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Case reports

HPV RELATED RECTAL SQUAMOUS CELL CARCINOMA IN A PATIENT WITH ULCERATIVE COLITIS: A CASE REPORT AND REVIEW OF THE LITERATURE

HPV I PLANOCELULARNI KARCINOM REKTUMA KOD PACIJENTA SA ULCEROZNIM KOLITISOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Ključne reči

Ulcerozni colitis, planocelularni karcinom rektuma, imunosupresija, HPV, karcinom cerviksa

Key words

Ulcerative Colitis, Rectal Squamous Cell Cancer, Immunosupression, HPV, Cervical Cancer Abbreviations: HPV-human papillomavirus; SCC- squamous-cell carcinoma; UC-ulcerative colitis

Abstract

BACKGROUND AND AIMS: Primary squamous-cell carcinoma of the colon and rectum is a rare malignancy with an incidence of 0.025% to 0.1% of all colorectal carcinomas. Most cases have been reported in the setting of ulcerative colitis and other chronic disease states. Although cervical and anal SCC have been linked to human papillomavirus infection, the role of human papillomavirus in rectal SCC has not been well reported. We present a case of primary rectal squamous-cell carcinoma with positive p16 immunohistochemistry consistent with HPV, in a patient with chronic ulcerative colitis.

CASE PRESENTATION: A 57 year old female presented with steroid dependent pan-ulcerative colitis diagnosed 3 years prior to her evaluation at our institution. Her surveillance colonoscopy showed a focus of low-grade dysplasia. As the patient refused surgery, surveillance colonoscopy was repeated in 6 months. This was significant for a flat lesion in the distal rectum, not contiguous with the dentate line. Biopsies were consistent with in situ squamous-cell carcinoma with positive p16 immunostain consistent with HPV.

CONCLUSIONS: Immunodeficiency is an established risk factor for the development of anal and cervical squamous-cell carcinoma. The presence of human papillomavirus 16 in this case and other reports in literature, can lead us to believe that the pathogenesis of rectal squamous-cell carcinoma is similar to that of cervical squamous-cell carcinoma. One of the proposed theories includes squamous metaplasia secondary to chronic inflammation. Regardless of the pathogenesis it is important for physicians to recognize that squamous-cell carcinoma can occur above the dentate line, particularly in ulcerative colitis and other immunocompromised patients, and to manage them accordingly.

INTRODUCTION

Primary squamous cell carcinoma (SCC) of the colon and rectum is a rare malignancy, with most cases reported in the setting of ulcerative colitis (UC) and other chronic disease states such as chronic infections (schistosomiasis, amoebic colitis) or anatomical variations (colon duplication). It is now well established that integration of high-risk human papillomavirus (HPV) into host cellular DNA and expression of virus oncogenes result in highly specific overexpression of p16 protein, a cyclin-dependent kinase inhibitor, in tumor tissue.Although cervical and anal SCC have been strongly linked to human papillomavirus (HPV) infection, the role of HPV in rectal SCC has not been well established.

We present a case of primary rectal SCC with positive p16 immunohistochemistry consistent with HPV, in a patient with chronic UC, along with a comprehensive literature review. The case presentation was previously published in the Clinical Gastroenterology and Hepatology Journal in October 2009 in the Image of the Month section.1

CASE PRESENTATION:

A 57 year old female presented with extensive chronic UC diagnosed 3 years prior to her evaluation at our institution. She reported onset of intermittent bloody diarrhea at least 5 years prior to her initial evaluation. Following her initial diagnosis, she was treated with prednisone, and maintained in clinical remission on 6-mercaptopurine (6MP) for a period of 2 years. However, she eventually developed refractory symptoms with steroid dependence. The patient was hence referred to our institution and was initiated on infliximab, 5 mg/kg induction followed by maintenance therapy. She had excellent clinical response to the infliximab, and the 6MP was subsequently discontinued.

Colonoscopy with surveillance biopsies revealed a single focus of low-grade dysplasia in the ascending colon. As the patient opted to defer colectomy, surveillance colonoscopy was repeated in 6 months. Findings at follow up colonoscopy were significant for moderate inflammation in the sigmoid colon and rectum, and a distinct flat lesion in the distal rectum, not contiguous with the dentate line. The rectal lesion was biopsied in addition to random surveillance biopsies done throughout the colon. The biopsies from the rectal lesion revealed SCC in a distinct fragment. The possibility of invasion into the stroma could not

