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Review

Virus-related inflammatory bowel disease oncogenesis: HPV-related cervical dysplasia and EBV-related intestinal lymphoma

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INTRODUCTION

Cervical cancer is a major public health issue with approximately 500,000 cases per year worldwide. In developing countries cervical cancer represents the most common female malignancy while in developed countries the closely follows it incidence rates of breast cancer.[1] Epidemiological studies on cervical neoplasia have suggested a direct causal relationship with family history, oral contraceptive use, sexual activity measured by the number of multiple sexual partners as well as sexual activity of early onset. Chronic cervical infection with human papilloma virus (HPV) appears to be etiologically linked to neoplastic changes of the cervix.[2] However, little is known about the interaction between HPV and other risk factors of cervical cancer, but it could be possible that factors including family history, HLA type, sex, steroid hormones, pregnancy, immunosuppression, smoking and use of oral contraceptives may alter the natural history of HPV infection and may influence the progression of a latent HPV infection to a low or high grade cervical intraepithelial neoplasia (CIN) and finally, to an invasive form of cervical cancer.[3-5] It is of note that studies on the prevalence of such cervical neoplastic and preneoplastic conditions are lacking in female patients diagnosed with inflammatory bowel disease (IBD).

Another important issue concerning virus-related neoplasia in IBD is some occasionally reported primary intestinal Hodgkin lymphoma cases in Crohn's disease (CD) patients.[6-14] Authors of these reports hypothesize many pathogenetic scenarios for this CD-lymphoma sequel including IBD duration, Ebstein-Barr virus (EBV) presence and long-term immunosuppressive treatment.

Key words: Inflammatory bowel disease, cervical intraepithelial neoplasia, cervical dysplasia, human papilloma virus, Epstein Barr virus

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1. HPV AND EBV ONCOGENESIS AND IBD

a. HPV oncogenesis and IBD

Chronic HPV infection is important for the development of cervical squamous cell carcinomas. The degradation of tumor suppressor gene p53 which is induced by E6 and E7 proteins of the genital oncogenic HPV types has been suggested as an important mechanism of human papilloma-virus (HPV) induced carcinogenesis.[15] It is also noteworthy that multiple HPV types may be found in one single lesion.

A patient with perianal condylomata and ileostomal HPV-negative papillomatous lesion[16] implies the importance of early recognition of HPV infection in IBD pa-

Abbreviations

***IBD** = inflammatory bowel disease,*
***CD** = Crohn's disease,*
***UC** = ulcerative colitis,*
***CIN** = cervical intraepithelial neoplasia,*
***HPV** = human papilloma virus,*
***EBV** = Epstein Barr virus*

tients, although according to a retrospective study of Crohn's disease related anal cancer it has been demonstrated that this type of cancer is not correlated with HPV type 16.[17]

To the best of our knowledge there is lack of sound studies investigating cervical HPV status in female IBD patients, especially those under long-term immunosuppression.

b. EBV oncogenesis and IBD: Intestinal Hodgkin lymphomas

Eleven cases with primary intestinal Hodgkin lymphomas in Crohn's disease patients have so far been reported.[6-14] In six of them EBV was positive while in the remaining five cases EBV status was not tested [Table].[9-18] Eight of these IBD-intestinal lymphoma cases included patients on immunosuppressive treatment (namely azathioprine or methotrexate) and among them there were two Crohn's disease cases[13-14] who had received short term Infliximab induction treatment [Table]. In addition, a unique case of perianal Hodgkin lymphoma in a CD patient has been also reported.[18]

The probable association of Infliximab with malignancies has been discussed widely. However, preclinical data and clinical experience on long term use of Infliximab do not provide evidence for a causal relationship between TNFα antagonism and the increased risk of lymphoid or non-lymphoid cancers.

Until today it seems that Infliximab administration has not changed the natural history and epidemiology of gastrointestinal Hodgkin lymhomas in IBD patients. Patients with the triplet "active Crohn's disease-prolonged disease duration-intestinal lymphoma diagnosis" who have been so far reported still remain in their great majority young males with the exception of one female case. We may attribute to Infliximab therapy an increase in incidence of primary gastrointestinal lymphomas in Crohn's disease when, irrespective of age, the number of females increases in such case reports or when numbers of cases with early intestinal lymphoma diagnosis following Crohn's disease diagnosis and subsequent Infliximab therapy appear more frequently in the worldwide literature. At least for the moment, it seems that there is a strong male preponderance of primary intestinal Hodgkin lymphoma in active Cronh's disease patients. This preponderance remains stable regardless of disease duration and regardless any kind of concomitant immunosuppressive drug administration.

