

CASE REPORT

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Malignancy, a real risk in patients using anti-TNF drugs for Crohn's disease?

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ABSTRACT

Introduction: Crohn's disease (CD) is a subtype of inflammatory bowel disease. Mucosal healing has become the main target in therapy and the most consequential treatment has been biologic agents, such as anti-TNF agents. The benefits of anti-TNF agents are associated with an increase in the risk of opportunistic infections and the development of malignancies.

Case Report: A 58-year-old woman with the diagnosis of a stricturing, non-penetrating Crohn's disease, underwent a surgical intervention for treatment of both Crohn's disease and an ovarian tumor. The diagnosis was of two primary tumors, an ovarian and an endometrial carcinoma.

Conclusion: The association between the use anti-TNF agents and tumors has been narrowed to specific tumors. There is no association between the development of genitourinary tumors and treatment with anti-TNF

agents. However, current data has demonstrated synchronicity between IBD and endometriosis. The pro-inflammatory profile seen in IBD might enhance the occurrence and transformation of endometriotic foci. Their link to ovarian tumors seen in IBD patients remains an open question.

Keywords: Anti-TNF, Crohn's disease, Endometrial cancer, Ovarian cancer

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INTRODUCTION

Crohn's disease (CD), a subtype of inflammatory bowel disease (IBD), is considered an autoinflammatory disease with no clear cause, though several genetic, immunological, and environmental factors are known to increase its development. Crohn's disease is characterized by a Th1/Th17 led mucosal inflammation.

The inflammation usually takes place in specific sites of the intestinal tract, including the small and large bowel. The location usually remains stable over the course of the disease. Nevertheless, the cyclic nature of the inflammatory process causes changes in the disease phenotype and location. The severity of bowel damage is

considered a prognostic factor and, thus, mucosal healing has become the main target in therapy [1].

Among the anti-inflammatory drugs used for treatment in CD, the most consequential have been biologic agents, specifically, anti-TNF agents. The anti-TNF agents available are monoclonal antibodies (some without the Fc unit) against TNF- α . Food and Drug Administration approved agents include infliximab, adalimumab, certolizumab, and golimumab [2–5]. Though all four drugs bind soluble and membrane TNF, they do so in variable degrees. Anti-TNF agents are used in patients with a steroid refractory disease or in patients with no response to immunomodulators [5]. Anti-TNF agents block soluble and transmembrane TNF- α , a potent pro-inflammatory cytokine known to simultaneously control apoptosis, proliferation, morphogenesis, and activate NF- κ B, through the balance created by downstream signaling cascades [3, 4]. Particularly in CD, blocking TNF- α reduces the overt inflammation caused by defective neutrophils and dysfunctional intraepithelial lymphocytes [1, 2]. These mechanisms translate to less inflammatory infiltrates in the mucosa and the re-establishment of the anti-inflammatory cells necessary to keep homeostasis in the gut.

Despite the benefits of anti-TNF agents, their use increases the risk of opportunistic infections, and they are associated with the development of malignancies. The latter may not prove paramount when treating severe CD, but knowledge of the risk is relevant during maintenance.

Malignancy in autoinflammatory diseases such as CD is a known long-term consequence considering the carcinogenic effect of chronic inflammation [6–8]. For instance, the effective mucosal healing seen with anti-TNF drugs is associated with a decrease in the risk of colorectal carcinoma [9]. Be that as it may, immunosuppressive drugs may pose a risk in CD when used for longer intervals, and they may harmonize with anti-TNF agents, increasing the risk for the development of malignancies associated with immunosuppression, like skin cancer, cervical cancer, and lymphomas [8, 10, 11]. As for solid tumors, many studies report an increased incidence. Nonetheless, when adjusted for exposure to immunomodulators or comparing anti-TNF agents versus immunomodulators, the risk for solid tumors seems to decrease [11]. The attributable risk given by anti-TNF agents in the development of more than one neoplasia is thus vague. We here present a case of advanced stage, extraintestinal, solid tumors in a patient with stricturing, non-penetrating CD.

CASE REPORT

A 58-year-old woman with the diagnosis of a stricturing, non-penetrating Crohn's disease, was seen at the Gastroenterology Department. She had received

infliximab for eight months, as well as adalimumab for six months. During follow up, the magnetic resonance imaging (MRI) studies indicated activity at the ileum. Adalimumab was thus changed to ustekinumab. She was not a candidate for endoscopic treatment and thus surgery was considered. The computed tomography (CT) scans prior to the surgical intervention identified a 3 cm tumor at the left ovary, as well as multiple iliac lymphadenopathies. The report was dictated as an O-RADS 4. The laboratories reported a CA125 of 110 U/mL. The surgical team agreed to perform an oophorectomy together with the ileocectomy. An intraoperative consultation was done for the ovarian tumor, reporting a high-grade carcinoma (Figure 1A). A radical hysterectomy with bilateral oophorectomy was thus performed with lymphadenectomy and omentectomy. There were no surgical complications.