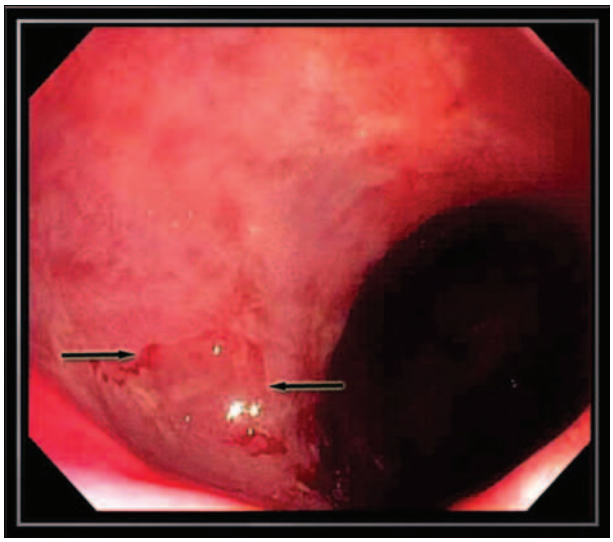

Image 1: Flat lesion seen in distal rectum on white light endoscopy

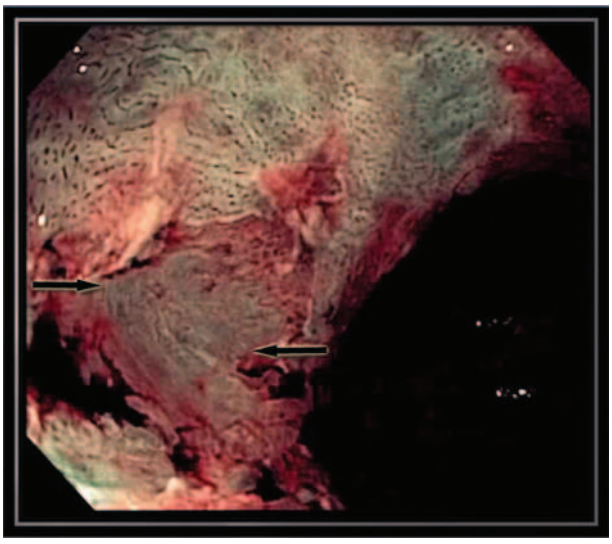

Image 2: Flat lesion in distal rectum examined with narrow band imaging (NBI)

Colonoscopy pathology slides:

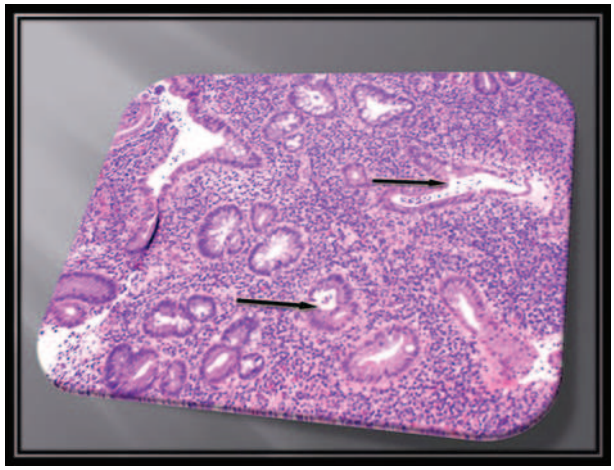

Image 3: Random rectal biopsy from the patient with UC. The findings include distortion of the glandular architecture, marked expansion of the lymphoplasmocytic infiltrate in the lamina propria and crypt abscesses

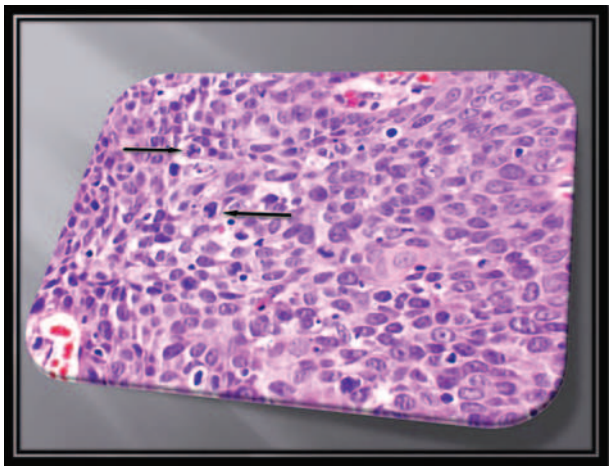

Image 4: Biopsy from rectal lesion: Findings are consistent with squamous cell carcinoma in situ characterized by irregularly shaped enlarged nuclei, with mitoses, and often touching the adjacent nuclei with necrotic cells. The change is seen to extend throughout the thickness of the biopsy specimen.