2. CERVICAL CANCER IN PATIENTS UNDER IMMUNOSUPPRESSION

Azathioprine use in IBD is still off label. The official

Table. Hodgkin intestinal lymphomas and EBV status in Crohn's disease patients.

Author	Year	Patient age/sex	CD (ys)	Site	Histology	Immunohi stochemistry	EBV status	Remicade doses	Immuno-suppression
Hecker et al.[6]	1978	32/M	12	S+C+N*	MC**	NT ***	NT	-	Azathioprine
Morrisson et al.[7]	1982	22/F	7	C	MC	NT	NT	-	-
Shaw et al.[8]	1982	39/M	2	S+N+L	MC	NT	NT	-	-
Vanbockrijck et al.[9]	1993	34/M	3	S	NS	CD15+, CD30-	NT	-	-
Kelly et al.[10]	1995	31/M	7	S+N	NS	CD15+, CD30+	NT	-	Azathioprine
Kumar et al.[11]	2000	79/M 30/M 44/M	9 8 8	C+N+L C+N S	MC NS MC	CD15+, CD30+, CD20± in all 3 cases	+ in all 3 cases	-	Azathioprine in 2 of 3
Li et al.[12]	2001	38/M	24	S	NS	CD15+, CD30+, fascin+, CD20±	+	-	Azathioprine
Losco et al.[13]	2004	42/M	2	S	MC	CD20+, CD30+, CD3-, CD43-, CD15+, EMA-.	+	1 dose	Azathioprine
Bai et al.[14]	2006	35/M	7	C (rectal)	MC	CD15+, CD30+, CD45-, CD20-, CD3-, EMA-.	+	2 doses	Methotrexate

**S=small bowel, C=colon, N=node, L=liver*

***MC=mixed cellularity, NS=nodular sclerosis*

****NT=not tested*

on label azathioprine indications still remain prevention of rejection in renal homotransplantation and management of active rheumatoid arthritis. Azathioprine has been listed as a known carcinogen according to the 7th Annual report on carcinogens (PB95-109781, 1994, P.32). Azathioprine is mutagenic in animals and humans, carcinogenic in animals, and may increase patients' risk of neoplasia. The use of azathioprine in nursing mothers is not recommended as azathioprine and its metabolites are transferred at low levels both transplacentally and in breast milk.[19] However, it has not yet been possible to define in clinical practice the precise risk of neoplasia during azathioprine therapy.

Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors; therefore it is strongly advised that immunosuppressive therapy should be maintained at the lowest effective levels.[19]

Data on risk of neoplasia among patients with rheumatoid arthritis treated with azathioprine are limited. Available data suggests that neoplasia risk may be elevated in patients with rheumatoid arthritis, though lower than that in renal transplant patients.[20] Acute myelogenous leukemia as well as solid tumors have been reported rheumatoid arthritis patients on azathioprine. The rate of lymphoproliferative diseases in rheumatoid arthritis patients receiving higher than recommended doses of azathioprine (5mg/kg daily) was 1.8 cases per 1000 patient-years compared to 0.8 cases per 1000 patient-years of follow up in patients not receiving azathioprine. However the risk of lymphomas attributed to azathioprine or to other immunosuppression regimens cannot be safely determined as the incidence of lymphoproliferative diseases in patients with rheumatoid arthritis appears to be significantly higher compared to that of the general population. [20]

In a 40-month follow up study no significant differences on the overall occurrence of malignancy was found between azathioprine-treated and non-azathioprine treated rheumatoid arthritis patients (36 and 49 patients respectively). In the azathioprine group one patient had a positive Pap smear and was subsequently diagnosed with uterine carcinoma.[20]

Cancer is responsible for a 5-8% mortality rate of organ transplant recipients. Chronically altered immune responsiveness in transplant recipients is associated with an increased risk of malignancy, most frequently non-Hodgkin lymphomas and skin cancer.[21] Various risk factors, such as exposure to sun and infections with oncogenic viruses such as HPV and EBV may also be added to the already existing increased risk of dysplasia in patients requiring lifelong immunosupression treatment. Therefore, prophylactic strategies included the development of virus-like particles (VLPs) as anticancer vaccines in these patients are necessary. These vaccines can be regarded as a very interesting approach towards prevention of Epstein-Barr virus-associated non-Hodgkin lymphoma and HPV-associated cervical cancer. [22]

Chemical carcinogenesis always remains an attractive scenario in transplanted patients receiving immunosuppressive therapy. A study with 108 renal transplant recipients treated with azathioprine (0.8-2.9 mg/Kg/day) showed an association of raised 6-thioguanine nucleotide concentrations in red blood cells with actinic keratoses and malignant skin tumors diagnosis. [23]

