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Cixutumumab-Associated Pancolitis in a Prostate Cancer Patient

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Keywords

Prostate cancer; insulin-like growth factor 1 receptor; cixutumumab; IMC-A12; pancolitis

Introduction

New therapies for cancer have emerged as we have gained better understanding of the molecular mechanisms that underlie those diseases. Several types of tumors, including prostate cancer (PC), overexpress the insulin-like growth factor 1 receptor (IGF1R).[1] The antitumor effect of IGF1R inhibition has been noted in both *in vitro* and *in vivo* models of PC.[2,3] Several different agents, including such monoclonal antibodies as IMC-A12 (cixutumumab), have been developed as antagonists to IGF1R.[4-6] Because of its antitumor activity in tumor cell models, cixutumumab has advanced into clinical studies.[7] Recent phase I and II studies in patients with various cancers showed that this agent is well tolerated and without unreasonable side effects.

We describe here, to our best knowledge, the first case of a patient with PC who developed pancolitis while participating in a clinical trial of cixutumumab.

Case Report

A 53-year-old white man was seen by a local physician for musculoskeletal pain in the lower back and neck ultimately resulting in upper-extremity weakness. Further evaluation, including a prostate biopsy performed in March 2007, revealed Gleason score 9 (4+5) prostatic adenocarcinoma. At that time, his prostate-specific antigen (PSA) concentration was 953 ng/mL, a bone scan showed diffuse bony metastasis, and computed tomography (CT) scanning revealed retroperitoneal and pelvic lymphadenopathy.

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That same month, the patient sought evaluation at The University of Texas MD Anderson Cancer Center for further care. Here, he was initially treated with androgen-ablation therapy, including bicalutamide and leuprolide acetate, which yielded a transient favorable response. His PSA decreased to a nadir of 0.4 ng/mL. Nine months later, his PSA concentration was 0.7 ng/mL, so bicalutamide treatment was stopped.

In another 6 months, his PSA had increased to 4.9 ng/mL, and his testosterone concentration was 22 nmol/L. The staging workup identified progressive bony metastasis involving the spine, ribs, hemipelvis, scapula, and proximal femurs. The patient agreed to participate in a randomized phase II clinical trial of docetaxel and dasatinib. He was given two cycles of docetaxel (75 mg/m^2 intravenously [IV] every 3 weeks), dasatinib (100 mg orally [PO] once daily for 14 days), and prednisone (5 mg PO twice daily). He developed nausea (grade 1) and diarrhea (grade 1) during this treatment.

Two months later, he was hospitalized for *Aspergillus* pneumonia, withdrawn from the study, and treated with voriconazole. His subsequent PSA concentration was 1.5 ng/mL. Within 3 months after that, his PSA was 5.8 ng/mL, so treatment was restarted with docetaxel (75 mg/m^2 IV every 3 weeks). He underwent a total of six cycles, but 5 months later, his PSA concentration had increased further, to 7.7 ng/mL.

After 2 more months, with his PSA concentration still increasing, he agreed to participate in a randomized phase II clinical trial testing either cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone. His PSA was 17.4 ng/mL at enrollment. He was randomized to treatment with cixutumumab (6 mg/kg IV weekly), mitoxantrone (12 mg/m^2 IV every 3 weeks), and prednisone (5 mg PO twice daily). After 3 months on that regimen, his left ventricular ejection fraction decreased, but the measure returned to normal 5 months after the mitoxantrone was discontinued. He received a total of 32 cycles of cixutumumab plus prednisone according to the study protocol and experienced a favorable response, with a PSA nadir of 1.6 ng/mL.

Although the patient had tolerated the treatment, afterward he was hospitalized with abdominal pain, severe watery diarrhea, dehydration, and malnutrition. Cixutumumab and prednisone were discontinued. Abdominal CT scanning revealed thickening of the ascending, transverse, and descending colon walls with minimal stranding of the adjacent fat, suggestive of pancolitis (Figure 1A). Stool cultures and *Clostridium difficile* toxin tests revealed no pathogenic colonization.

