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# Immunosuppression and Malignant Neoplasms: Risk-Benefit Assessment in Patients with Inflammatory Bowel Disease

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Conflict of interest:** None declared

**Patient:** Male, 70-year-old
**Final Diagnosis:** Ulcerative colitis
**Symptoms:** Abdominal pain • bloody diarrhea
**Medication:** Azathioprine • infliximab
**Clinical Procedure:** Clinical treatment • surgical treatment
**Specialty:** Gastroenterology and Hepatology

**Objective:** Adverse events of drug therapy

**Background:** The treatment of inflammatory bowel disease aims to induce and maintain disease remission, avoid complications, and restore quality of life. The treatments include the use of immunosuppressants and biological therapy. Despite the effectiveness of these treatments in controlling disease activity and in limiting complications, there remains an increased risk of developing malignancies.

**Case Report:** A 70-year-old male patient with ulcerative colitis who had pancolitis was initially treated with mesalazine. In 2010, the medication was changed to azathioprine due to clinical disease activity. The patient demonstrated clinical and endoscopic response to the medication, but presented recurrent facial lesions identified as non-melanoma skin cancer in 2014, 2015, and 2016. Azathioprine was discontinued and anti-TNF therapy was started, but no satisfactory clinical or endoscopic response was observed. The patient developed hematuria and a ureter tumor was found with subsequent ureteronephrectomy. Moreover, the patient underwent total colectomy with ileostomy as a treatment for refractory ulcerative colitis.

**Conclusions:** Immunosuppressive therapy can facilitate the development of malignant neoplasms, accelerate tumor growth, and favor the onset of metastases. The types of tumors most associated with its use are lymphoproliferative tumors and non-melanoma skin cancer. The benefits of adequate control of inflammatory bowel disease are clear and the use of immunosuppressants should not be limited by these potential adverse outcomes; however, the risk-benefit profile of immunosuppression should always be assessed on a case-by-case basis.

**MeSH Keywords:** Azathioprine • Biological Therapy • Immunosuppressive Agents • Inflammatory Bowel Diseases • Skin Neoplasms

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## Background

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by continuous inflammation of the colon, which affects the rectum and progresses continuously to a variable extent into the colon and causes considerable reduction in patients' quality of life [1,2]. The exact etiology is unknown and the disease arises from an interaction between genetic and environmental factors [1,2].

Medical treatment is based on the degree of colonic involvement and course, response to previous medications, and the presence of inflammatory activity and extra-intestinal manifestations [1]. The medications prescribed are aminosalicylates, immunosuppressants, and biological therapies, consisting of anti-TNF and anti-integrin agents [2]. Immunosuppressive agents such as thiopurines are indicated for maintenance of remission in patients with previously moderately to severely active UC in remission due to corticosteroid induction [2]. Anti-TNF therapy, such as infliximab agents, is recommended in patients with moderately to severely active UC for induction and maintenance of remission [2]. Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor α, which acts by neutralizing its biologic activity, leading to disease control [3].

The main complications of prolonged immunosuppressive therapy are the increased risk of infections and malignancies [4,5]. Immunosuppressive therapy can promote the development of malignant neoplasms, accelerate tumor growth, and favor the onset of metastases [6]. Mechanisms involved include decreased immune surveillance of emerging cancer cells, the potentiation of oncovirus action, and the direct carcinogenic effect of some medications such as azathioprine [5,6]. Therefore, the benefit-risk profile of immunosuppression should be assessed on a case-by-case basis.

Here, we describe a patient with refractory UC who developed non-melanoma skin cancer while receiving immunosuppressive therapy, and we present a literature review on the subject. The study was approved by the local Research Ethics Committee (protocol: 85672218.1.0000.5411) and the patient provided written informed consent.

## Case Report

A 70-year-old white man was diagnosed with UC at 46 years of age. At the time of diagnosis, in 1995, he presented with bloody diarrhea, abdominal pain, anemia, and weight loss and was started on treatment with mesalazine, showing clinical and endoscopic remission. In 2010, the patient presented clinical and endoscopic activity and the medication was replaced by azathioprine, with adequate response (Mayo 1 endoscopic score). In May 2014, the patient presented with an elevated and ulcerated lesion in the nose, measuring 1.5 cm in diameter, consistent with a moderately differentiated squamous cell carcinoma (SCC). New SCCs were removed in December 2014, December 2015, and April 2016. At that time, the patient was asymptomatic, presenting with mild endoscopic disease activity (Figure 1) and, due to control of the inflammatory process, the azathioprine was changed to mesalazine based on the risk of non-melanoma skin cancer recurrence.

