

## Case report

## Perianal condylomata and HPV-negative ileostomal papillomatous lesion in Crohn's disease during Infliximab therapy

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### SUMMARY

All patients with inflammatory bowel disease (IBD) with peristoma and stoma disorders who receive immunomodulatory therapy must undergo a detailed clinical, histological and microbiological examination including detailed history for pre-existing skin diseases.

A 34-year old woman with Crohn's disease during Infliximab treatment presented with tender verrucous lesions in the perianal area and a small verrucous lesion involving the ileostoma. Perianal lesions were enlarged and had a condylomatous appearance, and had become painful. At the same time, a small grayish-white papillomatous plaque on the upper circumference of the ileostoma, with a sharp outline but with no downward extension into the ileum, was noticed. Light microscopic analysis of the stoma lesion demonstrated only signs of mild chronic inflammation but no definite koilocytosis. In addition, immunohistochemical analysis for HPV was negative. Cryotherapy of perianal lesions was performed successfully while Infliximab infusions were interrupted. The patient was on regular follow-up and was receiving azathioprine and low doses of steroids.

In all IBD cases with long-term immunomodulatory drug use, clinical follow-up is mandatory as long term toxicity and carcinogenicity of these new biological agents still remain under investigation.

**Key words:** human papillomavirus (HPV), Crohn, inflammatory bowel disease, Infliximab, Remicade, anti-TNFa

### INTRODUCTION

Dermatological lesions in patients with inflammatory bowel disease (IBD) can be categorized as specific lesions (perianal fissures, metastatic Crohn's disease), as reactive lesions (erythema nodosum, pyoderma gangrenosum, hidradenitis suppurativa) and finally, as cutaneous manifestations (dermatoses) which are connected, with high probability, with inflammatory bowel diseases, such as epidermolysis bullosa acquisita and acne fulminans.<sup>1-4</sup> Furthermore, the introduction of novel immunosuppressive and immunomodulatory therapies in inflammatory bowel disease (IBD) contributes with other types of cutaneous manifestations, to this long list. These additional types of cutaneous manifestations seem to be more common in immunocompromized than immunocompetent patients.

It is also obvious that the techniques of temporary or permanent stoma construction during IBD surgery are opening new areas in disease therapeutics and management for stoma-related diseases. The pathology of stoma-related skin lesions can involve irritant reactions, allergic contact dermatitis, infections, pre-existing skin disorders, pyoderma gangrenosum, or non-specific dermatitis. Papillomatous stoma-related skin lesions may be caused by irritant reactions or infection with human papillomavirus (HPV) types<sup>5</sup>. In fact, human papillomaviruses infect epithelial cells of mucous membranes and of the skin and can lead to a variety of benign and malignant epithelial tumors.<sup>6</sup>

Herein we report a Crohn's disease (CD) patient with HPV-negative ileostomal papillomatous lesion and perianal condylomata during Infliximab infusions.

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## CASE REPORT

A 34-year old woman presented with tender verrucous lesions in the perianal area and a small verrucous lesion involving the ileostoma. The patient had been diagnosed with Crohn's disease 6 years earlier and underwent colectomy with Brooke ileostomy because of very severe large bowel involvement in the disease.

During a disease flare up the patient underwent endoscopy, which showed patchy inflammatory lesions in the residual ileum. Biopsies taken from the inflamed areas, as well as laboratory blood tests, were compatible with moderate Crohn's disease relapse. At clinical examination the stoma and peristomal area was disease free. The patient was, at that time, on azathioprine and low doses of corticosteroids and received additionally 3 doses of Infliximab (Remicade, 5mg/kg) in order to achieve full remission.



**Fig.** Human papillomavirus-negative ileostomal papillomatous lesion during Infliximab infusions in patient with Crohn's disease and ileostomy.

During Infliximab infusions the patient noticed papillomatous perianal lesions, which became enlarged over several weeks, had a condylomatous appearance and became painful. The patient denied aberrant sexual behavior. No other cutaneous or mucosal lesions were noticed elsewhere. The patient was immunocompetent and human immunodeficiency virus-negative.