He was treated with piperacillin–tazobactam and metronidazole for a week. Colonoscopy revealed pancolitis with extensive ulceration in the cecum (Figure 1B). Multiple biopsy specimens from the right, transverse, and rectosigmoid colon showed markedly increased lymphoplasmacytic infiltration of the lamina propria and submucosa (Figure 2A), neutrophilic inflammation with cryptitis and crypt abscess formation (Figure 2B), and focal granuloma in the lamina propria (Figure 2C). No viral inclusions or microorganisms were identified on Gomori's methenamine silver and acid-fast staining. Immunohistochemical staining for CD3 (Figure 2D) and CD20 revealed the lymphoplasmacytic infiltration of the lamina propria. Immunohistochemical staining for IGF1R detected no evidence of the receptor.

On the basis of those findings, a diagnosis of autoimmune colitis was made, so methylprednisolone treatment (125 mg IV every 6 hours) was begun. The diarrhea subsided, and the patient's nutritional status improved quickly. His preadmission prealbumin concentration of 5.5 mg/mL had improved to 15.2 mg/dL at his discharge, and he was given a tapering dose of prednisone for 4 weeks.

At his first follow-up visit 2 months after his hospitalization for the colitis, his diarrheal symptoms had resolved, his appetite had improved, and he had gained weight. At another follow-up visit 2 months later, his PSA concentration was 28.5 mg/dL. Treatment with abiraterone acetate (1 g PO daily) plus prednisone (5 mg PO twice daily) was initiated, and his PSA level decreased to 10.2 mg/dL within the next month. On his last clinical follow-up in December 2011, he was still alive and well. However, in January 2012, the patient died from a cause not directly related to his prostate cancer or treatment.

Discussion

IGF1R is a receptor with tyrosine kinase activity that is stimulated by two ligands, the IGFs 1 and 2; the fibrotic and antiapoptotic effects of the IGFs are mediated by IGF1R.[6,7] Experimental data suggest that IGF1R and its ligands play a key role in several different cancers, including PC.[6-8] Immunohistochemical studies have shown that human PC tissue stains positively for IGF1R.[9] In addition, patients with high concentrations of circulating IGF1 are at higher risk for developing PC.[10]

Agents developed to target IGF1R include antisense oligonucleotides, inhibitory peptides, and monoclonal antibodies.[4-6] One such agent, cixutumumab, is a fully human IgG1 monoclonal antibody that specifically targets human IGF1R, [6,7] blocking ligand binding and inducing receptor internalization and degradation. [6,7] Wu et al. showed the effect of cixutumumab on androgen-dependent and -independent prostate xenografts.[11] Favorable results led to the initiation of clinical studies.

Phase I and II trials showed that cixutumumab is well tolerated with a reasonable toxicity profile. Adverse events considered potentially related to cixutumumab monotherapy in a PC study included diabetes or hyperglycemia, fatigue, and single observations of hyperkalemia, leukoencephalopathy, pneumonia, and thrombocytopenia.[12] Colitis has not been reported to date, as far as we know.

The possible involvement of IGF1R in the pathogenesis of inflammatory bowel disease has been suggested, but direct evidence is lacking and data are conflicting. For example, serum IGF1 concentrations appeared to be downregulated in both ulcerative colitis and Crohn's disease.[13,14] However, it was also shown that IGF1 administration partially reduced colonic damage induced by orally administered dextran sulfate sodium.[15] Further, the level of IGF1R protein was significantly upregulated in the colons of patients with ulcerative colitis.[16] Another study's results suggested a role for IGF1R in the maintenance of chronic inflammation and stricture formation in Crohn's disease.[17] In contrast to these findings suggesting a role for IGF1R in inflammation, those from one recent study showed that IGF1-coated sutures improved healing of an anastomosis in an experimental model of colitis.[18]

None of these investigators discussed the degree of inflammation and whether inflammation correlates with IGF1R expression. However, Sipos et al. categorized the inflammation in ulcerative colitis as mild, moderate, or severe on the basis of pathologic findings, and they compared the degree of IGF1R expression in colonic tissues.[19] In cases of mild and moderate inflammation, they found increased IGF1R expression, whereas decreased epithelial mRNA expression of IGF1R occurred in severe inflammation.[19]

Although no conclusive causal relationship between cixutumumab and pancolitis was shown, the patient's clinical presentation and findings during treatment suggest such an association. Another possible mechanism underlying the development of colitis is immune mediation, although immune-related adverse events have not yet been reported.[20,21] According to the literature, colitis is one of the main adverse effects of ipilimumab, the

monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4) that enhances cell activation by blocking CTLA-4–induced inhibitory signals.[22] Like our patient, patients with severe colitis secondary to ipilimumab responded well to temporary or permanent suspension of antibody treatment and management of the colitis with steroid administration.[22,23] The histologic samples from patients who developed colitis after ipilimumab showed neutrophilic and lymphocytic infiltration.[23] In our patient, the T-lymphocyte infiltration evident on histologic examination may have been the mechanism triggering his colitis. A correlation between immune-mediated side effects and clinical efficacy has been shown in the literature: Beck et al. found a high response rate to ipilimumab in patients with colitis. [23] Our patient also showed a significant response to treatment, possibly indicating a similar relationship with cixutumumab.