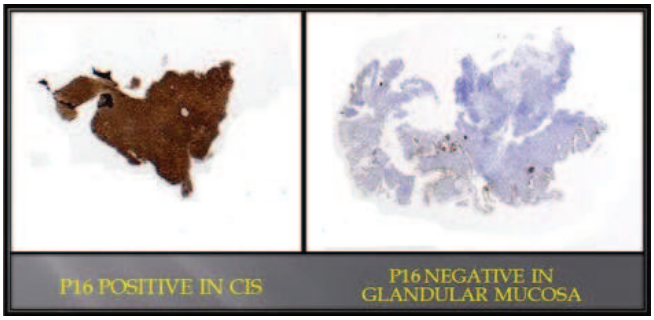

Image 5: Immunohistochemical stain with p16: Findings consistent with strong and diffuse immunoreactivity to p16 in the squamous cell carcinoma in situ (CIS). This pattern of stain by p16 is typical of squamous cell CIS; p16 is a surrogate marker of retinoblastoma pathway inactivation and often of high risk HPV infection. No staining is present in glandular mucosa.

be assessed. P16 immunostain was strongly positive in squamous epithelium, consistent with HPV-induced dysplasia of squamous epithelium. The remainder of surveillance biopsies throughout the colon, were otherwise negative for dysplasia. The patient is scheduled for rectal examination under anesthesia, with biopsy mapping of the distal rectal mucosa to determine management options.

DISCUSSION:

Chronic UC is characterized by chronic inflammation of the colonic mucosa. It almost invariably involves the rectum, and may extend in a contiguous manner to involve the more proximal colon. A major complication related to UC is an increased risk for developing colorectal adenocarcinoma (CRC). The risk of acquiring CRC is related to several factors, including both the duration and extent of disease.2,3 Patients with disease extending proximal to the splenic flexure have the greatest risk of CRC. The approximate cumulative incidence of CRC is 5 to 10 % after 20 years, and 12 to 20 % after 30 years of disease duration 4-8. Other factors that may influence risk for CRC include younger age at presentation, concomitant primary sclerosing cholangitis (PSC), severity of colonic inflammation, and family history of CRC. Patients with PSC appear to have a much higher risk of CRC, and should hence undergo colon surveillance at initial presentation.

Primary SCC of the colon and rectum is rare, accounting for 0.025% to 0.1% of all colorectal cancers 9. Secondary involvement of the rectum by direct extension from an anal SCC or metastases is far more common 9. To our knowledge there are only 3 case reports of squamous cell dysplasia/carcinoma in UC patients positive for HPV 9-11. We report the fourth case of a patient with moderate to severe UC, on chronic immunosuppressive therapy, who developed HPV-related rectal SCC.

The first case of colon SCC was reported by Schmidtman in 1919 12, and Railford subsequently reported the first case of rectal SCC in 193313. The diagnosis of primary colorectal SCC requires fulfillment of the following criteria 14:

1. SCC at any other site must be excluded as a source of metastasis or direct extension to the colon and rectum
2. The affected segment should not be in continuity with any squamous-lined fistula
3. There should not be continuity between the tumor and the anal squamous epithelium
4. Glandular differentiation should not be present

The presence of squamous epithelium in the colorectum is presumed to be the result of 9,14:

1. The proliferation of uncommitted reserve or basal cells after mucosal injury
2. Squamous metaplasia of colorectal mucosa as a result of chronic irritation
3. Squamous metaplasia within a colorectal adenoma or adenocarcinoma
4. Malignant change in persistent ectopic embryonal nests of ectodermal cells
5. Transitional-cell anal ducts which can extend cephalad beneath the rectal mucosa15

Coexistent diseases with SCC previously reported in the literature include ulcerative colitis,9,11,14,16-24 schistosomiasis,10,25 colonic duplication,26,27 amebiasis, 28 ovarian cancer, 29 endometrial carcinoma, 30 prostate cancer, 31 and prior history of radiation.10,29

Data on the prognosis of these patients is limited, due to the rarity of this malignancy. Rectal SCC appears to be locally invasive, and more likely to involve regional lymphatics, as compared to adenocarcinoma. Surgical resection remains the most definitive curative potential treatment for most patients. The role of neo-adjuvant/adjuvant radiotherapy or chemotherapy is currently unknown because of anecdotal nature of the reports.15

Anal and cervical SCC are similar in terms of their histology, risk factors and patient population. Anal squamous intraepithelial lesions and cervical intraepithelial neoplasia are both pre-malignant states. Over 80% of anal SCC are positive for HPV. In addition, the vast majority of women with cervical cancer have associated infection with HPV. Risk factors for both malignancies include sexual promiscuity, cigarette smoking and immune suppression.10

The role of HPV in the etiology of primary colorectal SCC has not been well defined. A literature review revealed about 100 cases of pure SCC of the rectum, 9,14-16 of which, about 17 cases were reported in patients with UC. 9,11,14,16-24 Of the cases associated with UC, two patients reportedly had HPV positive colorectal squamous cell dysplasia, 10,11 and a third patient had HPV positive high grade dysplasia/carcinoma in situ. 9

