REVIEW ARTICLE

Extra-intestinal malignancies in inflammatory bowel disease: Results of the 3rd ECCO Pathogenesis Scientific Workshop (III)

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Received 26 March 2013; accepted 5 April 2013

KEYWORDS:
Extraintestinal cancers; IBD; Crohn's disease;

Abstract

The incidence of lymphoproliferative disorders (LD) is increasing in developed countries. Patients with inflammatory bowel disease (IBD) exposed to thiopurines are at additional risk of

Abbreviations: BCC, basal cell carcinoma; CD, Crohn's disease; CIN, Cervical intra-epithelial neoplasia; COC, Combination oral contraceptive; EBV, Epstein–Barr Virus; HLH, Haemophagocytic lymphohistiocytosis; HPV, Human papilloma virus; HSTCL, Hepatosplenic T-cell lymphoma; IBD, Inflammatory bowel diseases; LD, lymphoproliferative disorder; OR, Odds ratio; PaP, Papanicolaou; SCC, Squamous cell carcinoma; SIR, Standardized incidence ratio; UC, Ulcerative colitis; UV, Ultraviolet; XLP syndrome, X-linked lymphoproliferative syndrome

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http://dx.doi.org/10.1016/j.crohns.2013.04.006
three specific forms of LD: Epstein-Barr-Virus-related post-transplant like LD, hepato-splenic T-cell lymphoma and post-mononucleosis lymphoproliferation. The risk of the two latter forms of LD can be reduced when considering specific immunosuppressive strategies in young males. It is still unclear whether the risk of uterine cervix abnormalities is increased in IBD women, irrespective of the use of immunosuppressants. Given the excess risk demonstrated in various other contexts of immunosuppression, it is currently recommended that all women with IBD, particularly those receiving immunosuppressants, strictly adhere to a screening program of cervical surveillance and undergo vaccination against HPV, when appropriate. Patients with IBD receiving immunosuppressants are at increased risk of skin cancers. The risk of non-melanoma skin cancer is notably increased in patients receiving thiopurines. Recent data suggest that the risk of melanoma is mildly increased in patients exposed to anti-TNF therapy. All IBD patients should adhere to a program of sun protection and dermatological surveillance, whose details should take into account the other non-IBD-related risk factors.

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1. Introduction

Inflammatory bowel disease (IBD)-related cancers are those attributable to chronic tissue inflammation and/or to drug-induced immunosuppression. Extra-intestinal cancers belong to the second category. We focus here on lymphoproliferative disorders (LD), skin cancers and uterine cervix abnormalities, because recent epidemiological
advances in these fields have significant consequences in clinical practice.

1.1. Lymphoproliferative disorders

LD in IBD have become a major concern for both patients and physicians. The role of immunosuppressive therapy, as well as the role of local and systemic inflammation, is interlinked, and thus difficult to distinguish. Although LD are globally infrequent in young patients, their incidence can be relatively high in some specific subpopulations and their outcomes are often severe and sometimes rapidly fatal. Here we review available data on LD pathogenesis, risk factors and epidemiology.

1.2. Epidemiology and Risk Factors

The incidence of LD has increased markedly worldwide since the 1970s and particularly in western countries. The current lifelong risk for a male reached approximately 2%. Although case series and hospital-based studies suggested an increased risk of LD in IBD patients, population-based studies showed no increase or very little increase risk of LD in IBD. However, the risk of LD has been shown to be increased by some immunosuppressants and in some specific subpopulations of IBD patients.

1.2.1. General Risk Factors for LD

Immunosuppression is one of the well established risk factor for LD. Most of the immunodeficiency-associated LD are of diffuse large B cells type and often arise in extra-nodal sites such as brain or gastrointestinal tract. Defective immune surveillance of Epstein-Barr virus (EBV) is often involved in the lymphomagenesis process in this setting. In the post-transplant setting, EBV viral load is a good marker of the risk of LD, but this strategy has not been evaluated in IBD, because it would require very large cohort studies given the relatively low incidence of LD in this population.

The other general risk factors of LD have been less studied. The incidence of LD increases with age and is slightly higher in men. Genetic factors are also involved because familial clusters have been described. In addition to EBV, other specific infectious agents have also been involved, such as human herpes virus 8 (HHV-8), human T lymphotropic virus 1 (HTLV-1), Helicobacter pylori and hepatitis C virus (HCV).

1.2.2. Specific Risk Factors for LD in IBD

1.2.2.1. Role of Local Inflammation and Immune Activation. Inflammation and immune activation themselves are considered to be involved in lymphomagenesis in inflammatory and autoimmune setting, and might play a role in LD onset in IBD. In autoimmune diseases, such as lupus erythematosus, Hashimoto thyroiditis and Sjögren’s syndrome, the risk of LD is increased 3-to 18-fold and seems to correlate with disease severity. Moreover, LD are often located in the organ in which occurs the auto-immune reaction. In inflammatory diseases such as rheumatoid arthritis, there is an increased risk of LD (approximately 2-fold) which seems to correlate with disease activity, independently of the treatment. In chronic suppuration such as long-standing pyothorax, characterized by pure inflammation without auto-immunity, there is an increased risk of pleural LD with a major role of EBV infection. Only few data are available in IBD, but it has been shown recently that those patients have an excess risk of primary intestinal LD. In this context, LD arise in IBD lesions and are often EBV-associated. Moreover, it has also been shown in the CESAME study that the duration of the disease is an independent risk factor for LD. These results suggest a role of local inflammation (and possibly of EBV) in IBD-associated lymphomagenesis.