Conclusion

Overall, evidence of the role of IGF1R in colonic inflammation is lacking. To the best of our knowledge, this is the first reported case of a patient who experienced severe pancolitis after receiving cixutumumab. We believe that our experience may be informative for many oncologists, because novel therapies targeting IGF-1R is of general interest in oncology.

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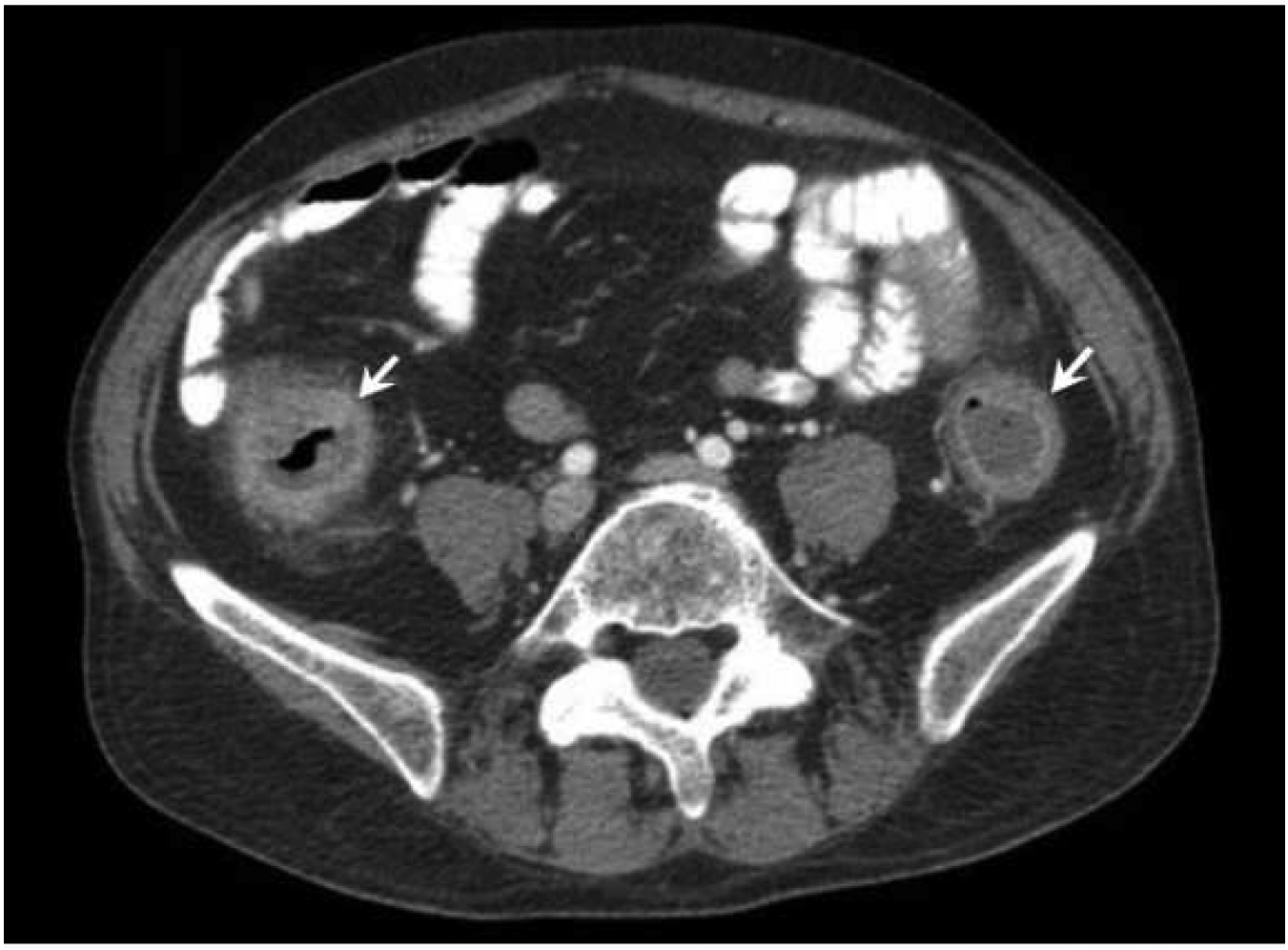
References