One year after the change in medication, in April 2017, the patient returned, presenting with bloody diarrhea (>6x/d), moderate abdominal pain, weight loss >10%, CRP 6.0 mg/dl (<1.0 mg/dl), and hemoglobin 9.3 g/dl (13.5–17.5 g/dl), classified as severe disease activity. Colonoscopy demonstrated severe disease activity throughout the colon (Figure 2). The patient showed no improvement with this therapy, and induction treatment using infliximab 5 mg/kg was prescribed. After the first dose of infliximab, he showed significant clinical improvement in symptoms. Six months after the start of infliximab therapy and 2 weeks after corticosteroid tapering, he returned, presenting with bloody diarrhea 15–20 times per day, abdominal pain, urgency and fecal incontinence, nausea, vomiting, asthenia, arthralgia, and CRP 8.5 mg/dl (<1.0 mg dl), consistent with severe clinical activity, which was confirmed by endoscopy (severe endoscopic disease activity, Figure 3). The patient was hospitalized, and a new skin lesion was diagnosed in the temporal region of the face, identified as SCC, which was removed (Figure 4). At this time, total colectomy was indicated as the definitive treatment for UC, but the patient declined. In 2018 the patient entered a clinical trial to receive anti-integrin therapy, without adequate clinical response. The patient presented with microscopic hematuria and a few months later, was diagnosed with right ureter cancer. The patient underwent ureteronephrectomy to treat the ureteric tumor and total colectomy to treat the UC (see Figure 5).

## Discussion

Patients with IBD are at increased risk for developing certain types of tumors compared to the general population [4]. Patients with UC are at increased risk of developing leukemia and liver and biliary tract cancer; and Crohn's disease (CD) patients are at increased risk of developing cancer in the gastrointestinal tract, lung, and bladder, as well as lymphoma and non-melanoma skin cancer [4].

Non-melanoma skin cancer is the most common cancer worldwide, with increased incidence in recent years, especially in people over the age of 80 years [7], and squamous cell carcinoma and basal cell carcinoma are the most common in IBD





