ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Cutaneous Malignancies in Patients with Inflammatory Bowel Disease

Millie D. Long, MD, MPH
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
University of North Carolina
Chapel Hill, North Carolina

G&H How common are cutaneous malignancies in patients with inflammatory bowel disease?

MDL We are starting to recognize cutaneous malignancies more frequently in patients with inflammatory bowel disease (IBD), and we also have a greater awareness of how IBD medications increase the risk of nonmelanoma skin cancer (NMSC). The most common cutaneous malignancy in this population, NMSC is a group of cancers that includes squamous cell carcinoma (SCC) and basal cell skin cancer. NMSC is also the most common cutaneous malignancy in the general population. The risk of NMSC among patients with IBD is 912 cases per 100,000 person-years, compared to 623 cases per 100,000 person-years in the general population. The incidence rate ratio for NMSC was found to be 1.46 for the IBD population compared to the non-IBD population. The risk of melanoma is also increased in IBD patients, although the absolute risk is much lower than that of NMSC, at 57 cases per 100,000 person-years.

G&H Why do cutaneous malignancies occur in patients with IBD?

MDL The pathophysiology underlying the increased risk of NMSC in IBD patients is likely related to increased photosensitivity associated with particular medications. For example, the thiopurine class of medications (including 6-mercaptopurine and azathioprine) is associated with increased photosensitivity to ultraviolet A (UVA) light. Many patients are inadvertently exposed to this harmful radiation, as UVA light makes up a majority of incident midday solar radiation, can penetrate glass, and is present throughout the year.

Patients treated with azathioprine have been shown to have a reduced minimal erythema dose (the lowest amount of radiation required to produce erythema 24 hours after irradiation) for UVA light but not ultraviolet B (UVB) light. The selective sensitivity to UVA light in azathioprine-treated patients is consistent with the production of 6-thioguanine DNA photoproducts. Studies of patients with rheumatoid arthritis, psoriatic arthritis, and psoriasis have also shown that methotrexate is associated with photosensitivity. Because methotrexate is not used as commonly for the treatment of IBD, there are no studies specific to this population, but the data from other populations suggest that heightened awareness and dermatologic screening may be appropriate for IBD patients receiving methotrexate.

The risk associated with thiopurines appears to be further increased when thiopurines are used for a longer duration and/or when they are used in combination with other immunosuppressant medications. Importantly, Peyrin-Biroulet and the CESAME group recently showed that the risk of skin cancer persists even after discontinuation of the thiopurine, possibly because the damage resulting from the increased ultraviolet light sensitivity has already occurred and cannot be reversed.

In addition to medication-induced photosensitization, several other risk factors for skin cancer have been identified in the general population, many of which also apply to IBD patients. Known environmental risk factors for NMSC include sun exposure, exposure to ionizing radiation, cigarette smoking, and exposure to certain

chemicals, such as arsenic. Other risk factors include genetic susceptibility, a family history of skin cancer, skin type, age, and the presence of certain types and/or large numbers of moles. Patients with fair skin types—those with pale skin, light eyes, and freckles—are at particularly increased risk of skin cancer.

Use of anti–tumor necrosis factor (anti-TNF) therapy is also associated with a slightly increased risk of melanoma, but we do not yet have data showing whether duration of use affects this risk. In addition, the mechanism underlying the increased risk of melanoma requires further study. One possibility is that a melanoma that was previously held in check by the immune system is unleashed following administration of an anti-TNF agent. Alternately, melanoma could develop de novo after an anti-TNF medication is initiated, due to increased photosensitivity or some other mechanism.

G&H How can clinicians minimize the risk of cutaneous malignancies in patients with IBD?

MDL Reducing the risk of cutaneous malignancies in IBD patients is an important goal. Traditionally, gastroenterologists have not been focused as much upon extraintestinal complications of IBD therapies, but primary care providers may not know about some of the complications associated with these medications. Thus, gastroenterologists should be aware of and educate patients about the possible dermatologic side effects of IBD medications.

There are 2 forms of prevention that can be considered: primary prevention and secondary prevention. Primary prevention refers to prevention of disease, and secondary prevention refers to early detection of disease so that treatments can be rendered earlier, when they are potentially more effective. In the case of cutaneous malignancies, primary prevention consists of counseling patients about sunscreen use and avoidance of tanning beds or other sources of ultraviolet light. Since the mechanism of disease is thought to be related to photosensitivity, use of a broad-spectrum sunscreen that protects against both UVA and UVB light can prevent NMSC.

Additionally, a screening skin examination by a dermatologist should be considered in patients who are receiving immunomodulators and/or biologics. Just as gastroenterologists perform screening colonoscopies in the general population to detect colonic polyps and remove them before they become cancerous, dermatologists can perform a screening examination to detect skin lesions at an early stage. Such dermatologic examinations are recommended annually for patients who have undergone organ transplantation, in whom the risk of skin cancer has been shown to correlate with the degree of immunosuppression. While an individual who has received a heart transplant is under much greater immunosuppression than a patient with IBD, an increased risk of skin cancer has been demonstrated in IBD patients receiving immunosuppressants, so a dermatologic screening examination may be warranted in some cases; such an examination could greatly impact an individual if a lesion is caught early, when treatments are more effective.

G&H Have any large studies examined the link between cutaneous malignancies and IBD?

