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LETTERS TO THE EDITOR

Men in the spotlight: A rare case of penile squamous carcinoma associated with human papillomavirus (HPV) infection in a patient with ulcerative colitis (UC)

Los hombres en el punto de mira: un caso raro de carcinoma escamoso de pene asociado a la infección por virus del papiloma humano (VPH) en un paciente con colitis ulcerosa (CU)

Dear Editor,

HPV is the most common sexually transmitted infection in the world. HPV 16 and 18 are found to account for 90% of all HPV-related cancers in men. We are reporting a rare case of penile squamous carcinoma associated with HPV infection in a patient with ulcerative colitis and under immunosuppressants (IMMs).

A 72-year-old male patient with a personal history of severe chronic obstructive pulmonary disease was diagnosed with ulcerative colitis in 2007. He achieved initial remission with topical and systemic salicylates. But months later he presented a severe flare that required treatment with corticoids. After that episode he was started on thiopurines for corticoid-dependency. He maintained a long-lasting remission thereafter.

In January 2013 he was diagnosed with penile squamous carcinoma that required glansectomy and urethroplasty. Histological results showed a well-differentiated squamous cell carcinoma, with perineural invasion. Inmunohistochemistry was positive for p16. *In situ* hybridization confirmed HPV 16/18 positive and HPV 6/11 negative. After the diagnosis of penile cancer he stopped azathioprine and was de-intensified to mesalazine 4 g per day, maintaining ulcerative colitis remission. On October 2013, he developed an inguinal lymphadenopathy that was a metastatic squamous cell carcinoma. No adjuvant therapy was decided upon in light of the poor prognosis and comorbidity of the patient. He finally died in June 2014.

HPV is highly prevalent in men and it is related to the development of genital warts, penile intraepithelial neoplasia and invasive penile carcinomas. Approximately 40% of invasive penile carcinomas are attributable to HPV 16/18. There are no previous reports of HPV-related cancers in male patients with IBD taking IMMs. Although a cause–effect relationship with IMMs cannot be demonstrated in this case, long-lasting immunosuppression has been shown to increase the number and persistence of HPV-induced lesions.[1]

Recently, the Second European evidence-based consensus on the prevention, diagnosis, and management of opportunistic infections in IBD recommended HPV vaccination for females aged 11–14 years before onset of sexual activity. They also recommend routine vaccination of males according to national guidelines.[2] Vaccinating boys improves cervical cancer eradication, reduces virus transmission, and contributes to the prevention of HPV-associated diseases in both genders[3]; therefore more substantial incremental benefits are expected from adding males to vaccination programs.

In the present case we have shown an HPV-positive penile cancer developed under therapeutic immunosuppression with thiopurines. To the best of our knowledge, this association has not been reported before. Male vaccination has been shown to significantly reduce HPV-associated anogenital infection and related lesions in men. Therefore, we believe that HPV surveillance and vaccination programs in IBD should actively take into account the male population.

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Fulminant *Clostridium difficile* colitis☆

Colitis fulminante por *Clostridium difficile*

To the Editor,

Fulminant *Clostridium difficile* colitis (FCDC) is characterised by the development of severe acute inflammation of the colon, associated with systemic toxicity. It is a clinical entity with high mortality that requires intensive medical treatment and early surgery in non-responders. The incidence of *C. difficile* infection—as well as its severity and mortality—has increased significantly in recent years.[1] It is a common cause of infectious diarrhoea in hospitalised patients, and the main cause of antibiotic-induced diarrhoea. Symptoms vary from mild diarrhoea to potentially fatal fulminant disease; its diagnosis is based on the detection of toxins in faeces.

We present 2 clinical cases of FCDC. The first case was a 77-year-old man, immunocompromised as a result of chemotherapy and on treatment with metronidazole for *C. difficile* colitis for 12 days, who presented with acute abdominal pain, changes in his general condition, septic state and persistent diarrhoea. He also had haemodynamic instability, elevated blood lactate levels and Quick index of 57%. Abdominal examination was remarkable for diffuse pain with signs of peritoneal irritation. Plain abdominal X-ray revealed pneumoperitoneum and double wall sign (Fig. 1); urgent surgery was indicated, in which a perforated megacolon was found. Subtotal colectomy was performed, with ileostomy and mucous fistula. He was admitted to the intensive care unit for multiple organ dysfunction syndrome (MODS), remaining there for 7 days. He was treated with intravenous metronidazole and oral vancomycin, and made satisfactory progress. Macroscopic analysis of the surgical specimen showed signs of pseudomembraneous colitis (Fig. 2). He is currently awaiting intestinal passage reconstruction.

The second patient was a 57-year-old man who had been admitted to the surgery department following a right hemicolectomy for caecal cancer. He was admitted for febrile syndrome, treated with intravenous ertapenem 10 days prior to the intervention. On the first postoperative day, he passed a melaena stool with no analytical or haemodynamic effects. Hours later he presented a bloody stool with coffee ground vomitus and a drop in blood pressure. Urgent laboratory tests showed a fall in the Quick index and the red and white cell count. Emergency gastroscopy was normal, but following a new episode of massive rectorrhagia, the patient underwent urgent surgery. Intraoperative colonoscopy ruled out bleeding of the anastomosis, but found abundant traces of blood and a greyish mucosa, which detached easily (Fig. 3). Suspecting fulminant pseudomembraneous colitis, subtotal colectomy was performed with ileostomy and distal mucous fistula. Faecal samples were taken, where the diagnosis of *C. difficile* was confirmed after detecting toxin A and B by enzyme immunoassay, and the toxin B gene by polymerase chain reaction (PCR). Recovery was favourable and months later the intestinal passage was reconstructed.

In addition to antibiotic treatment, other factors such as advanced age, chronic diseases, hospital stays or treatments with immunosuppressants, antacids and antiperistaltics have been related with the development of *C. difficile*-associated disease.[2,3] Another factor traditionally associated with this pathology is surgery and/or manipulation of the gastrointestinal tract,[4] although in a recent study, only preoperative stent placement was identified as an independent factor in the multivariate analysis[3], while the use and duration of oral vs intravenous antibiotics did not affect the incidence of colitis.

Evolution to FCDC develops in between 3% and 8% of infected patients. Although predicting the clinical course of the disease is difficult, factors predisposing to progression to FCDC have been identified, such as age, neoplastic disease, chronic obstructive pulmonary disease, immunosuppression or history of inflammatory bowel disease.[5] Identification of these factors may help select those patients who require intensive follow-up.

The timing of the surgical intervention is unquestionably a key factor in survival. Although there are clear situations that indicate urgent surgery, the exact moment is not defined and continues to be empirical to a large extent. Some authors[6] have proposed a scoring system to identify patients who would benefit from an early surgical approach, jointly assessing clinical, analytical, radiological and therapeutic criteria.

All studies highlight the importance of surgery before the development of MODS.[1,7] Subtotal colectomy with ileostomy provides the best outcomes.[8] Different studies have suggested increased lactate, decreased serum albumin, age, need for vasopressors or immunosuppression as predictive factors of postoperative mortality.[9] Perera et al.,[10] after

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