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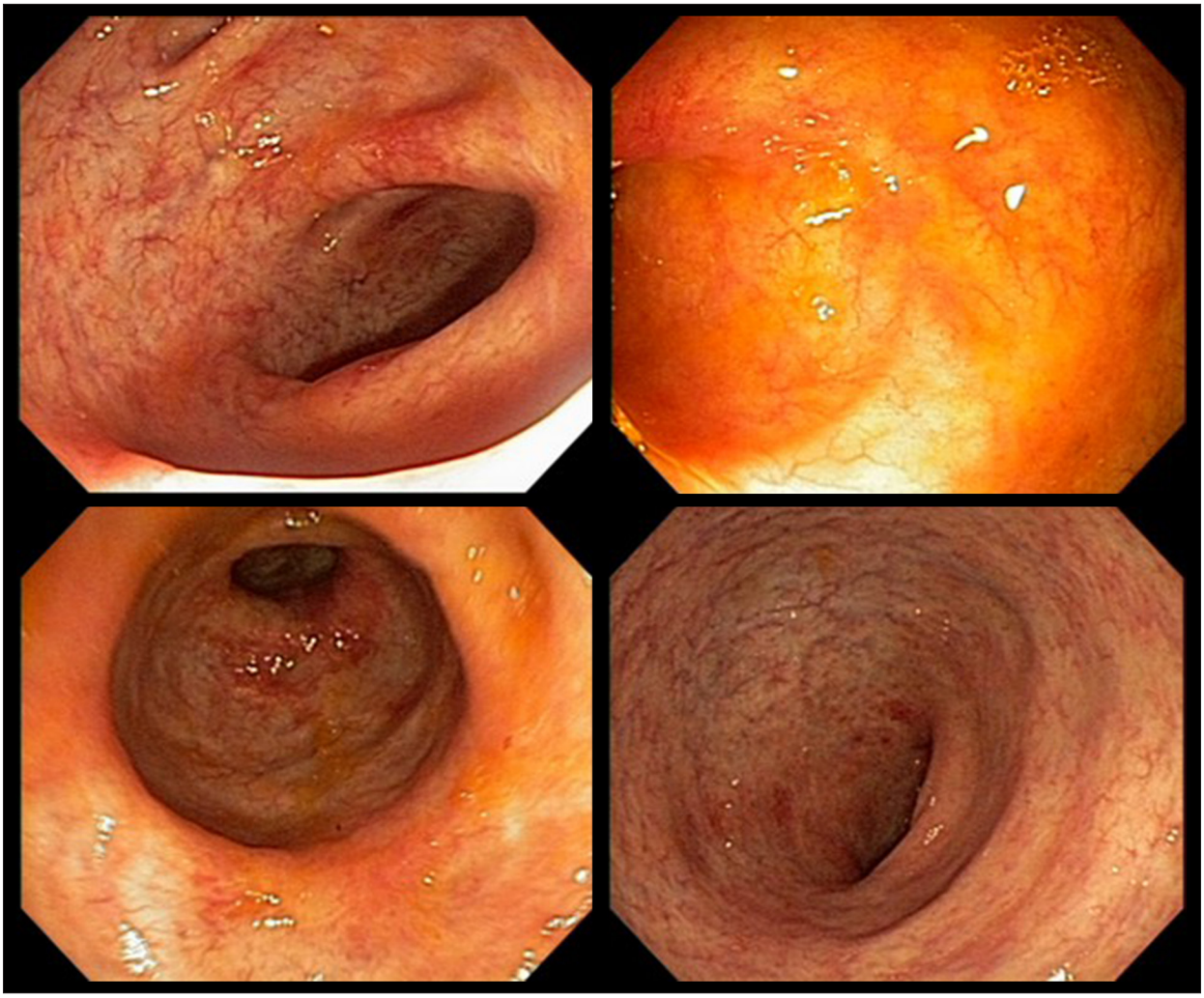

**Figure 1.** Colonoscopy performed in April 2016 showing mild edema and erythema throughout the colon, consistent with mild endoscopic activity (Mayo endoscopic subscore of 1).

patients [4]. Advanced age [4] and thiopurine exposure [8] are the main risk factors for these tumors. The CESAME study [9] observed that both current use (HR: 5.9; CI 95%: 2.1–16.4; p=0.0006) and previous use of thiopurine (HR: 3.9; CI 95%: 1.3–12.1; p=0.02) were associated with increased risk of skin cancer in IBD patients, suggesting that DNA damage and gene mutations can persist even after discontinuation of medication; therefore, the use of thiopurine is not recommended in patients over 60 years of age. In addition, patients should be advised to use sunscreen daily as soon as IBD is diagnosed and to have annual skin examinations [4].

Thiopurines act on T lymphocytes, disabling key processes related to the inflammatory response [10]. In CD4+ T lymphocytes, azathioprine acts on Rac 1, a GTPase essential for intestinal T cell activation, which plays an important role in various cellular processes such as growth, differentiation, and cell movement. Random incorporation of this GTPase into DNA can lead to sequence errors, which can lead to complications such as liver toxicity and tumor development and growth [10].

In the present reported case, the most appropriate medication for the treatment was biological therapy, but access to biological therapy for UC patients is restricted in Brazil. In addition, the patient presented with other risk factors for the development of non-melanoma skin cancer, such as previous exposure to solar radiation, advanced age, and white race, as well as a deficit in immune surveillance as a result of IBD. Although aware of the patient's cancer risks and the recommendations of guidelines that contraindicate the use of thiopurines in patients over age 60 years [4], our patient started using the medication due to the lack of other available treatments. Furthermore, he refused to undergo surgery, and the moderate-active disease required an efficient treatment.