After histopathological analysis, an ovarian and an uterine endometrioid carcinoma were identified (Figures 1C–G and 2D). The ovarian endometrioid carcinoma had a higher grade than the uterine carcinoma (Figures 1 and 2). Both carcinomas had retained mismatch repair proteins (MSH2, MSH6, MLH-1, and PMS2) (not shown), had no loss of PTEN and no nuclear translocation of beta-catenin (Figure 1H and I). There was loss of ARID1A expression in the ovarian carcinoma (Figure 1J). The ileum presented severe chronic active inflammation, consistent with a stricturing, non-fistulizing Crohn's disease (Figure 3A–E). There were iliac and pelvic lymph nodes metastasis of a high grade endometrioid carcinoma (Figure 3F). There was no evidence of metastasis to other organs. Currently, the patient has no gastrointestinal complaints and is tolerating the adjuvant chemotherapy.

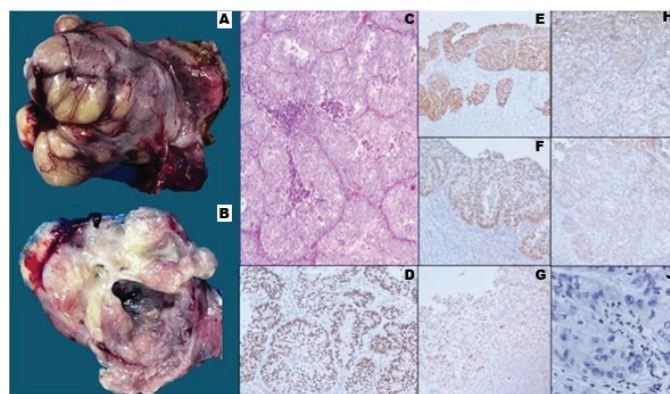


Figure 1: The ovarian tumor received as a transoperative consultation. (A and B) The tumor had a dimension of 5×3 cm, was multilobulated, with a solid-cystic cut surface. (C) Upon microscopic examination, the neoplasm was composed of glands with marked nuclear pleomorphism, abundant mitotic activity and apoptosis, as well as central necrosis. (D) Immunohistochemistry analysis showed positivity for ER, (E) CK7, (F) PAX8, (G) wild-type p53, (H) retained PTEN, (I) cytoplasmic β -catenin, and (J) loss of ARID1A.

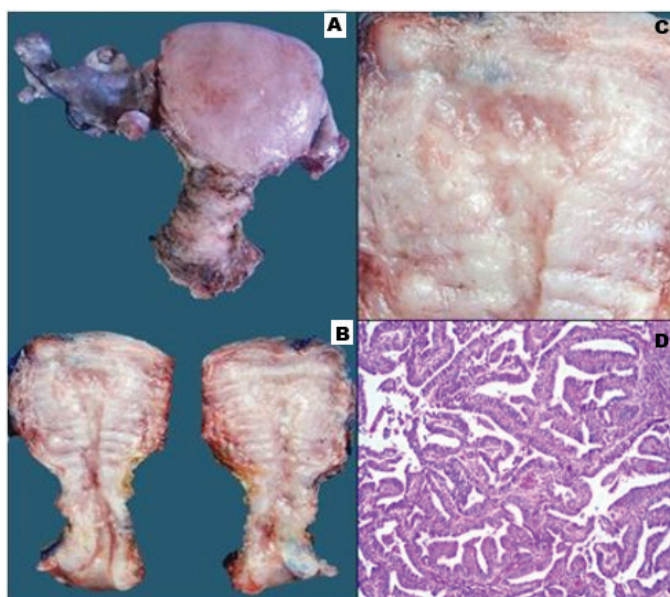


Figure 2: The uterine specimen. (A) No lesions were identified on the serosal surface. (B and C) The endometrial cavity showed marked irregularity. (D) Upon microscopic examination, a malignant neoplasm composed of irregular and branching glands, with unpolarized nuclei was identified. It had no necrosis and a low mitotic activity.