1.2.2.2. Immunosuppressants. Immunosuppressants are the other major factor of lymphomagenesis in IBD. Of note, it is difficult to distinguish between the role of autoimmunity/inflammation and that of immunosuppressants in IBD patients, as these treatments are usually prescribed to patients with severe disease.

1.2.2.2.1. Thiopurine-associated LD. Thiopurines have been particularly implicated in IBD-associated LD risk. Besides immunosuppression itself, thiopurines might have specific pro-carcinogenic effects. It has notably been suggested that azathioprine promotes clonal expansion of rare mismatch repair (MMR)-defective myeloid cells, thus possibly playing a role in the development of some haematological malignancies. Meta-analysis of cohort studies and nationwide studies has shown that patients with IBD exposed to thiopurines have a three- to fivefold increased risk of developing LD.

Three subtypes of thiopurine-associated LD must be considered (Table 1).

1.2.2.2.1.1. LD due to Proliferation of Chronically EBV-infected Lymphocytes. Most of the cases of LD observed in IBD patients treated with thiopurine are associated with EBV. This suggests that, similarly to post-transplantation setting, immunosuppression plays a major role in lymphomagenesis through a defect in EBV immuno-surveillance (see paragraph on immunosuppression as one of the general risk factors for LD).

1.2.2.2.1.2. Post-mononucleosis Lymphoproliferation. Recently, concerns were expressed regarding the risk of early postmononucleosis lymphoproliferation associated or not with haemophagocytic lymphohistiocytosis (HLH) in thiopurine-treated IBD patients. Two fatal cases in the CESAME cohort and one other fatal case have been reported in young males, but the frequency of this dramatic complication is possibly underreported and underestimated. Although the overall risk of early postmononucleosis lymphoproliferation is very low in the total IBD population, the crude risk in young (< 35 years) male seronegative for EBV and exposed to thiopurines is high (Table 1). It seems thus reasonable to consider avoiding thiopurine in this subset of patient and preferring anti-TNF monotherapy, because this complication has not been reported yet in patients treated with anti-TNF alone.

1.2.2.2.1.3. Hepatosplenic T Cell Lymphoma. Hepatosplenic T cell lymphoma (HSTCL) is an infrequent non-EBV-related LD with about 200 cases reported in the literature, but it is often rapidly fatal. Less than forty cases have been reported in IBD to date. Patients were all treated by...
thiopurines either alone or in association with anti-TNF therapy (more than 50% of cases). Median duration of thiopurine exposure in these patients is around 6 years (more than 2 years of thiopurine intake). When data are available, patients are in most cases treated with thiopurine monotherapy (without thiopurines for less than two years of thiopurine intake) or in association with anti-TNF therapy (50% of cases). Median duration of thiopurines either alone or in association with anti-TNF therapy (more than 50% of cases). Median duration of thiopurine exposure in these patients is around 6 years (more than 2 years of thiopurine intake).

1.3. Clinical Presentation and Diagnosis (Including Imaging Techniques if Necessary)

Clinical presentation and diagnosis do not differ from cases of LD in patients without IBD.

1.4. Early Diagnosis or Detection/Surveillance

There is no specific method for early diagnosis of LD. In IBD patients receiving thiopurines, LD should be suspected in case of unexplained headache, fatigue or fever, acquired adenopathy not attributable to intestinal inflammation, increase size of spleen or liver, unexplained biological inflammatory syndrome, with or without increase in the blood level of LDH and beta2-microglobulin and HLH. In these situations, routine workup should be performed, EBV viral load should be assessed and hematologist opinion should be requested.

| Table 1 Azathioprine-related lymphoproliferative disorders. |
|------------------------------------------------------------|
| Post-transplant-like lymphoma with EBV reactivation         |
| Early Postmononucleosis lymphoproliferation in EBV-seronegative young (35 years) male⁶ |
| Hepatosplenic T cell lymphoma in young (35 years) male treated with thiopurine alone or in association with anti-TNFa |
|                                                                      |
| Crude risk in patients exposed to thiopurines per 1000 patient-years * | Recommended Risk of LD | To be discussed in the near future | To be investigated |
| 0.60 | EBV viral load in case of unusual symptoms⁷, unexplained biological inflammatory syndrome, with or without increase in the blood level of LDH and beta2-microglobulin and HLH | Avoiding thiopurines in EBV-seronegative young (<35 years) male | Monitoring EBV viral load or T cells cytotoxic functions |
| 2.90 | | | - Identify involved genes and mutations |
| 0.06 | | | - Genetic testing before treatment |

* Data from the CESAME study ; # in the absence of EBV serological test for most patients in the CESAME study, the prevalence of EBV-seronegative young male was estimated to be 20% ; $ unexplained headache, fatigue or fever, acquired adenopahies not attributable to intestinal inflammation, increase size of the spleen or the liver.

1.4.2. Methotrexate, Anti-TNF Therapy, and Risk of LD

The impact of methotrexate on lymphomagenesis has been poorly studied in IBD and can be extrapolated only from studies performed in other inflammatory conditions and particularly in rheumatoid arthritis. In the context of rheumatologic diseases, the role of methotrexate on the risk of LD is controversial. Several cases of LD have been reported in methotrexate-treated patients with RA, but a French nationwide study showed that the risk of non-Hodgkin lymphoma was not significantly increased in patients receiving methotrexate. Although no similar studies are available (or will be available in the near future) in IBD, the risk of LD associated with methotrexate seems to be low in IBD.