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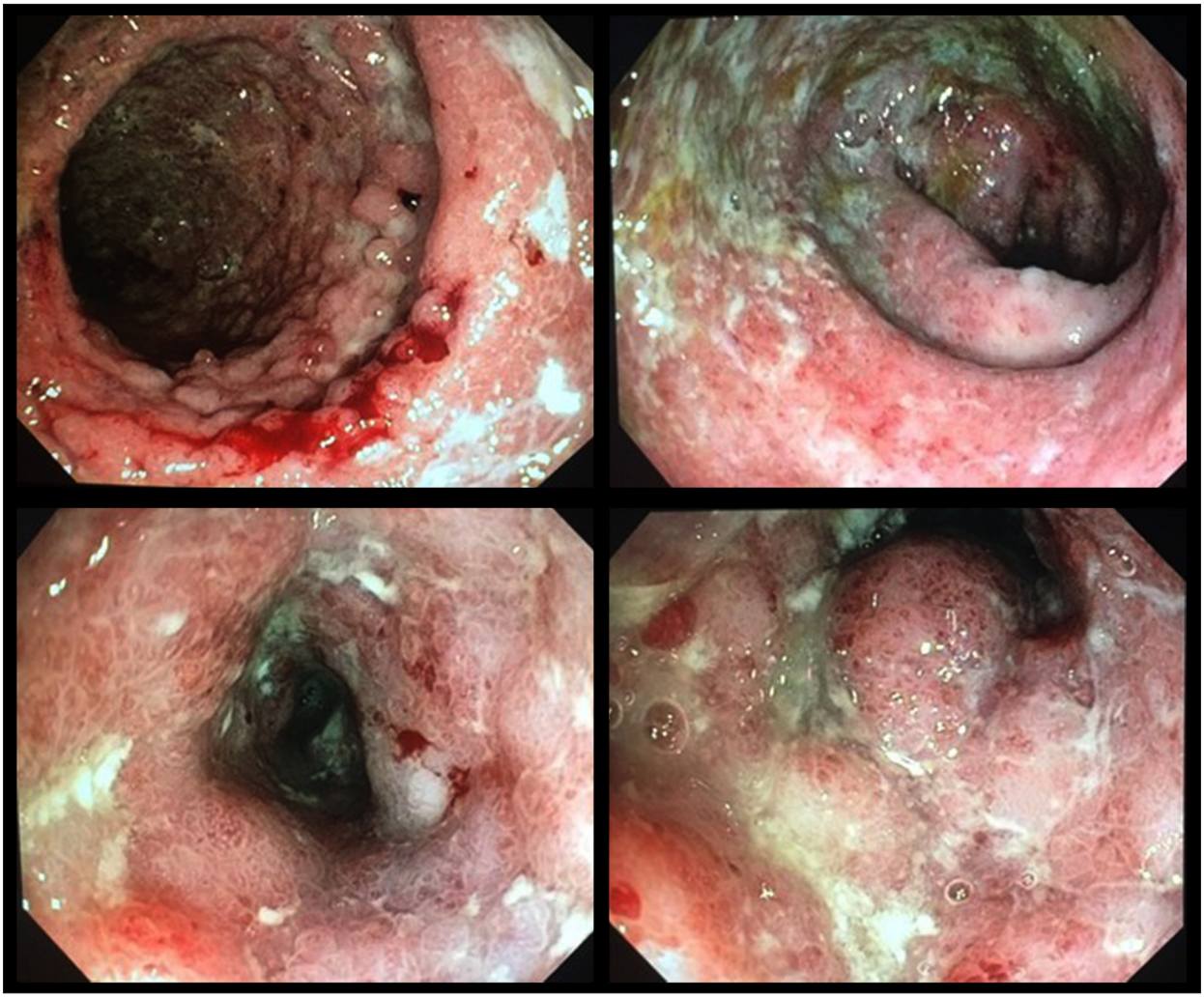

**Figure 2.** Colonoscopy performed in May 2017 showing fibrin-coated ulcerations, friability and spontaneous bleeding, consistent with pancolitis with severe endoscopic disease activity (Mayo endoscopic subscore of 3).

Renal cell carcinoma is the most common adult renal cancer and the most lethal of the urological malignancies [11]. Infliximab has been indicated for the treatment of renal cell carcinoma, as well as in immunotherapy-resistant or refractory tumors [12]. Wauters and colleagues [13] conducted a retrospective cohort study comparing the risk of renal cell carcinoma in IBD patients exposed to anti-TNF therapy versus no anti-TNF exposure, and concluded that there was no increased risk related to the medication. In contrast, thiopurine use was found to be associated with a higher risk of urinary tract cancer in the CESAME cohort study [14].