1. Ouban A, Muraca P, Yeatman T, et al. Expression and distribution of insulin-like growth factor-1 receptor in human carcinomas. Hum Pathol. 2003; 34:803–808. [PubMed: 14506643]
2. Krueckl SL, Sikes RA, Edlund NM, et al. Increased insulin-like growth factor I receptor expression and signaling are components of androgen-independent progression in a lineage-derived prostate cancer progression model. Cancer Res. 2004; 64:8620–8629. [PubMed: 15574769]
3. Nickerson T, Chang F, Lorimer D, et al. In vivo progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). Cancer Res. 2001; 61:6276–6280. [PubMed: 11507082]
4. Wang Y, Ji QS, Mulvihill M, et al. Inhibition of the IGF-I receptor for treatment of cancer. Kinase inhibitors and monoclonal antibodies as alternative approaches. Recent Results Cancer Res. 2007; 172:59–76. [PubMed: 17607936]
5. Bohula EA, Playford MP, Macaulay VM. Targeting the type 1 insulin-like growth factor receptor as anti-cancer treatment. Anticancer Drugs. 2003; 14:669–682. [PubMed: 14551500]
6. Rowinsky EK, Youssoufian H, Tonra JR, et al. IMC-A12, a human IgG_1 monoclonal antibody to the insulin-like growth factor I receptor. Clin Cancer Res. 2007; 13:5549s–55s. [PubMed: 17875788]
7. McKian KP, Haluska P. Cixutumumab. Expert Opin Investig Drugs. 2009; 18:1025–233.
8. Pollak M, Beamer W, Zhang J-C. Insulin-like growth factors and prostate cancer. Cancer Metastasis Rev. 1999; 17:383–90. [PubMed: 10453282]
9. Cardillo MR, Monti S, Di Silverio F, et al. Insulin-like growth factor (IGF)-I, IGF-II and IGF type I receptor (IGFR-I) expression in prostatic cancer. Anticancer Res. 2003; 23:3825–35. [PubMed: 14666684]
10. Hellawell GO, Turner GD, Davies DR, et al. Expression of the type 1 insulin-like growth factor receptor is up-regulated in primary prostate cancer and commonly persists in metastatic disease. Cancer Res. 2002; 62:2942–50. [PubMed: 12019176]

