

Recalcitrant plantar warts during azathioprine therapy for Crohn's disease

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Abstract

Dermatological complications of long-term immunosuppressive therapy in inflammatory bowel disease (IBD) are rarely reported. We present the case of a 29-year-old man with worsening of plantar warts while on azathioprine therapy for Crohn's disease. This case underlines the need to perform thorough skin examination of IBD patients before and during immunosuppressive therapy.

Keywords Azathioprine, Crohn's disease, plantar warts, human papillomavirus

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Introduction

Immunosuppression is a well-documented risk factor for severe systemic infections, such as pneumonia, sepsis and tuberculosis [1]. Immunocompromised patients are also at a higher risk of cutaneous infections such as warts caused by the human papillomavirus (HPV) which have been described mostly in transplant recipients [2]. However, patients on immunosuppression for other diseases such as inflammatory bowel disease (IBD) are also at risk. This is important especially with the increasing use of azathioprine for the maintenance of remission in IBD.

Case report

We present a case of a 29-year-old man with ileo-cecal Crohn's disease (CD), diagnosed 15 years ago. Initially, the patient received prednisone for induction therapy and was maintained on clinical remission with azathioprine 200 mg and budesonide 9 mg q.d. for the last 8 years. At the time of the patient's first visit to our department he presented with persistent abdominal pain with alternating loose, non-

bloody stools and constipation. Physical examination revealed mild left lower abdominal pain. Laboratory investigation showed no signs of inflammation. Imaging with magnetic resonance enteroclysis did not reveal any abnormalities. An ileocolonoscopy with biopsies did not show any active signs of CD activity. He was discharged on osmotic laxatives resulting in relief of his abdominal complaints.

During our evaluation, the patient also reported severe warts at the soles of his feet. A few small warts were already present at the time of diagnosis of his CD, but they progressed after introduction of azathioprine. Physical examination showed hyperkeratotic plaques of coalescing warts, covering major parts of the weight-bearing areas of his feet (Fig. 1). In addition to their unsightly cosmetic effect, the warts have started to impede his walking. He had been thoroughly evaluated by dermatology for alternative causes of plantar lesions. His warts had failed to respond to conventional therapies including liquid nitrogen (20-25 times), salicylic acid, and coagulation therapy. Eventually, azathioprine therapy was withdrawn, after considering the risks of reactivating his quiescent CD. However, withdrawal of azathioprine did not result in resolution of his warts. Currently, the patient is scheduled for laser surgery of his recalcitrant plantar warts.

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Conflict of Interest: None

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Discussion

Until recently, only retrospective studies suggested an increased incidence of cutaneous infections in patients with IBD [3]. This observation has been confirmed by a prospective study which reported an increased risk of cutaneous warts in patients receiving azathioprine, as compared to patients without azathioprine consumption (17.2% vs. 3.3%, $P=0.004$) [4]. In this cohort, disease activity was not documented during follow up. The disease activity and its consequences



Figure 1 Worsening of plantar warts in a 29-year-old man during azathioprine therapy for his Crohn's disease

(e.g. vitamin depletion and weight loss) can already attribute to the infectious risk. Therefore it remains unclear to which extend the infectious risk is caused by the disease itself or by the drugs used to control the disease.

Based on our literature review, this is the first reported case of a patient with well-controlled CD with worsening of plantar warts while on azathioprine. Although a direct association between azathioprine use and the development of plantar warts can not be established from a single case report, azathioprine may lead to the reactivation of latent viruses such as HPV. Albeit not life-threatening, plantar warts can be very painful, especially because they particularly develop beneath pressure points on the soles of the feet. Cutaneous warts in patients receiving immunomodulators are considered a therapeutic challenge, as they are often refractory to conventional treatments [5]. The current ECCO Consensus on the prevention, diagnosis and management of opportunistic infections in IBD recommends that discontinuation of immunomodulatory therapy should be considered in case of extensive cutaneous warts [6].

The increased incidence of cutaneous HPV infections in IBD patients receiving long-term azathioprine also raises questions on skin cancer risks. HPV infection is increasingly recognized as an important carcinogenic risk factor [7]. Nonmelanoma skin cancer (NMSC) is the most common malignancy in transplant recipients and HPV may play an important role in the carcinogenesis of squamous-cell carcinomas that are usually associated with multiple warts.

The incidence of HPV-associated cancer in the anogenital region in transplant recipients is increased 30-100 times as compared to the general population [8]. Long *et al* have reported the association between medication exposure and the risk for NMSC in patients with IBD. In a retrospective nested-case control study, persisted thiopurine use (>365 days) was associated with NMSC (adjusted OR, 4.27; 95% CI, 3.08-5.92) [9]. Another recent retrospective study reported similar findings [10]. Prospective studies in IBD patients are warranted to further elucidate the association between immunomodulators and NMSC in respect of HPV infections in patients with IBD.

Physicians should be aware of the increased risk of cutaneous warts during azathioprine therapy in IBD and inform their patients. Our case report supports the recommendation to include a detailed history of skin lesions with a comprehensive skin exam in IBD patients being considered for azathioprine therapy.

References

1. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929-936.
2. Lally A, Casabonne D, Imko-Walczuk B, et al. Prevalence of benign cutaneous disease among Oxford renal transplant recipients. *J Eur Acad Dermatol Venereol* 2011;**25**:462-470.
3. Warman JI, Korelitz BI, Fleisher MR, et al. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. *J Clin Gastroenterol* 2003;**37**:220-225.
4. Seksik P, Cosnes J, Sokol H, et al. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. *Aliment Pharmacol Ther* 2009;**29**:1106-1113.
5. Schmook T, Nindl I, Ulrich C, et al. Viral warts in organ transplant recipients: new aspects in therapy. *Br J Dermatol* 2003;**149** (Suppl 66):20-24.
6. Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47-91.
7. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens-Part B: biological agents. *Lancet Oncol* 2009;**10**:321-322.
8. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003;**348**:1681-1691.
9. Long MD, Herfarth HH, Pipkin CA, et al. Increased risk for non-melanoma skin cancer in patients With inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010;**8**:268-274.
10. Setshedi M, Epstein D, Winter TA, et al. Use of thiopurines in the treatment of inflammatory bowel disease is associated with an increased risk of non-melanoma skin cancer in an at-risk population: a cohort study. *J Gastroenterol Hepatol* 2012;**27**:385-389.