Tumor necrosis factor presents a dual and antagonistic effect on tumor progression [15]. It can stimulate apoptosis through the caspase pathway and induce tumor necrosis. However, it can facilitate survival and proliferation of neoplastic cells through the NF-κB cascade. Thus, the effect of anti-TNF therapy on tumorigenesis in chronic inflammatory diseases is difficult to predict.

A systematic review including 23 RCTs of TNFα antagonists in IBD showed that there was no significant increase in risk of malignancy (20/4442) when compared to placebo (16/2778), a finding which is corroborated by data from registry studies and real-world observational studies [16]. However, there is conflicting evidence on whether TNFα antagonists are associated with an increased risk of melanoma [16].

There is limited data on the risk of malignancy with newer biologics, including vedolizumab and ustekinumab, in patients with IBD. Regarding vedolizumab, a selective α4β7 integrin antibody, data from 5 studies showed that the malignancy risk was low (<1%) [17,18]. The majority of the patients who developed cancer reported previous use of thiopurines and anti-TNF agents. Decreased immune surveillance as a consequence of inhibition of leukocyte traffic is a concern for the development of gastrointestinal tract neoplasms. Similarly, studies with ustekinumab, a monoclonal antibody against





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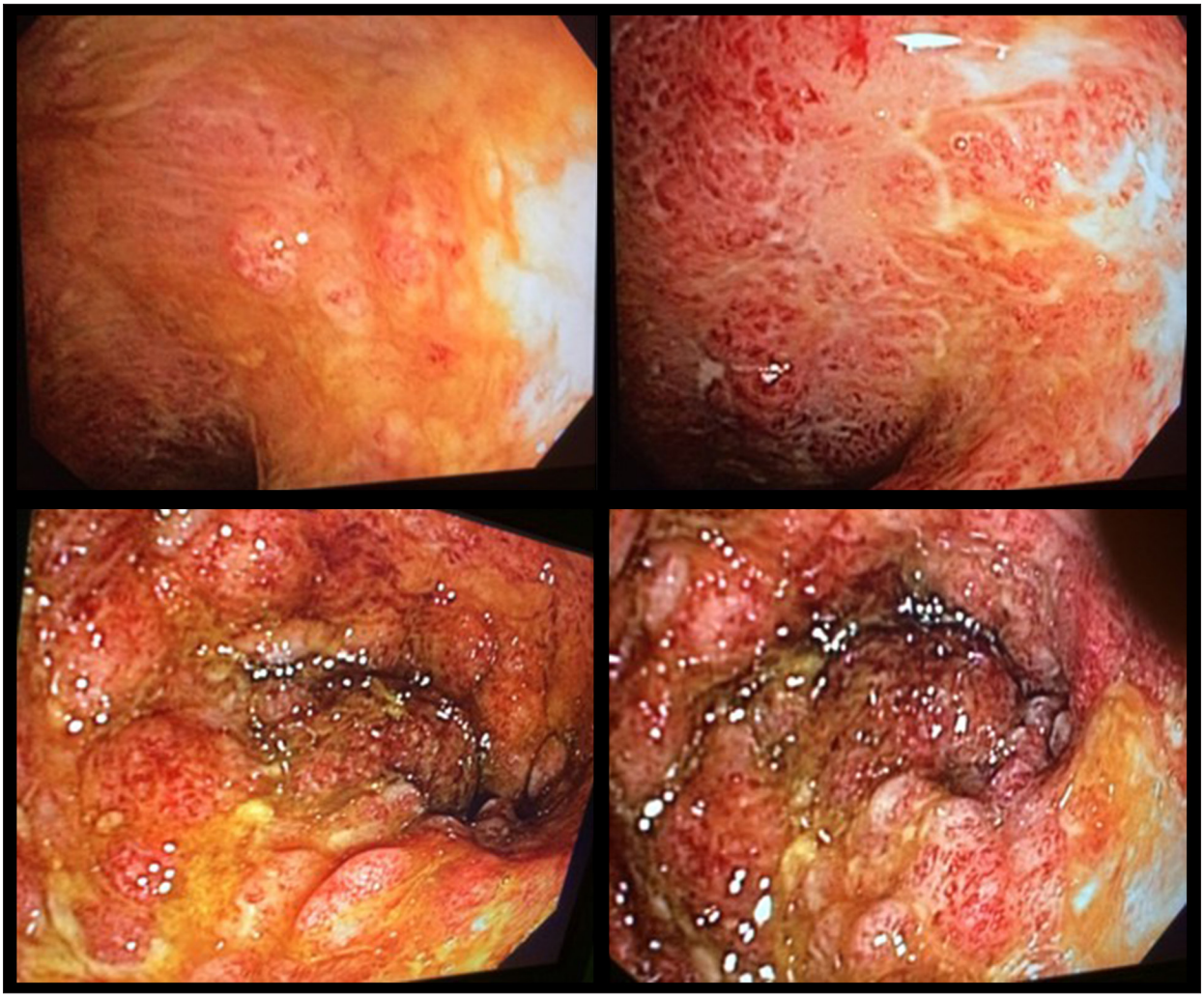