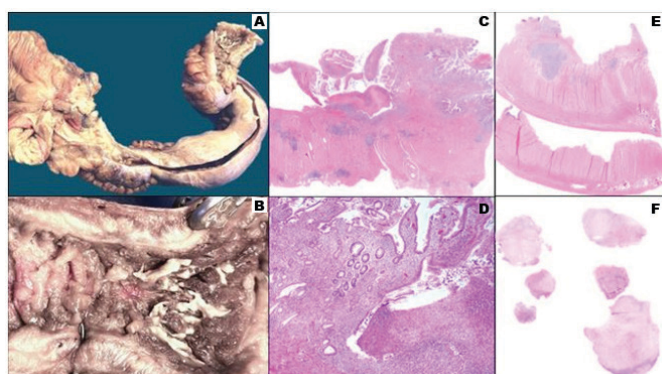


Figure 3: The ileocecectomy specimen. (A) It showed areas of stenosis with focal thickening of the wall, accompanied by proximal dilation. (B) The mucosa showed non-continuous ulcers with pseudopolyps. (C–E) Microscopic examination showed an active, fistulizing Crohn's disease, with abundant ulcers and transmural multifocal lymphoid aggregates. (F) Mesenteric and pericolic lymph nodes presented metastasis of a high grade endometrioid carcinoma.

DISCUSSION

According to numerous epidemiological studies, there is a link between Crohn's disease and the incidence of tumors, having a slightly elevated risk of developing specific types of neoplasms [11]. Their development might be influenced by factors such as the use of immunosuppressive medications and chronic inflammation, which constitute a common feature of Crohn's disease. Chronic inflammation creates a

conductive environment for abnormal cell growth and proliferation, encompassing the main characteristics of tumors. Additionally, an altered immune system and an exacerbated immune response, as observed in Crohn's disease, could also be involved in promoting the development of solid tumors.

In CD, the immune response promotes oncogenesis through the release of oxidative stress and promotion of wound healing transcriptional programs [12]. As such, chronic intestinal inflammation in inflammatory bowel disease has been associated with an increased risk of colorectal cancer (1.5–2 fold relative risk ratio), small-bowel adenocarcinoma, cholangiocarcinoma [odds ratio of 4.09 in patients with ulcerative colitis (UC)], and anal cancer [11, 13–15]. Colorectal cancer in IBD patients, particularly those with long-standing and extensive disease and concomitant primary sclerosing cholangitis, have an elevated risk of developing this cancer. The risk is higher in individuals with both Crohn's disease and ulcerative colitis [16–18]. Surveillance with colonoscopy is recommended to detect colorectal cancer.

The effect of immunosuppressant provides support for the immunosurveillance hypothesis [19], as described with other autoimmune diseases [15, 20]. In patients with transplanted organs, there is a higher risk for the development of skin cancer and Epstein–Barr virus-associated post-transplant lymphoproliferative disorders. As such, recommendations have been made for screening of malignancies associated with immunosuppression, like cervical cancer, skin cancer, and lymphoproliferative disorders [21].

An association has been described between T lymphoproliferative disorders and cases of patients receiving anti-TNF- α agents in the context of rheumatoid arthritis (RA) and IBD [21–24]. Anti-TNF drugs for the treatment of CD appear to be associated with an increased risk of non-Hodgkin's lymphoma (NHL). However, when compared with CD patients taking immunomodulators alone, the risk is similar [25–27]. Emerging treatments for IBD, such as vedolizumab and ustekinumab, have shown acceptable safety profiles for malignancy risk and immunosuppression appears to be safe for use in IBD patients with current and prior malignancies.

Some medications used to manage IBD, such as thiopurines and certain biologics, have been associated with a slightly increased risk of lymphoma. However, the risk must be weighed against the potential benefits of these drugs in controlling the underlying inflammatory process [9, 16, 28, 29]. Proper control of inflammation with biologics allows remission of the disease while discontinuing the treatment [30, 31]. Animal models show contradicting evidence on the premise that biologics, such as anti-TNFs, promote tumorigenesis [19, 32]. In the same line, clinical studies lack statistical power and have many biases to account for. Some common issues include a limited sample size, selection bias, publication bias, and even confounding factors not accounted for [17, 32–34]. Accordingly, except for gastrointestinal tumors, there are

no guidelines recommending screening for solid tumors and hematolymphoid tumors in patients with IBD [11].