MDL There have been several important studies in this area. My coauthors and I described the association between cutaneous malignancies and IBD in a retrospective study published in 2010 in *Clinical Gastroenterology and Hepatology*. We found a particularly increased risk of NMSC in patients with IBD who were receiving thiopurines. We also found increased risk with increasing duration of use. Additionally, combination therapy with a thiopurine plus an anti-TNF agent was associated with an incremental increased risk.

Two separate publications in *Gastroenterology* have also evaluated this risk prospectively. Singh and colleagues found similar associations in a prospective cohort study—in particular, an increased risk of SCC with thiopurines. Importantly, Peyrin-Biroulet and coworkers found that this risk persists even after discontinuation of thiopurines. In other malignancies that also occur more frequently in patients taking thiopurines, such as lymphoma, the risk returns to baseline once the drug is discontinued. However, the persistence of an elevated risk of skin cancer makes sense, given the potential mechanism of action for thiopurine-induced skin damage. Because of the photosensitization caused by UVA light, by-products accumulate within the skin, and these by-products may remain even after the thiopurine is discontinued. From a clinical standpoint, this finding reinforces the importance of wearing sunscreen and preventing ultraviolet light exposure while on thiopurines, in order to prevent any downstream risk. An important point regarding these 3 studies is that they were performed in different geographic areas—Canada, France, and the United States—so the risk associated with thiopurine use is not localized to one latitude or region of the country.

Finally, my group recently published a separate large, retrospective cohort study in *Gastroenterology* that looked at both NMSC and melanoma risk. Importantly, this publication was the first to demonstrate an increased melanoma risk in the IBD population. Melanoma is a very rare cancer, so prior studies have not had a large enough sample to determine whether there is an increased risk in patients with IBD. In our study, we used administrative claims data to identify over 100,000 patients with IBD, which provided

sufficient numbers for assessing this rare outcome. We found that the risk of melanoma was increased in patients receiving anti-TNF therapy, which supports the notion that a dermatologic screening examination is warranted in these patients. Prevention is particularly essential with melanoma, as this cancer can spread distally and metastasize fairly quickly, in which case treatment will require more than just excision of a local skin cancer.

G&H How can clinicians promptly recognize cutaneous malignancies in patients with IBD?

MDL I do not perform a screening examination on every patient, but I do ask patients whether they have noticed any new skin lesions. Questioning patients about any skin changes is important because IBD patients are often younger, so they are not necessarily thinking about NMSC. I do not think any gastroenterologist would feel comfortable diagnosing or treating skin cancer, as it is not our area of expertise, but awareness of these lesions can help to ensure that patients are referred to a dermatologist when necessary. Particularly for SCC and melanoma, early recognition can allow for local treatment before the tumor spreads to other parts of the body, resulting in better curative outcomes.

A basal cell carcinoma usually begins as a small, dome-shaped bump and is often covered by small, superficial blood vessels called telangiectases. Superficial basal cell carcinomas often appear on the chest or back and look like patches of raw, dry skin; they grow slowly over the course of months or years. SCC can start as a lesion called an actinic keratosis, which appears as rough, red bumps on the scalp, face, ears, or the backs of the hands. SCC usually begins as firm, skin-colored or red nodules. Any changes in the characteristics of a mole are also important to note, as they could indicate a melanoma. Specifically, clinicians should look for asymmetry, an irregular border, color change, or a change in diameter. Any lesion matching one of these descriptions warrants prompt referral to a dermatologist for biopsy and management.

G&H If an IBD patient is diagnosed with a cutaneous malignancy, how should he or she be managed?

MDL First, prompt referral to a dermatologist is warranted for treatment of the lesion. Multidisciplinary management with an oncologist may also be necessary in some cases, particularly for patients with advanced lesions or melanoma.

Clinicians must also decide how to manage the patient's IBD in the setting of a cutaneous malignancy; particularly if the patient has a melanoma, it would be preferable to minimize or discontinue IBD medications in that situation, if possible. However, the decision to continue, discontinue, or alter IBD therapy depends on the type of cutaneous malignancy, whether it is local or has spread distally, the type of immunosuppression, and the extent and severity of the patient's IBD. Some questions to consider include: Is the IBD such that it could be managed by surgery, thus allowing for withdrawal of immunomodulators or biologics? Or is the disease severe enough that the benefits of proceeding with therapy may outweigh the risks? After answering these questions, clinicians should develop an individualized approach to management that takes into account these various factors.

G&H What further research is needed in this area?

MDL Further research into the mechanism underlying the increased risk of melanoma associated with anti-TNF therapy is needed. Additionally, there is a great need for better data on how best to manage IBD patients following treatment for cutaneous malignancies.

Suggested Reading

Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2010;8:268-274.

Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. *Gastroenterology*. 2011;141:1612-1620.

Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al; Cesame Study Group. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. 2011;141:1621-1628.e1-e5.

Setshedi M, Epstein D, Winter TA, Myer L, Watermeyer G, Hift R. 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.

Long MD, Martin C, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and non-melanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012 May 11. Epub ahead of print.

Long MD, Kappelman MD, Pipkin CA. Nonmelanoma skin cancer in inflammatory bowel disease: a review. *Inflamm Bowel Dis*. 2011;17:1423-1427.