The risk of LD associated with anti-TNF therapy is difficult to assess in IBD because most patients receiving these biologics are also treated, or have been treated, with thiopurines or methotrexate. In a systematic review of registries and prospective observational studies of patients with rheumatoid arthritis, the pooled estimate for the risk of LD in patients exposed to anti-TNF therapy was not significantly increased. Analysis of the five-year follow-up of the Crohn’s Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, showed a similar overall incidence of LD in infliximab-treated patients (0.05 per 100 patient-years) and those who received other treatments only (0.06 per 100 patient-years). Although these results seem reassuring, a large safety cohort is urgently needed to compare the risk of neoplasia and infections associated with monotherapy and comorbidity, with an adjustment for IBD activity.

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1.5. Prevention and Risk Reduction

Theoretically, EBV-induced thiopurine-associated LD could be prevented if immunosuppressants are withdrawn before the occurrence of LD. Unfortunately, there is no defined method to identify this "prelymphoma" state. In the post-transplant setting, the risk of LD is particularly high in the first year after transplantation, notably in EBV-seronegative recipients. Transplant specialists have developed strategies, mainly based on the monitoring of EBV viral load, to identify prelymphoma state and initiate preemptive treatment. However, there is no consensus on this topic regarding the method to use and the threshold for EBV viral load. Moreover, this strategy is not validated in IBD as transient increase in EBV viral load can be observed during IBD flare. The appropriate monitoring of thiopurine-treated IBD patients regarding EBV-induced LD is thus not defined and would benefit from specific investigations.

Based on the epidemiology of HSTCL in IBD, it seems reasonable to consider avoiding association of anti-TNF therapy and thiopurine treatment beyond two years in young (<35 years) men. Regarding the risk of post-mononucleosis lymphoproliferation, thiopurine treatment should be avoided in young (<35 years) men seronegative for EBV. In this line, systematic EBV serology before initiating immunosuppressants should be discussed, even though this measure is not recommended in the current ECCO guidelines.

1.6. Treatment and Prognosis of IBD-related LD

Besides stopping immunosuppressants, which may result in some cases in LD regression, there is no specificity in the treatment of LD in IBD patients. There is no specificity in the prognosis of LD in IBD patients.

1.7. Key-messages

- Thiopurine-treated IBD patients have a three- to fivefold increased risk of developing LD. This risk increases with age and disease duration.
- Adding anti-TNF therapy to thiopurines treatment do not significantly increase the risk of LD compared to patients treated by thiopurines alone.
- Determination of systemic EBV viral load should be performed in case of clinical suspicion of LD in IBD.
- Avoiding thiopurines (preferring other immunosuppressants) should be considered in EBV-negative young males.
- Avoiding to prolong combo-therapy of anti-TNF therapy and thiopurines beyond two years in young men with controlled IBD could limit the risk of HSTCL.

1.8. Areas for Future Research

- The risk of LD associated with anti-TNF monotherapy in IBD should be identified. A large European-wide prospective safety cohort is needed.
- In parallel, we should work at identifying markers of "prelymphoma state" in order to be able to prevent, and if not possible, to detect early IBD-related LD.

2. Uterine Cervix Abnormalities

Cervical cancer is the second most common cancer in women world-wide, and the incidence of cervical cancer is higher in developing countries than in developed countries that developed an effective cervical screening program.

2.1. Epidemiology in the General Population

The worldwide prevalence of human papillomavirus (HPV) infection in women is about 10%. High-risk HPV is now considered to be the causal agent of almost all cases of invasive cervical cancer and cervical intra-epithelial neoplasia (CIN). HPV has been identified as the 'necessary cause' of cervical cancer. In other words, cancer does not develop in the absence of persistent HPV DNA. More than 95% of cervical cancer biopsies contain HPV genomes. The development of cervical cancer subsequent to HPV infection is not unavoidable. Seventy percent (70%) of women experience a viral clearance within 12 months after infection (91% within 24 months), leading to frequent spontaneous resolution of early dysplastic changes. It has been estimated that among one million women who become infected, only 10% (100,000) will develop pre-cancerous cervical cell changes. Among these, approximately 8% (8,000) will develop early cancer (carcinoma in situ) and approximately 1600 of these women will develop invasive cervical cancer. HPV infection is the most common sexually transmitted infection and the infected women become asymptomatic carriers. HPV transmission may occur with skin-to-skin genital contact. More than 40 subtypes of HPV have been identified, of which at least 15 are known to be oncogenic. According to the potential oncogenic effect, HPV genotypes are classified into two groups: high-risk (or oncogenic) types and low-risk types. HPV types 16, 18, 45 and 31 are the most ongogenic types, while HPV-6 and 11 cause benign warts and lesions that do not become malignant. Types 16 and 18 together are the causative agent of more than 50% of cervical pre-cancerous lesions (high-grade dysplasia), as well as more than 70% of all cases of cervical squamous cell carcinoma and adenocarcinoma, and 25% of low-grade cervical lesions.

