

Colonic perforation secondary to metastatic lung adenocarcinoma during anti-TNF treatment for ankylosing spondylitis

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ABSTRACT

Biological agents targeting inflammatory cytokines such as tumour necrosis factor alpha (TNF- α) have emerged in recent years as effective medications for a variety of inflammatory arthropathies. Although the relationship between the use of anti-TNF drugs and an increase in the rate of infections is well established, the role of these drugs in the development of different types of cancer is unclear. Randomized clinical trials and national registries have not demonstrated a significant increase in the risk of cancer in patients treated with anti-TNF drugs, but numerous cases of the appearance of malignant tumors in patients receiving these drugs have been reported. We describe the case of a 73-year-old man, ex-smoker, who developed a lung cancer during treatment with infliximab further complicated by perforation of a metastasis in the sigmoid colon, which is a very infrequent event in the course of this malignancy. A few similar cases previously reported in the literature are reviewed.

Keywords: Lung Adenocarcinoma; Anti-TNF Drugs; Infliximab; Colon Metastasis; Colonic Perforation.

INTRODUCTION

Patients with ankylosing spondylitis, in contrast with rheumatoid arthritis, do not appreciably show an increase in cancer risk, and it is assumed that their average risk is similar to the general population¹. The role of anti-TNF- α therapies in the development of neoplasms is unclear and randomized clinical trials² and national registries^{3,4} have not clearly shown an increase in the incidence of cancer in patients treated anti-

-TNF- α agents, including infliximab. However, cases of lung cancer in smoker patients receiving infliximab have occasionally been reported^{5,6}.

We here describe an exceptional case of a patient with ankylosing spondylitis treated with infliximab who developed a lung adenocarcinoma further complicated by intestinal perforation secondary to metastatic disease in the sigmoid colon. To our knowledge, metastatic colonic perforation during treatment with infliximab has not been previously documented.

CASE REPORT

The patient was a 73-year-old man, ex-smoker (36 pack-year until age 68), with history of chronic infection with hepatitis B virus under treatment with lamivudine and diverticulosis of the descending and sigmoid colon without previous episodes of diverticulitis. The patient was followed at the Department of Rheumatology because of axial and peripheral ankylosing spondylitis, positive for HLA-27, treated with infliximab for the past 5 years (dose 5 mg/kg every 8 weeks) with adequate control of symptoms, although maintenance treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin 75 mg twice a day), low-dose corticosteroids (prednisone 10 mg/day) and methotrexate (15 mg/week, started 6 years ago) was needed. The patient was admitted to the Department of Internal Medicine because of asthenia and weight loss of 4 kg in one month (5% of his baseline body mass).

Physical examination showed a limited axial mobility, with lumbar flexion (modified Schober) 3 cm, lateral lumbar flexion 7 cm, occiput to wall 6 cm, finger-floor distance 35 cm, chest expansion 2,5 cm and cervical rotation 70°. However, no signs of peripheral arthritis and enthesitis were identified at this moment. A decreased respiratory murmur in the left upper lobe was evident on auscultation of the lungs. Laboratory tests showed an increase of serum aminotransferases

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and an increase in HBV viral load in relation to reactivation of infection and for this reason, treatment with tenofovir was started. The chest X-ray showed a left upper lobe mass that in the computed tomography (CT) scan corresponded to a 10-cm infiltrating tumor with ipsilateral mediastinal adenopathies (Figure 1). The patient denied having cough or other respiratory symptoms and a review of a chest X-ray performed one year ago did not show any abnormality. Cytological examination of brush samples taken at fiberoptic bronchoscopy was compatible with lung adenocarcinoma. CT staging showed thickness of the sigmoid colon which was attributed to the presence of diverticula at this level, without evidence of tumor dissemination to other organs. Treatment with infliximab was definitively withdrawn. During hospitalization, he presented episodes of hypotension, postural instability, hypoglycemia and self-limited febrile peaks without evidence of infection which were initially attributed to possible adrenal insufficiency secondary to chronic corticosteroid treatment. The dose of corticoids was then increased and the patient was discharged from the hospital under treatment with fludrocortisone (0.1 mg/day) and low-dose prednisone (5 and 10 mg/day on alternate days).