**Figure 3.** Colonoscopy performed in October 2017 showing fibrin-coated ulcerations, edema, erythema, friability, and spontaneous bleeding, consistent with pancolitis with severe endoscopic activity (Mayo endoscopic subscore of 3).

interleukin-12 and -23, did not show an increased risk of cancer in exposed patients [19,20]. In psoriasis, in a case-control analysis of the PSOLAR registry (Psoriasis Longitudinal Assessment and Registry) of 12 090 patients, treatment with ustekinumab was not associated with increased odds of malignancy versus no exposure [21].

Long-term extension studies of tofacitinib, a small-molecule inhibitor, in patients with UC and rheumatoid arthritis showed there was no significant increase in risk of malignancy in exposed patients [16]. However, registry studies and large real-world observational studies of tofacitinib in UC are not yet available.

Regarding cancer recurrence or appearance of a new tumor and use of immunosuppressive therapy, a retrospective study [22] analyzed 333 patients divided into 4 groups: anti-TNF monotherapy (n=50), combined therapy (anti-TNF with methotrexate or azathioprine) (n=52), methotrexate or azathioprine monotherapy (n=78), and patients not exposed to any immunosuppression (control group, n=149). No increased risk of *de novo* or recurrent cancer was observed in any of the groups analyzed.

The patient in the present case report continued thiopurine use, even after the onset of the first skin cancer in 2014. The use of thiopurine should be avoided for non-melanoma skin cancer, and the use of anti-TNF with or without methotrexate would be an option. Patients presenting with melanoma should avoid anti-TNF exposure.

In general, the use of aminosalicylates, nutritional therapy, and local corticosteroids appears to be safe in IBD patients with previous history of cancer, and the use of anti-TNF, methotrexate, systemic corticosteroids, and/or surgery should be considered in moderate-to-severe disease [4]. For all tumors, it is recommended to wait 2–5 years after the end of tumor treatment for reintroduction of immunosuppressive therapy [4].





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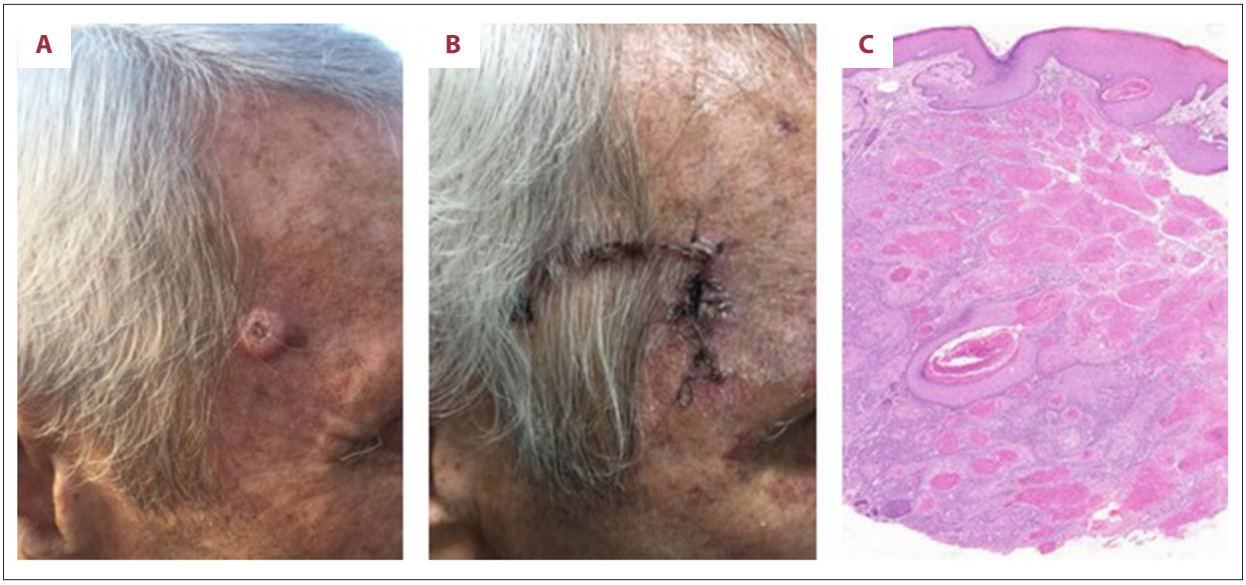