11. Wu JD, Odman A, Higgins LM, et al. In vivo effects of the human type I insulin-like growth factor receptor antibody A12 on androgen-dependent and androgen-independent xenograft human prostate tumors. Clin Cancer Res. 2005; 11:3065–74. [PubMed: 15837762]
12. Higano CS, Alumkal JJ, Ryan CJ, et al. A phase II study of cixutumumab (IMC-A12), a monoclonal antibody (MAb) against the insulin-like growth factor 1 receptor (IGF-IR), monotherapy in metastatic castration-resistant prostate cancer (mCRPC): Feasibility of every 3-week dosing and updated result. ASCO Genitourinary Cancers Symposium Abstracts. 2010 (abstr 189).
13. Katsanos KH, Tsatsoulis A, Christodoulou D, et al. Reduced serum insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 levels in adults with inflammatory bowel disease. Growth Horm IGF Res. 2001; 11:364–7. [PubMed: 11914023]
14. Eivindson M, Grønbaek H, Flyvbjerg A, et al. The insulin-like growth factor (IGF)-system in active ulcerative colitis and Crohn's disease: Relations to disease activity and corticosteroid treatment. Growth Horm IGF Res. 2007; 17:33–40. [PubMed: 17126585]
15. Howarth GS, Xian CJ, Read LC. Insulin-like growth factor-I partially attenuates colonic damage in rats with experimental colitis induced by oral dextran sulphate sodium. Scand J Gastroenterol. 1998; 33:180–90. [PubMed: 9517530]
16. Sipos F, Molnár B, Zágoni T, et al. [Insulin-like growth factor receptor, hepatocyte-derived growth factor receptor and telomerase expression in ulcerative colitis] [article in Hungarian]. Orv Hetil. 2006; 147:1835–41. [PubMed: 17066600]
17. Zhao D, Bakirtzi K, Zhan Y, et al. Insulin-like growth factor-1 receptor transactivation modulates the inflammatory and proliferative responses of neurotensin in human colonic epithelial cells. J Biol Chem. 2011; 286:6092–9. [PubMed: 21212273]
18. Rijcken E, Fuchs T, Sachs L, et al. Insulin-like growth factor 1-coated sutures improve anastomotic healing in an experimental model of colitis. Br J Surg. 2010; 97:258–65. [PubMed: 20084676]
19. Sipos F, Galamb O, Herszényi L, et al. Elevated insulin-like growth factor 1 receptor, hepatocyte growth factor receptor and telomerase protein expression in mild ulcerative colitis. Scand J Gastroenterol. 2008; 43:289–98. [PubMed: 18938767]
20. Andrews DW, Resnicoff M, Flanders AE, et al. Results of a pilot study involving the use of an antisense oligodeoxynucleotide directed against insulin-like growth factor type I receptor in malignant astrocytomas. J Clin Oncol. 2001; 19:2189–200. [PubMed: 11304771]
21. Wiersinga WM. Autoimmunity in Graves' ophthalmopathy: the result of an unfortunate marriage between TSH receptors and IGF-1 receptors? J Clin Endocrinol Metab. 2011; 96:2386–94. [PubMed: 21677036]
22. Graziani G, Tentori L, Navarra P. Ipilimumab: A novel immunostimulatory monoclonal antibody for the treatment of cancer. Pharmacol Res. 2012; 65:9–22. [PubMed: 21930211]
23. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol. 2006; 24:2283–9. [PubMed: 16710025]

Clinical Practice Points

- Several types of tumors, including prostate cancer, overexpress the insulin-like growth factor 1 receptor (IGF1R), and IGF1R inhibition produces an antitumor effect
- Cixutumumab (tested under the name IMC-A12) is a monoclonal antibody developed as an antagonist to IGF1R.
- Recent phase I and II studies in patients with various cancers showed that this agent is well tolerated and without unreasonable side effects.
- Here we describe, to our best knowledge, the first case of a patient with prostate cancer who developed pancolitis while participating in a clinical trial of cixutumumab.



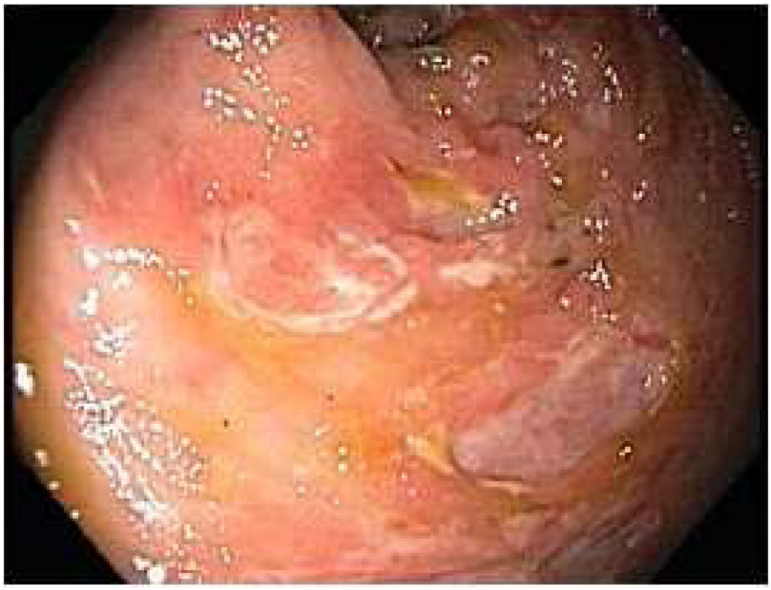


Figure 1.

(A) Computed tomography of the abdomen revealed thickening of the ascending (*arrow on right*), transverse, and descending (*arrow on left*) colon walls with minimal stranding of the adjacent fat. **(B)** Colonoscopy revealed extensive ulceration in the cecum.