2.2. Carcinogenesis

Human papillomavirus (HPV) is a double-stranded DNA virus that is non-enveloped and has an icosahedral capsid. It has been shown that viral oncoprotein E6 is involved in the transformation of host cells. Malignant cells show deregulated overexpression of E6 and E7 oncoproteins, which ultimately leads to the development of cancer. The inactivation of p53 compromises the integrity of the replicated DNA and causes DNA damage and chromosomal instability. These abnormalities result in cell proliferation or tumor development. HPV E6 proteins are also capable of immortalizing the host cell by preventing the shortening of telomere length, and thereby immortalizing the host cell.
2.3. Risk Factors for Uterine Cervix Abnormalities in the General Population

Several risk factors have been associated with the development of cervical cancer, namely prolonged combination oral contraceptive use, number of sexual partners, parity, early age at first intercourse (before the age of 20 years), tobacco smoking, co-infection with other sexually transmitted agents, concomitant infection with multiple HPV types, HPV viral load, low social class, and multiplicity of sexual partners. Increasing parity is directly related to an increased risk for developing cervical cancer. Women with one/two or seven prior full-term pregnancies have a two-fold and four-fold increased risk compared with nulliparas, respectively. The strong confounding effects from the lifestyle behavioural factors must be taken into account, while interpreting the data on oral contraceptive use. Similarly, it now seems that the increased risk (if any) of cervical cancer among smokers seems to be attributed to the increased acquisition of high-risk HPV infections, of which the smoking status is an independent predictor in a multivariate model.

In IBD current smokers, women aged less than 20 years at diagnosis, extensive disease, exposure to 10 or more prescriptions of oral contraceptives and oral contraceptives were found as risk factors for cervical dysplasia. However, in most of these studies, important HPV risk factors were not evaluated, such as the number of sexual partners, sexual transmitted diseases and education level.

2.4. Data From other Immune Related Diseases than IBD

Previous studies have demonstrated an increased prevalence of atypical cervical smears in patients with systemic lupus erythematosus. In a meta-analysis, the OR was 4. In some studies, the risk of cervical neoplasia was higher in those women exposed to cyclophosphamide. Patients using this drug developed cervical dysplasia in a shorter time. A direct relationship between the cumulative dose of cyclophosphamide and the risk of cervical dysplasia was also identified. In women with rheumatoid arthritis, an increased prevalence of abnormal cervical cytology was found compared with a control population. However, this may be related to chronic inflammatory disease and sexual behavior, because women with rheumatoid without abnormal cervicovaginal cytology have less sexual partners than those with rheumatoid arthritis and abnormal cytology.

Cervical cancer accounts for 3% of post-transplant malignancies and is reported to be the commonest form of neoplasia, after skin cancer, in female transplant recipients. In the study by Courtney et al., in 173 women submitted to renal transplantation, the incidence of smear test abnormalities was 20% in renal transplant recipients compared with 7% in the general population. In contrast, in two recent cohorts it was suggested that transplant recipients receiving long-term immunosuppression are not at increased risk of HPV infection and CIN than healthy controls. HIV-positive women are also at increased risk of developing dysplasia and invasive carcinoma of the uterine cervix.

2.5. Risk Factors of Uterine Cervix Abnormalities in IBD

One of the first reports on the links between immunosuppressant use in IBD and cervical cancer comes from Connell et al. in 1994. Two cases of invasive cervical cancers among 366 women exposed to azathioprine (0.5 expected, $P = 0.090$) were reported. More recently, two population-based studies, one from North of California, and the other from Manitoba, were published. The former, retrospective, showed an adjusted odds ratio (OR) of 1.45 for risk of cervical cancer in IBD patients. Odds ratios associated with drug use were 1.65 for 5-amino salicylates, 2.79 for corticosteroids, and 3.45 for immunomodulators ($P < 0.05$). The latter study was a case–control study nested in a population-based cohort. There was no association between cervical abnormalities and ulcerative colitis. The increase in risk in women with Crohn’s disease was limited to those exposed to 10 or more prescriptions of oral contraceptives. The combined exposure to corticosteroids and immunosuppressants was associated with an increased risk of cervical abnormalities. There was no interaction between the effect of IBD and corticosteroids and/or immunosuppressants.

In a retrospective study from a tertiary care center in Scotland, 362 women with IBD were compared with 1644 controls from the community. There was no difference in the proportion of abnormal smears between women with IBD and matched controls. There was no association with exposure to any immunosuppressant specifically, even when limited to women who were on drug at the time of smear. Bhatia et al. in a tertiary center conducted a retrospective case–control study with 116 women with IBD and a similar number of controls. Eighteen percent of IBD patients and 5% of controls had an abnormal Papanicolaou (Pap) smear ($P = 0.004$). There was no association with the use of immunosuppressive medications. Kane et al. reported the comparison between 40 IBD patients and 120 controls. The incidence of any abnormal Pap smear and higher-grade lesions was statistically higher in the IBD group versus controls. Patients on an immunosuppressant were significantly more at risk than controls and non-exposed IBD patients. Finally, two retrospective studies published as abstracts suggested higher HPV prevalence in IBD patients on immunosuppressants and an increased risk of Pap smear abnormalities in patients exposed to immunosuppressants and smokers. Taking into account these conflicting data, no definite conclusion on the role of exposure to immunosuppressants on the risk of cervical cancer in IBD patients can be made at the moment. In addition, we have few data on sexual activity and frequency of cervical screening in the IBD population, with or without immunosuppressants. It was reported that only 20% of women with IBD report moderate to high sexual activity and it is known that sexual activity and the number of partners have an impact on the rate of cervical dysplasia. Immunosuppressants were found independent predictors of lower use of Pap testing in IBD. The prevalence of surveillance in the different studies was small and varied from 11 to 65%, 40,41,38,39,42 Of note, in the two studies that demonstrated an impact of immunosuppressant use on the risk of cervical lesions, the number of IBD patients taken these drugs was lower than 60.
2.6. Screening and Prevention