Though there is no association between IBD, biologic agents such as anti-TNF, and genitourinary tumors (except for cervical cancer), there are data demonstrating synchronicity between IBD and endometriosis (incidence ratio of 1.5 and 1.6 in UC and CD respectively) [35–37]. Endometriosis is a differential diagnosis for IBD, both clinically and morphologically. Endometriosis is a known risk factor for endometrioid carcinoma, most specifically for ovarian endometrioid carcinoma [38, 39]. Recent studies have proven a clonal relationship in endometrioid ovarian and uterine neoplasms, confirming one can be the metastasis of the other or vice versa [40–42]. They behave as two independent tumors, specifically when the tumors are organ-confined and have low-grade characteristics [40]. Cases like the one presented challenge such observations. The tumor burden and the histological grade support the theory of an ovarian origin. The molecular pathways associated with the development of endometrioid carcinoma were sought, including the SWI/SNF complex, which is determined by immunohistochemistry for ARID1A [43]. ARID1A is lost in endometrioid carcinomas associated with endometriosis [39]. Under such circumstances, endometriosis is a likely risk factor for the ovarian carcinoma presented in this case.

Inflammation is a key feature of endometriosis. Likewise, pro-inflammatory cytokines are pro-tumorigenic in the context of ovarian neoplasms [38, 39, 44]. The pro-inflammatory profile seen in IBD might enhance the occurrence and transformation of endometriotic foci. The connection between these factors and the development of ovarian tumors seen in IBD patients remains an open question.

CONCLUSION

Patients with CD have a risk for the development of gastrointestinal neoplasia. There is no synergy between the autoinflammation in CD and the use of biological agents, such as anti-TNF- α , for the development of solid tumors. Cases presenting exceptional neoplasms in patients with IBD are best explained by the chronic inflammatory response seen in undertreated or mistreated scenarios. The most important element in treatment of IBD should be striking a right balance between controlling inflammation and minimizing the risk of tumor development.

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Author Contributions

Karla Gabriela Díaz – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Grecia Guadalupe Rodriguez-Paredes – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

María José Lizardo-Thiebaud – Conception of the work, Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Alessandra Prado-Aguirre – Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sara Burbano-Rodriguez – Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Guarantor of Submission

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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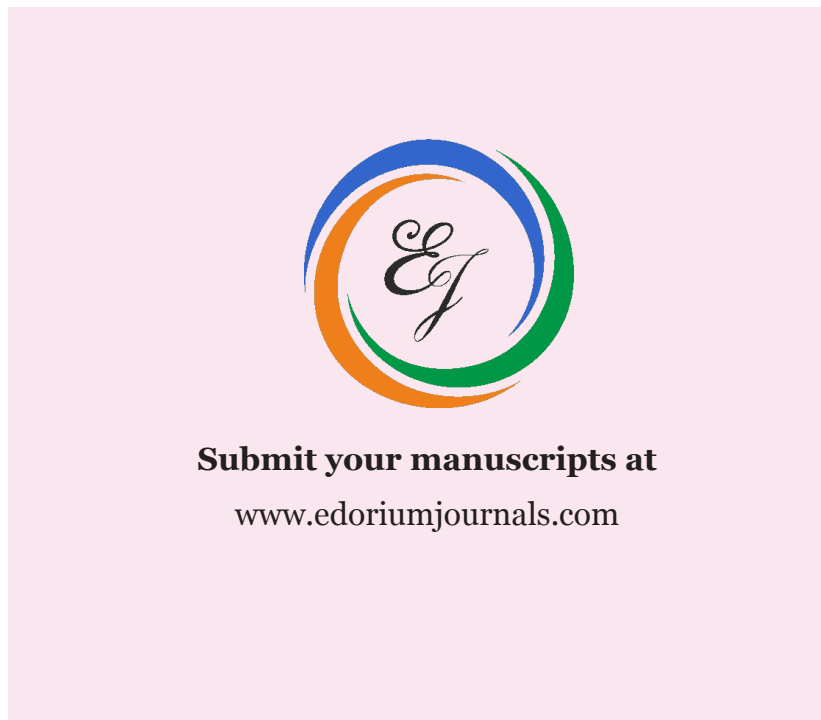
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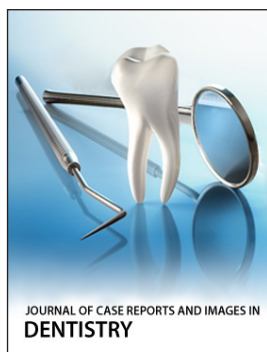
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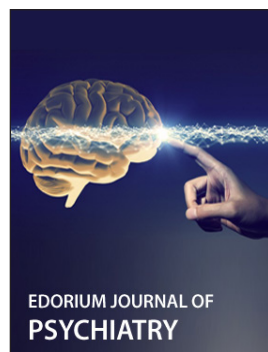
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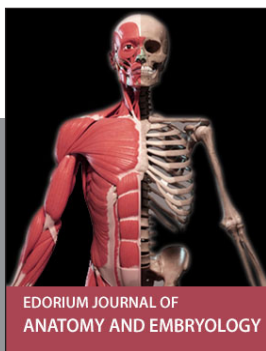
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