In the same time, a small grayish-white papillomatous plaque on the upper circumference of ileostoma with a sharp outline but with no downward extension into the ileum was noticed (Figure). The lesion was a fleshy, multilobulated, and verrucous plaque, with hyperkeratosis, hypergranulosis, and marked papillomatosis. The clinical features were suggestive of a condyloma. In the skin surrounding the ileostoma no irritation was present. Light microscopic analysis of the stoma lesion demonstrated only signs of mild chronic inflammation but no definite koilocytosis was identified. In addition, immunohistochemical analysis for HPV was negative.

Cryotherapy of perianal lesions was performed successfully and Infliximab infusions were interrupted while the patient was on follow-up on azathioprine and low dose steroid treatment.

## DISCUSSION

Reported herein is a patient with Crohn's disease and perianal condylomas and an ileostomal papillomatous lesion that was suspected, clinically, to represent a condyloma. However the gross and microscopic appearance of the lesion prompted consideration of HPV as an etiology.

Papillomaviruses are phylogenetically classified into groups A-E. Human papillomaviruses belong to group A (mainly genital HPV), group B (epidermiodysplasia verruciformis HPV) and group E (cutaneous HPV). It must be emphasized here that different HPV types may prevail in cutaneous, mucocutaneous and mucosal lesions.<sup>5</sup> The hypothetical scenario of detection of HPV-DNA by PCR does not necessarily prove that a patient's stoma lesions are caused by an HPV infection, however, the perianal lesions preceding stoma lesions make a causal connection very likely.

Recurrent leukoplakial cutaneous and mucosal lesions located around the ileostoma of a woman with ulcerative colitis were examined for HPV in one study. Cutaneous, mucocutaneous and mucosal ileostoma-biopsies were analyzed and genital/mucosal or cutane-

ous HPV types were not found.<sup>6</sup> It has to be considered, however that the intestinal mucosa described there differed from normal intestinal mucosa; the stoma surgery caused almost direct contact with the skin.

In fact, in temporary stomas the separated distal end of the intestine is also brought to the skin surface as a “mucous fistula”, the effluent from which consists of small amounts of intestinal mucous. Ileostomies produce frequent fluid effluent, which may contain high concentration of active digestive enzymes, particularly in the more proximal stomas such as jejunostomies. In a large retrospective study of skin disorders in patients with abdominal stoma the following dermatoses were reported; physical or chemical irritant reactions, pre-existing skin disorders, allergic contact dermatitis, pyoderma gangrenosum, chronic papillomatous dermatitis, overgranulation, infections, eczema, cutaneous Crohn’s disease, peristomal metastatic carcinoma and dermatitis artefacta.<sup>7</sup>

Whether or not the patient reported here with a perianal condylomata and ileostomal HPV-negative lesion represents a high-risk candidate for anal cancer is a topic that needs careful overview. Things are more complicated, as Infliximab relation to IBD malignancy has not been yet precisely evaluated, as long-term follow up comparable with that of azathioprine is not yet available.<sup>8-9</sup>

Epidermoid cancer of the anus is a rare entity, which represents 2% of all gastrointestinal tract cancers. Possible predisposing causes include smoking and sexual behavior, chronic inflammation including perianal Crohn’s disease, anal fistula, fissure, sepsis, hydradenitis suppurativa and transmission agents such as human papillomavirus type 16 and 18 and condylomata.<sup>10-11</sup>

In addition, in a population based, case-control study for anal adenocarcinoma risk factors, including IBD patients in Denmark and Sweden, it has been shown that anal fissure or fistula was more common among HPV-positive patients.<sup>12</sup> However, according to that study, ulcerative colitis and Crohn’s disease were not found as high risk factors for anal cancer.

It seems that infection with HPV may be important for the development of squamous cell carcinomas. In addition, multiple HPV types can be found in single lesions. Degradation of the tumour suppressor gene p53 induced by the E6 protein of genital oncogenic HPV types is also an important mechanism for human papilloma-virus induced carcinogenesis.<sup>13</sup> However, according to a retrospective study of Crohn’s disease-related

anal cancer it has been shown that this type of cancer is not correlated with human papillomavirus type 16.<sup>14</sup>

In summary, all IBD patients with peristomal and stoma disorders must undergo a detailed clinical, histological and microbiological examination, including detailed history for pre-existing skin diseases.

Furthermore, in IBD cases with long-term immunomodulatory drug use, clinical follow up is mandatory as long term toxicity and carcinogenicity of these new biological agents still remain under investigation and only preliminary results are available to date.

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