Papanicolaou (Pap) test is the reference screening test for cervical alterations, with a sensitivity ranging from 30% to 87% and a specificity ranging from 86% to 100%. Among women with IBD, differences in screening rate between women with and without exposure to immunosuppressants, according to age, socioeconomic status, prior diagnostic testing, and intensity of healthcare utilization, were tested by multivariate analysis. Older age, lower socioeconomic status, lower intensity of healthcare utilization, Crohn’s disease, and exposure to immunosuppressants were independent predictors of lower use of Pap testing. Gastroenterologists should strengthen recommendations of routine Pap smears in women with IBD patients, since Long et al. reported that only 70% of women with IBD received cervical testing at least once every 3 years. Risk factors for suboptimal screening included Medicaid insurance, immunosuppressant medication use, and increased age. Cytological screening at the population level every 3–5 years results in a substantial reduction (up-to-80%) in the incidence of cervical cancer. Reduction in incidence of grade 3 cervical intraepithelial neoplasia (CIN3) is a surrogate indicator of effectiveness. Cervical cytology is the currently recommended standard test for cervix screening, which should start in the age range of 20–30 years, but preferentially not before the age of 25–30 years, depending on the burden of the disease in the population and the available resources. It is recommended to continue screening at 3- to 5-year intervals until the age of 60 or 65. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal cytology results. Women under 30 years of age should not be screened for HPV, due to the high rate of viral clearance. Young women who are infected with HIV and/or are immunocompromised should obtain a Pap test twice in the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter.

The current HPV vaccines are tetravalent HPV4 and bivalent HPV2 and both provide protection against the most two prevalent oncogenic HPV genotypes, namely HPV 16 and 18, which account for about 70% of cervical cancers. HPV4 is directed against HPV types 6, 11, 16, and 18, and was licensed by the Food and Drug Administration (FDA) for use in females in June 2006. Bivalent HPV vaccine (HPV2; Cervarix, GlaxoSmithKline) is directed against HPV 16 and 18, and was licensed for use in females in October 2009. Both vaccines are not live vaccines. Therefore, these vaccines can be safely administered to persons who are immunocompromised as a result of infection (including HIV), disease, or medications. The immune response and vaccine efficacy might be less than that in immunocompetent persons. For immunocompromised males, ACIP (Advisory Committee on Immunization Practices) recommends routine vaccination as for all females, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series. ACIP recommends routine vaccination of females aged 11–12 years. Vaccination is also recommended for females aged 13–26 years who have not been previously vaccinated or who have not completed the full series. Ideally, vaccine should be administered in sexually naive individuals, before potential genital exposure to HPV. However, females who might have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types would receive full benefit from vaccination. It seems that vaccination provides less benefit to females who have already been infected with one or more of the four vaccine HPV types. Pap testing and screening for HPV DNA or HPV antibody are not needed before vaccination at any age (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm).

2.7. Key-messages

- The majority of the studies do not demonstrate an association between uterine cervical cancer and IBD.
- It is not clear whether immunosuppressants are associated with an increased risk of cervical dysplasia in IBD, while in some other immunomodulated diseases, exposure to immunosuppressants is associated with higher dysplasia prevalence.
- Smoking cessation and counseling about family planning (avoiding long term use of combination oral contraceptive) and sexual practices should be adopted as preventive proceedings in IBD women with cervix abnormalities.
- Gastroenterologists need to improve the rate of recommending routine Pap smears in women with IBD.
- Young immunocompromised women should obtain a Pap test twice in the first year after diagnosis and, if the results are normal, annually thereafter.
- Human papillomavirus (HPV) vaccine should be implemented in all women between 9 and 26 years prior initiation sexual activity.

2.8. Areas for Future Research

- Specifically designed epidemiological studies are needed for determining whether IBD women exposed to immunosuppressants are at increased risk for HPV infection, persistent HPV infection, abnormal cervical cytologies, uterine cervical dysplasia, cervical cancer and adverse outcome of cervical cancer.
- In patients with chronic inflammatory diseases, epidemiological and mechanistic studies should precise the individual roles of the type of disease, genetically-driven diseases, and the type, dosage and duration of immunosuppressants.

3. Skin Cancers

3.1. Introduction

Skin cancers are a real public health problem, with increasing incidence throughout the world. Non-melanoma skin cancer (NMSC) is the most common human cancer. Melanomas are much less frequent than NMSC, but the incidence of melanomas continues to increase worldwide. Diagnosis is made clinically and confirmed by histology. Surgical excision is the standard of care for the majority of cases, although multiple non-invasive treatments are validated for NMSC. Previous experience from transplant recipients indicates that exposure to thiopurines is associated with an increased risk of NMSC. A recent meta-analysis showed that anti-TNF treatment increases the risk of NMSC, and possibly that of melanoma among patients with rheumatoid arthritis.

Recent evidence in IBD indicates that ongoing and past exposure to thiopurines significantly increases the risk of NMSC in patients with IBD. The risk of melanoma in patients who receive thiopurines for IBD is not increased whereas this risk is increased by the use of biologics. Here
we demonstrate that IBD patients on immunosuppressants should be protected against UV radiation and receive lifelong dermatologic screening.