**Figure 4.** (**A**) Elevated nodular lesion in the right temporal region (October 2017). (**B**) Appearance after surgical resection of the skin lesion. (**C**) Histology with findings consistent with squamous cell carcinoma (2.5× magnification).

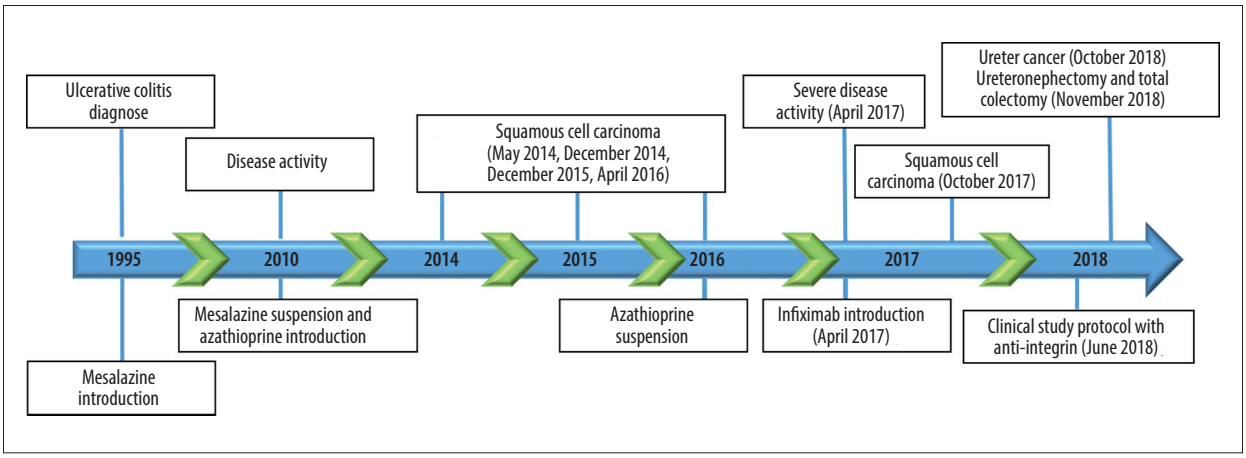


**Figure 5.** Patient medical history timeline.

Immunosuppressant drugs are vital tools in the therapeutic arsenal of IBD, but studies have showed an increased incidence of malignant neoplasms with these medications. Thus, the benefit of clinical efficacy must be balanced against the risks of infection and malignancies, taking into account the patient's own tumor risk factors. In the case of non-melanoma skin cancer, a previous history of skin cancer and significant exposure to ultraviolet rays should be taken into account, and sun protection in addition to regular visits to the dermatologist should be encouraged.

## Conclusions

Patients with IBD are at increased risk of developing malignant neoplasms. The use of immunosuppressive therapy such as thiopurines and anti-TNF therapy can facilitate the development or the recurrence of tumors, such as lymphoproliferative and urinary tract tumors and melanoma and non-melanoma skin cancer. The benefits of adequate control of IBD are clear and their use should not be limited by these potential adverse outcomes; however, the risk-benefit profile of immunosuppression should always be assessed on a case-by-case basis.

### Conflict of interest

None.





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