In a study of 3394 adult patients undergoing orthotopic liver transplantation and subsequent immunosuppression with cyclosporine A and FK 506, a total of 50 patients with solid tumors were identified; interestingly, 3.1% of them were cervical cancers.[23] By contrast, the frequency of malignancies in 207 multiple sclerosis patients treated with azathioprine (2 mg/Kg/day, mean duration 4.1 years) did not differ significantly from that of 247 non-azathioprine treated control patients.[24]

The development of severe cervical dysplasia under azathioprine treatment has occasionally been reported.[25-26] Few case reports and studies on the association of carcinoma of the cervix during azathioprine therapy have so far appeared. A case of a 34-year-old kidney transplant patient who developed carcinoma in situ of the cervix during azathioprine treatment has been reported.[27] Another case of a 31-year-old woman with simultaneous in situ carcinoma of the cervix, vulva and perineum after immunosuppressive therapy for renal transplantation has been also reported.[28]

It has been assumed that immunosuppression leads to either a reactivation of a latent HPV infection or to a reduction in the host's ability to contain a primary HPV infection, thereby increasing the risk of CIN and cervical cancer. A study in female renal transplant recipients showed that HPV infection was not highly prevalent among older, cytologically normal renal transplant recipients, particularly those who were monogamous or who were not sexually active presently. The authors of that study suggested that in renal transplant recipients recent sexual behaviors are more important determinants of HPV status compared to past sexual behaviors. Thus, it had been suggested that education concerning the

avoidance of high-risk sexual behavior is an important part of the female renal transplant recipient management.[29]

In a retrospective study it has been found that 19 of 80 women with systemic lupus erythematosus had atypical cervical smears compared to only 9 out of 80 age-matched women without the disease.[30] Finally, there is another report of cervical carcinoma after chronic active hepatitis treatment with prednisone and azathioprine.[31]

3. CERVICAL DYSPLASIA AND CANCER IN IBD

In a 9-year follow up study of 755 azathioprine-treated IBD patients 2 cases (vs 0.5 expected) of invasive cervical cancer were diagnosed.[32]

In the recent multicenter prospective 10-year study of the European Collaborative IBD (EC-IBD) Study Group 44 cases of intestinal and extraintestinal cancers were diagnosed in 1470 consecutive patients. [33]

Among these cases, two cases of cervical cancer, one in an ulcerative colitis and one in a Crohn's disease patient were diagnosed. The Crohn's disease patient was on azathioprine maintenance treatment. In total, cervical cancer in this study represented the 4.5% of all cancers diagnosed in this European cohort and its incidence did not significantly differ from that of the background population. In addition, no differences were noticed between northern and southern study centers regarding IBD related cervical cancer prevalence.

In the northwest Greece retrospective study on IBD related dysplasia and cancer and in a total of 89 IBD female patients, no cervical cancer case was recorded during an 18-year mean follow up time.[34]

It is important to mention that both of these studies were not targeting cervical cancer prevalence as a primary end point and that detailed gynecological history was not available in all these cases. None of these studies provided information on pre-malignant conditions (dysplasia) in the cervix or on HPV status of female patients on azathioprine or other immunomodulator maintenance treatments. However, these studies included female IBD patients of different age groups providing a nicely stratified IBD population (pre- and post- menopausal) for future analyses and further follow up.

4. AZATHIOPRINE-INDUCED MALIGNANCIES IN IBD

The exact lympho-oncogenic risk during long-term purine analog use has not been firmly assessed in IBD patients.[20, 22] Although immunosuppression has been traditionally associated with an increased risk of neoplasia, a study of 755 IBD patients on azathioprine who were followed up for 9 years (range 2 weeks to 29 years) failed to show any increased overall risk of neoplasia compared to that of the general population and despite the fact that a significant difference in the frequency of colorectal and anal carcinomas was noticed.[32]

The reason why patients with CD seem to have an increased risk for intestinal malignant lymphomas is unknown. It may occur secondary to chronic bowel inflammation following a scenario similar to that of gastric lymphomas arising in Helicobacter pylori-related chronic gastritis but it could also occur in patients with continuously active disease.[35-37]

Although there is an increased risk of non-melanoma skin cancer in immunosuppressed transplant recipients, a similar danger has never been reported in IBD patients.[38] However, IBD patients on azathioprine (AZA), especially those with fair complexion should be informed about the potential hazards of sunbathing. A woman with IBD who had frequently been sunbathing, developed intra-epidermal carcinoma of the skin after 8 years on azathioprine.[39]

Two IBD patients with early cervical cancer have been reported[40] and of interest, a unique case of invasive cancer of the cervix in a patient undergoing chronic treatment with 6-mercaptopurine for Crohn's disease has also been reported.[41] The authors of this report raised the important issue of pelvic irradiation in the view of co-existing IBD. This issue needs to be further investigated as pelvic radiotherapy for cervical cancer may induce acute and late onset post-radiation enteritis. Thus, in IBD patients irradiated for cervical cancer the probability of bowel inflammation seems not to be only a theoretical issue. In addition, an increased risk of bowel malignancies during irradiation cannot be excluded in IBD patients, although to date there is no supportive data and we are not aware of such studies.