3.2. Epidemiology and Risk Factors

3.2.1. General Population

Skin cancers encompass cutaneous melanomas and NMSC. Most of NMSC diagnosed are basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). The remaining cases of NMSC include cutaneous lymphomas, adnexal tumours, Merkel cell carcinoma, and other rare primary cutaneous neoplasms.

3.2.1.1. Epidemiology and Risk Factors of Cutaneous Melanoma. Since the mid 1960s, melanoma incidence has risen by 3–8% per year in most people of European background. For men, incidence of melanoma varies between 9.7 per 100,000 per year in the UK and 41.4 per 100,000 per year in Australia. In countries with high incidence rates, men have more melanomas than women, in contrast to countries with lower incidence rates. Caucasians and elderly people have also higher rates of melanoma. Risk factors for melanoma include a combination of constitutional predisposition: strong family history, multiple benign nevi (>100) and/or multiple atypical nevi, previous melanoma, previous NMSC, immunosuppression (transplant recipients or patients with AIDS), sun sensitivity ( Fitzpatrick type I skin, freckles), and exposure to environmental factors (UV exposure) and particularly blistering sunburns in early life.

3.2.1.2. Epidemiology and Risk Factors of NMSC. NMSC are the most common human cancers, and the incidence of BCC is increasing by 10% per year worldwide. In the US, NMSC constitute more than one-third of all cancers with over one million new cases per year, of which roughly 20–30% are of SCC. The standardized ratio of BCC to SCC is roughly 4:1. The incidence of BCC for men is approximately 128, 175 and 2,055 per 100,000 person-years in Europe, the US and Australia, respectively. These figures are 105, 124 and 385 days) were associated with NMSC, with adjusted odds ratio (OR) of 3.56 (95% CI = 2.81–4.50) and 4.27 (95% CI = 3.08–5.92), respectively. For Singh

3.2.2. Epidemiology in IBD Patients

Long et al., found an incidence rate ratio of NMSC of 1.64 (95% confidence interval [CI] = 1.51–1.78) among IBD patients compared to controls. Singh et al. showed an increased risk for BCC, compared with controls, with an hazard ratio [HR] of 1.20 (95% CI = 1.03–1.40). There was an increased risk of NMSC among Crohn’s disease (CD) patients, with a standardized incidence ratio (SIR) of 1.95 (95% CI = 1.50–2.50), whereas this was not statistically significant for melanoma, (SIR 1.23 (95% CI = 0.94–1.58). In the CESAME cohort study, an excess of NMSC was observed in the overall IBD population (SIR, 2.89; 95% CI = 1.98–4.08), while the risk of melanoma among the overall IBD population was similar to that observed in the general population (SIR, 0.64; 95% CI = 0.17–1.63). IBD patients are likely to have the same risk factors than general population, but in addition have treatment-specific risks. The increased risk of NMSC in IBD patients who receive thiopurines is now well-documented, with HR of 5.9 (95% CI = 2.1–16.4; p = .006) for ongoing treatment and 3.9 (95% CI = 1.3–12.1; p = .02) for past exposure in the CESAME cohort study. Consistently, Long et al. found that recent thiopurine use (≤90 days) and persistent thiopurine use (>365 days) were associated with NMSC, with adjusted odds ratio [OR] of 3.56 (95% CI = 2.81–4.50) and 4.27 (95% CI = 3.08–5.92), respectively. For Setschedi et al., a diagnosis of NMSC was significantly associated with thiopurine exposure in IBD patients (odds ratio 5.0, 95% CI = 1.1–22.8). For Singh
et al., use of thiopurines in IBD patients also increased the risk of SCC (HR 5.40; 95% CI = 2.00–14.56), compared with controls.94.

The use of methotrexate or calcineurin inhibitors (tacrolimus or cyclosporine) was not significantly associated with NMSC in IBD patients.93 For biologics (adalimumab or infliximab), there is an increased risk of NMSC in CD patients, with an adjusted OR of 2.07 (95% CI = 1.28–3.33) and 2.18 (95% CI = 1.07–4.46) for recent use (<90 days) and persistent use (>365 days), respectively.93

Combinations of immunosuppressants and biologics were associated with NMSC risk in CD patients, with an adjusted OR of 5.85 (95% CI = 3.2–10.8; p < 0.001) and 6.75 (95% CI = 2.74–16.65; p < 0.001) for recent use (<90 days) and persistent use (>365 days), respectively.93 In a recent study, the risk of melanoma was increased in IBD patients with biologics (OR, 1.88; 95% CI = 1.08–3.29).69

The impact of IBD-related medications on skin cancer risk among IBD patients is summarized in Table 2.

### 3.3. Carcinogenesis

#### 3.3.1. Cutaneous Melanoma

UV radiation has direct mutagenic effects on DNA, by stimulating the cellular constituents of the skin to produce growth factors, by reducing cutaneous immune defenses, and by promoting reactive oxygen species of melanin that cause DNA damage and suppress apoptosis.97 Main molecular pathways are shown in Fig. 1.

#### 3.3.2. Non-melanoma Skin Cancer

Similar to melanoma, UVB radiation causes direct damage to DNA and RNA, leading to generation of mutagenic photoproducts.98 UVA radiation is less mutagenic and causes indirect DNA damage.99 Main molecular pathways are shown in Fig. 2.

