological factors. The population enrolled is rather homogenous belonging to a geographically restricted area around Mediterranean Sea without a great variance in skin types but a high exposure to sun. The main aim of this study was to investigate the prevalence of dermatological lesions in IBD patients treated with anti-TNF factors.

The greatest part of our population was males with a greater prevalence of CD compared to women. Almost half of our patients were treated with Remicade. Most patients (42.6%) had a medium phototype (3-4??), a feature that is generally inherent and protective in the population of the specific geographic area (Saridi et al., 2014; Ergul and Ozeren, 2011). Professional

exposure (working outside), increased rates of sunburn (over 50% of patients) and smoking are three important risk factors affecting skin health that showed a great prevalence in our population.

Mild spider veins, actinic keratosis and scabs are important dermatological lesions that are not probably related to treatment. Relevant studies have shown a significant effect of Anti-TNF factors on skin health and the appearance of unfavourable dermatological conditions such as NMSC and MM (Brandse et al., 2015 ; Mocci et al., 2013; Sharara, 2016), although this is not always clear in several studies (Long et al., 2010).

The occurrence of two cases with SCC and BCC is an important finding. The absence of any case with MM should not quiet down but should strengthen our efforts for further implementation of preventive measures. Furthermore, education of patients to avoid deleterious sun exposure may help decrease MM incidence (Saridi et al., 2014; Bahi et al., 2017).

The small sample of our study should be reported as a limitation, as well as the inclusion of a population of a restricted geographic area, that may not permit the generalization of the results to a wide population. A larger and more representative of the general population specimen, could lead to more reliable conclusion of the entire Greek population. Furthermore, the study of IBD patients who are treated with anti-TNF factors is a long-term ongoing process, which may systematically lead to the identification of symptoms or complications related to the disease itself or the treatment.

In conclusions, our study showed that IBD patients treated with anti-TNF factors had various types of dermatological lesions that could be associated with immunosuppressive therapy. An increased incidence of skin cancer was not observed in our population despite the fact that these lesions may be seen as precancerous. Our findings are in agreement with previous studies. A systematic and long-term follow-up of these patients is needed to identify these dermatological lesion in time to establish early diagnosis and treatment and even better to prevent them from happening. Our center has focused on preventive dermatological follow-up in these patients who are going to start or already treated with classic immunosuppressive medications or biological factors.

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