Although patients with UC have a high risk of developing adenocarcinoma, 16 it is rare for these patients to develop SCC, suggesting that special etiological factors may be involved in its development. The presence of HPV 16 brings up a possibility that the pathogenesis of rectal SCC may be similar to cervical SCC, wherein HPV is considered necessary, but not the only cause for development of malignancy. As CUC is the most common preexisting condition in patients with colorectal SCC, it may be hypothesized that chronic inflammation leads to squamous metaplasia and secondary infection with HPV leads to development of SCC. 9 Not uncommonly, squamous metaplasia involves the distal 2 to 4 cm of the rectum as a continuous extension from the dentate line. It is speculated that there is a transition zone in the distal rectum, similar to the cervical transformation zone that is at comparable risk for HPV infection, squamous cell dysplasia, and/or carcinoma. 32 The chronic use of immunosuppression may contribute to the development of SCC in this area.

High-risk HPV types 16 and 18 are more frequently isolated in cervical cancer tissue than either intermediate or low-risk types, with type 16 accounting for approximately 50% of cases. 34 Interestingly, UC patients have higher rates of abnormal PAP smears compared to controls (35.5% vs. 14.6% respectively). Furthermore, UC patients on steroids, immunomodulators or biologics have higher rates of cervical dysplasia compared to UC patients, who are not on these agents (44.6% vs 22% respectively). 33

The two most important HPV proteins in the pathogenesis of malignant disease are E6 and E7. In the normal cell the p53 protein is a negative regulator of cell growth and functions as a tumor suppressor protein. Following E6 binding, p53, is degraded, which results in an anti-apoptotic effect, and thereby allows for unchecked cellular cycling,

and accumulation of chromosomal mutations, without DNA repair.34 The retinoblastoma (Rb) protein inhibits the effect of positive growth regulation and, in response to DNA damage, halts cell growth or induces cell apoptosis. When E7 binds to retinoblastoma (Rb) protein, it permits cells with damaged DNA to bypass the G1 growth arrest, 35 allowing unchecked cell growth in the presence of genomic instability. Both these effects therefore result in malignancy.

Regardless of pathogenesis, this case, and other prior reported cases have shown that colorectal SCC can occur in metaplastic tissue well above the dentate line. Both gastroenterologists and colorectal surgeons should be cognizant of this risk in patients with chronic UC. The evaluation and management of these patients should hence be modified accordingly. It is also a well known fact that evolution of HPV lesions, resulting in anal and cervical dysplasia, is greatly accelerated in immunosuppressed patients. With the increasing use of immunomodulators and biologics in patients with inflammatory bowel disease, there may hence be a potential role for the new Human Papilloma Virus (HPV) vaccine in this patient population.

Apstrakt

UVOD I CILJ: Primarni planocelularni karcinom kolona i rektuma je redak malignitet, incidenca iznosi od 0,025% do 0,1% od svih kolorektalnih karcinoma. Mnogi slučajevi bili su prikazani udruženo sa ulceroznim kolitisom i drugim hroničnim bolestima. Dok su planocelularni karcinomi cerviksa uterusa i anusa povezani sa **h**umanim **p**apiloma-**v**irusom, uloga ovog virusa još nije prikazana kod planocelularnog karcinoma rektuma. Prikazujemo slučaj primarnog rektalnog planocelularnog karcinoma imunohistohemijski pozitivnog na p16 komponentu HPV kod pacijenta sa hroničnim ulceroznim kolitisom.

PRIKAZ SLUČAJA: Pacijentkinja stara 57 godina, sa steroid-zavisnim pan-ulceroznim kolitisom dijagnostikovanim od pre tri godine, ispitana je u našoj instituciji. Na kolonoskopskom pregledu ustanovljen je focus niskostepene displazije. Kako pacijentkinja nije prihvatila operaciju, kolonoskopski pregled je ponovljen za 6 meseci. Nađena je ravna lezija u distalnom rektumu, bez kontakta sa zupčastom linijom. Biopsijom je ustanovljen „in situ" planocelularni karcinom pozitivan na p16 protein HPV.

ZAKLJUČCI: Imunodeficijencija je ustanovljen faktor rizika za razvoj analnog i cervikalnog planocelularnog karcinoma. Prisustvo HPV tip 16 u našem i drugim slučajevima publikovanim u literaturi, navode nas da verujemo da je patogeneza rektalnog planocelularnog karcinoma slična cervikalnom planocelularnom karcinomu. Jedna od predloženih teorija uključuje planocelularnu metaplaziju na bazi hronične inflamacije. Bez obzira na patogenezu, za lekare je važno da prepoznaju da se planocelularni karcinom može pojaviti iznad zupčaste linije, naročito kod ulceroznog kolitisa i drugih imunokompromitovanih pacijenata, te ih treba tretirati u skladu sa ovim.

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