For thiopurines, mechanisms which may predispose to skin cancers are now better understood. Azathioprine causes the accumulation of 6-thioguanine (6-TG) in patients’ DNA. Under the action of ultraviolet A (UVA), there is a production of reactive oxygen species (ROS). ROS lead to DNA mutations and oxidative stress, linked to oncogenesis. Azathioprine could also generate non sun-exposed BCC by causing mutations in PTCH, a candidate tumor suppressor gene.98

Mechanisms at the origin of the increased risk of skin cancer with biologics remain unclear. Indeed TNF-alpha produces a variety of cellular responses which, with sustained increased levels of activity, could either facilitate or inhibit tumorgenesis.100

### 3.4. Clinical Presentation and Diagnosis

Patients often point out moles or other skin lesions that are itching, tender, scaly, oozing, bleeding, red, swollen, and/or non-healing. While many skin lesions with these features are non-malignant, these cutaneous symptoms and signs may be indicative of a premalignant or malignant lesion. NMSC, including BCC, SCC, and variants, are the most common form of cancer diagnosed in humans. While varying by country, ethnicity, and gender, approximately 1 in 3 Americans will develop NMSC in their lifetime, usually after the 5th decade.64 However, NMSC may appear in all age groups, particularly in younger individuals with chronic immunosuppression.

BCC comprise the majority of skin cancers. BCC present with a variety of clinical and histological morphologies. BCC can appear as a firm pearly white, translucent, or waxy nodule, often with visible blood vessels, and occasionally with crusting or an ulcerated center. They commonly have a characteristic rolled border (Fig. 3A). BCC can also appear as flat, scaly, flesh-colored, red, or brown plaques (Fig. 3B). Less common variants can appear pigmented, scar-like, or cystic. Approximately 80% of BCC arise on the head and neck, 15% on the trunk, and less than 5% on the extremities and groin.101 BCC on the face often arise on the temples, forehead, and nose and may bleed easily with minor trauma. Other common locations include the scalp and posterior neck in men. BCC can arise on the upper back and chest in both genders.

SCC, while less common than BCC in the general population, are significantly increased in incidence in chronically immunosuppressed populations (65-fold in transplant recipients)102 and are more common than BCC in individuals with darker pigmentation. SCC often appear as a firm red nodule, a scaly growth that crusts or bleeds, or a non-healing sore (Fig. 3C and D). An indurated component may be appreciated on palpation. SCC development favors sun-exposed areas, including the nose, forehead, lower lip, ears, dorsal hands and forearms. Less common sites include chronic ulcers, chronic fistulas, burns, or sites of prior radiation exposure. SCC in situ (Bowen’s disease) presents as scaly red papules or plaques, often with crusting. Bowen’s disease can arise in sun-exposed areas and has also been associated with HPV infection of the genitals.

Melanoma, while much less common than NMSC, possesses risk for far greater morbidity and mortality. Most melanomas present as irregularly-bordered plaques and nodules that possess a wide range uneven pigmentation (Fig. 3E and F). Occasionally, melamnas can present without pigmentation or can have uniform coloration. They tend to grow and evolve over time. While melanomas often present in sun-exposed areas, several sub-types are more commonly found in sun-protected sites and even on mucosal surfaces.

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**Table 2** Impact of medications on skin cancer risk among inflammatory bowel disease patients.

|                      | NMSC | Melanoma |
|----------------------|------|----------|
| Thiopurines          | +    | −        |
| Methotrexate         | −    | −        |
| Calcineurin inhibitor | −    | −        |
| Biologic             | + (CD) | +        |
| Combination therapy  | + (CD) | ?        |

NMSC, non-melanoma skin cancers; CD, Crohn’s disease.

\[ ^{a} \text{Tacrolimus or cyclosporine.} \]

\[ ^{b} \text{Infliximab or adalimumab.} \]
3.5. Early Diagnosis or Detection/Surveillance

Patients with sustained immunosuppression are at increased risk of NMSC (and less commonly melanoma), but additional factors can affect the risk in particular individuals. Fair skin, atypical moles, advanced age, a history of painful or severe sunburns, outdoor occupation, and a family history of skin cancer add to skin cancer risk. A personal history of skin cancer also adds to the risk, as the 3-year cumulative risk of developing another NMSC is around 47%.

IBD patients on immunosuppressant therapy should be screened annually in a room with good lighting and while disrobed but covered modestly with a gown, which can be moved as appropriate to examine different body regions. Skin cancer screening can be done by a primary care physician, the gastroenterologist, or a dermatologist. If possible, it is recommended that patients perform "self-skin exams" in their homes at least every 2–3 months.

It is especially important to screen "hidden areas" that an individual patient might not readily see, including the scalp, the back, between the fingers and toes, the backs of the legs and the lower legs, the groin, and the soles of the feet. It can be helpful to take photos of any moles as a baseline for comparison to determine whether evolution of lesions is taking place.