Pelvic pouch operation for IBD may sometimes alter sexual behavior and by consequence change the overall risk for HPV-related cervical cancer. In a consecutive series of 30 IBD women who after pelvic pouch operation were gynecologically examined, one case of in situ cervical cancer was diagnosed.[42]

5. INFLIXIMAB: LYMPHOMAS AND CERVICAL CANCER

The probable association of anti-tumor necrosis factor alpha (TNFα) –chimeric monoclonal antibody (Infliximab) therapy with malignant conditions has been widely reported.[43] However, the clinical experience presented for anti-TNFα (Infliximab) does not provide evidence for a causal relationship between TNFα antagonism and the development of lymphoid or non-lymphoid cancers.[44]

The relationship of Infliximab administration with subsequent lymphoma looks extremely unlikely in the two cases with intestinal lymphoma after a short course of Infliximab therapy (1 or 2 doses). [13-14] In fact, the relationship between Infliximab and intestinal lymphoma in these cases is absolutely unclear as patients had intestinal symptoms before infliximab initiation. On the contrary, the probability that Infliximab accelerated progression and finalled to the clinical diagnosis of a pre-existing lymphoma cannot be overlooked, as there are few cases of lymphoma reappearance in patients with rheumatoid arthritis receiving Infliximab. By contrast, full regression of lymphoma after Infliximab discontinuation has been reported.[21]

Any concerns regarding lymphoma diagnosis among CD patients on Infliximab should be appreciated along the knowledge that these patients may have an increased risk for intestinal lymphomas even in the absence of any kind of immune modulating therapy.[23-25, 45-49] Careful long-term follow up of cases should be recommended until prospective results come up.

It has been also suggested that primary gastrointestinal lymphoma arising in the setting of CD may have a strong pathogenetic association with EBV similar to that found in post-transplantation immunosuppression-related lymphoproliferative disorders.[11]

The question of whether immunosuppressive drugs including Infliximab facilitate the emergence of a EBV-positive neoplastic clone still currently remains unexplored. However there is some emerging data[50] showing that larger numbers of EBV-infected cells are found in areas of active inflammation in UC and CD patients as compared to areas of inactive inflammation. In support of this an immunohistochemical study of seventeen cases with IBD related adenocarcinomas and nine cases with IBD associated colorectal Non-Hodgkin Lymphomas (NHL) showed that all IBD related adenocarcinomas were EBV(-) while 6 of 9 colorectal NHL cases were EBV(+).[51]

Since immunosuppressants and immunomodulators including IFX currently represent an important part of pharmaceutical therapy in IBD we need to identify the subgroup of IBD patients who are possibly at a greater risk of developing lymphomas. In this view, EBV-DNA in blood or in faeces has been suggested as a useful tumor marker.[52]

6. GUIDELINES FOR WOMEN WITH IBD DIAGNOSED OR NOT WITH HPV(+)

There is evidence that HPV16(+) women are at a greater risk of cervical neoplastic progression and in the presence of negative or mildly abnormal cytology, they are more likely to have a more severe histological lesion (i.e CIN grade III) in the near future.[53]

All transplanted IBD females who are using immunosuppressive agents should be followed up by Pap smears every six moths and by colposcopic evaluation every year. Avoiding high-risk sexual acts is also of importance. Before implementing official guidelines for cancer prevention in IBD patients receiving immunosuppressants, the risk of virus-related neoplastic conditions such as EBV(+) intestinal lymphomas and HPV(+) cervical cancer needs to be prospectively investigated. Screening for cervical dysplasia and cancer should include interview and family history, gynecological examination, colposcopy with biospies, Papanicolaou smear and a cervicovaginal lavage analyzed for HPV-DNA.

7. CONCLUSIONS

In all IBD cases with long-term immunomodulatory drug use, clinical follow up is mandatory. Long term toxicity and carcinogenicity of these agents still remain under investigation until results of prospective studies come up.

Virus-related carcinogenesis in IBD has to be more extensively assessed before any statements can be generally adopted as guidelines for patient follow up.

In our point of view, unless the absolute risk of IBD patients in developing colonic and extracolonic malignancies including intestinal lymphomas and cervical dysplasia is assessed extensively, no secure statements about hyperplastic or carcinogenesis effect of any kind of therapy, especially of azathioprine/6-mercaptopurine and the of new biological agents including Infliximab should be generalized or adopted in any current guidelines.

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