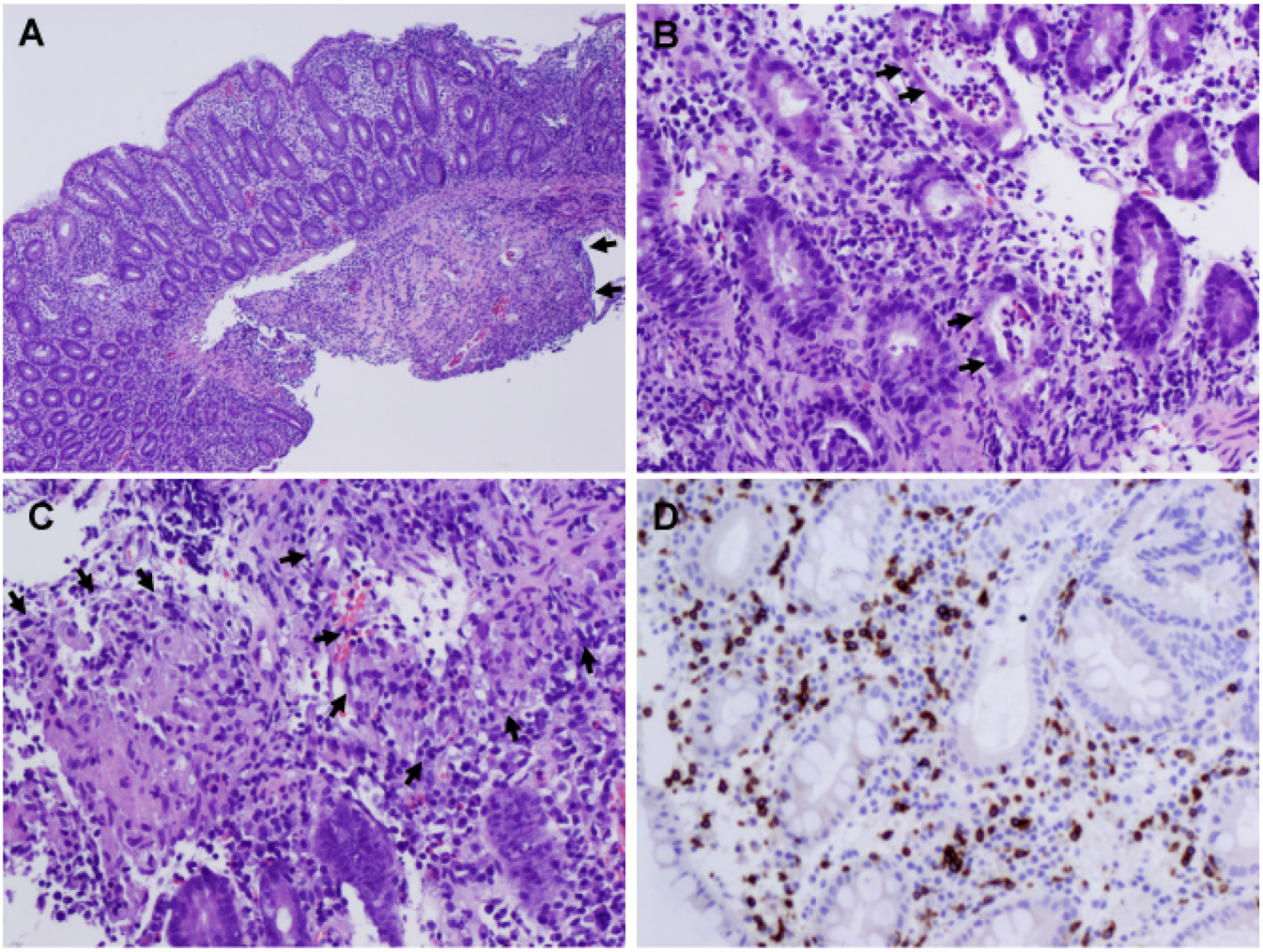


Figure 2.

Representative micrographs of colonic biopsies. **(A)** Markedly increased lymphoplasmacytic infiltration of the lamina propria and submucosa (*arrows*) (original magnification ×40); **(B)** neutrophilic inflammation with cryptitis and abscess formation (*arrows*) (original magnification ×200); **(C)** focal granuloma in lamina propria (*arrows*) (original magnification ×200); **(D)** immunohistochemical stain for CD3 highlights increased lymphocytes in lamina propria (*brown stain*, original magnification ×200).