Skin lesions, particularly those of a pigmented nature, should be evaluated with the ABCDE criteria: A, Asymmetry increases the risk of malignancy; B, irregular Borders increase the risk of malignancy; C, multiple Colors in one lesion increases the risk of malignancy; D, a Diameter greater than 6 mm increases the risk of malignancy; E, Evolution of a lesion over time increases the risk of malignancy. Skin lesions fulfilling any of the ABCDE criteria as well as any lesion that is...
bleeding, refuses to heal, is painful, or is otherwise suspicious to the patient or the practitioner should be biopsied for histopathological diagnosis. Obtaining tissue adequate for diagnosis and with a margin of healthy tissue surrounding (if possible based on size and location) allows for more accurate diagnosis. If the need for biopsy is uncertain or performing the biopsy would be challenging given the location or patient’s circumstance, referral should be made to a dermatologist as appropriate.

3.6. Treatment and Prognosis

BCC are rarely invasive and can generally be treated with simple local resection. The survival rate in the absence of metastasis is nearly 100%. Superficial BCC can be successfully treated with topical therapies (including imiquimod or 5-fluorouracil cream), liquid nitrogen cryotherapy, photodynamic therapy, or electrodermication and curettage. Neglected BCC can lead to significant local tissue destruction, but timely treatment generally removes BCC completely. Complicated tumors, including those in high-risk areas or cosmetically sensitive areas (around the nose, eyes, mouth, ears, or associated with the nail unit), recurrent tumors, those with indistinct borders, aggressive histological subtypes, or those in radiation fields should be treated with Mohs micrographic surgery. Resection is quite effective, with same site recurrence rate of 5-10% for standard excision and less than 1% at 5 years for Mohs micrographic surgery. For those lesions who are not candidates for surgery, radiation therapy can be considered. Cure rates for non-surgical modalities are somewhat lower, but still considered effective in low risk individuals. Individuals with high-risk tumors or comorbidities have somewhat higher rates of recurrence.

SCC has a similar rate of successful resection as BCC in non-complicated situations, and has a 5-year survival rate >90% with timely and complete resection. Approximately 2–6% will present with nodal or distant metastasis. For patients with lymph node metastases of the head and neck, the 5 year survival rate has recently been shown to be 44%. Immunosuppressed patients who develop SCC tend to develop more numerous and more aggressive tumors, particularly with increased duration of immunosuppression, composition of the immunosuppressive regimen (particularly thiopurines), and advanced age. These individuals have a worse prognosis. Other predictors of poor outcome in SCC include a diameter >2 cm, a depth >2 mm, recurrence at the same site, and perineural invasion. While many IBD patients with SCC can be treated with modalities similar to those used for BCC (including standard excision and radiation therapy), those with high-risk lesions (including the predictors of poor outcome above) as well as locations including the lips, ears, hands, feet, and genitals, require prompt and aggressive management with Mohs micrographic surgery and evaluation for and management of nodal disease, where appropriate.

Due to potential mortality and morbidity, melanoma requires wide local resection, and recommendations for resection margin increase with the depth of the melanoma. Sentinel lymph-node biopsy is recommended based on the clinical stage of the lesion, but can cause marked morbidity, and effect on overall mortality remains unclear. Until recently, the only FDA-approved adjuvant therapy for melanoma was high-dose interferon alfa-2b, for high-risk resected melanoma. Recently, both vemurafenib (a B-Raf inhibitor for use in individuals possessing a BRAF gene mutation) and ipilimumab (a fully human monoclonal antibody that promotes cytotoxic destruction of melanoma cells)
have been FDA-approved for individuals with late-stage melanoma. The most important prognostic factor in melanoma is the histological depth (Breslow depth) of the primary tumor. Prognosis worsens with increasing tumor depth, the presence of histological ulceration, and lymph node involvement.

There is a high rate of development of skin cancer in immunosuppressed IBD patients, and also a high rate of development of a second cutaneous malignancy in individuals with a history of NMSC. There is also a lower, but still elevated rate of developing a second melanoma, particularly in those who are immunosuppressed, making regular monitoring and skin exams essential in IBD patients who have been immunosuppressed.

3.7. Key-messages

- IBD patients are at increased risk of developing NMSC.
- Thiopurines increase the risk of NMSC among IBD patients whereas biologics are associated with an increased risk of melanoma.
- Methotrexate and calcineurin inhibitors do not seem to be associated with an increased risk of skin cancer in IBD.
- A regular dermatological screening and protection against UV radiation are recommended lifelong for all IBD patients receiving immunosuppressive therapy.

3.8. Areas for Future Research

- Whether IBD patients are at increased risk of having melanoma awaits confirmation, and the effects of combination therapy and methotrexate on skin cancer require further investigation.
- The impact of a regular dermatological screening and protection against UV radiation on skin cancer risk, as well as prognosis of such malignancies among IBD patients, need to be evaluated in large prospective studies.
- Recurrence rates of skin cancer among IBD patients are unknown. Anecdotal reports suggest that a minority of patients with prior NMSC will experience accelerated development of new NMSCs after initiation of anti-TNF therapy. Large prospective cohort studies are needed to elucidate the frequency and severity of this risk.

Disclosures

Fernando Magro discloses lecture fees from Abbott, Merck, Falk, Ferring and Lab Vitória. Laurent Beaugerie discloses lecture fees from Merck and lecture and consulting fees from Abbott. Laurent Peyrin-Biroulet disclose consulting and lecture fees from Merck and lecture and consulting fees from Falk, Ferring and Lab Vitória. Laurent Beaugerie discloses consulting and lecture fees from Abbots, Laurent Peyrin-Biroulet disclose consulting and lecture fees from Merck and lecture and consulting fees from Falk, Ferring and Lab Vitória. Laurent Beaugerie discloses consulting and lecture fees from MERCK.

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