Five days after discharge, he was re-admitted be-

cause of a new febrile episode associated with diarrhea and hypotension that could not be controlled with intravenous fluid administration. Physical examination revealed diffuse abdominal pain with signs of peritoneal irritation in the left iliac fossa. Findings on an abdominal CT scan with contrast were compatible with perforated acute diverticulitis and adjacent intraabdominal abscess (Figure 2). Emergency surgery was indicated and the patient underwent sigmoidectomy and end colostomy (Hartmann's procedure). The patient had a protracted postoperative clinical course with multiple complications, progressive clinical deterioration and evidence of hepatocellular insufficiency secondary to reactivation of HBV infection, and died after two months of surgery.

On gross inspection, the surgical specimen of the left colon showed fibrin plaques on the outer surface. Histological examination disclosed several invaginations of the intestinal wall penetrating into the mesocolon which were compatible with diverticula, one of which was found to be perforated with a large adjacent pericolic plastron formation (Figure 3). Moreover, infiltration of tumor cells compatible with metastatic adenocarcinoma of the lung was observed. Immunohistochemical study showed that tumor cells were positive for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1) and negative for cytokeratin 20 (CK20) and p63 (Figure 4).

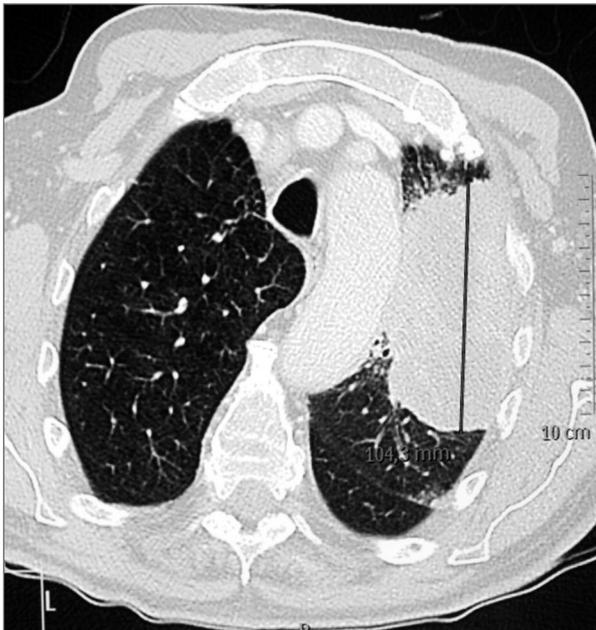


FIGURE 1. Thoracic CT scan showing an infiltrating mass, 10 cm of major diameter, with ipsilateral mediastinal metastatic lymph nodes

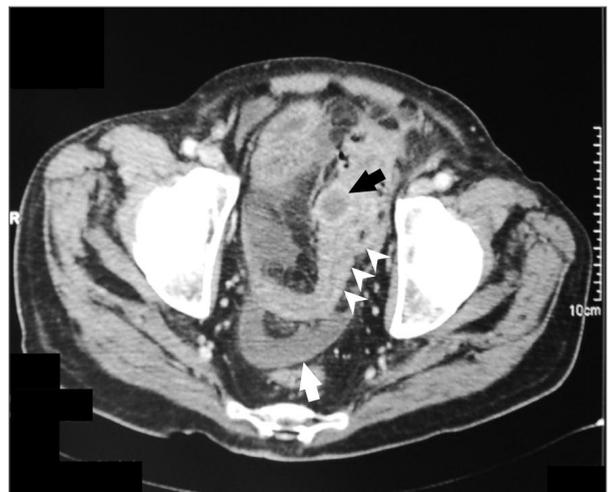


FIGURE 2. Abdominal CT scan showing the sigmoid colon with thickened walls (white arrowheads) with an adjacent collection (2.5 cm in diameter) compatible with an abscess (black arrow) and free fluid in the retrovesical space (white arrow)

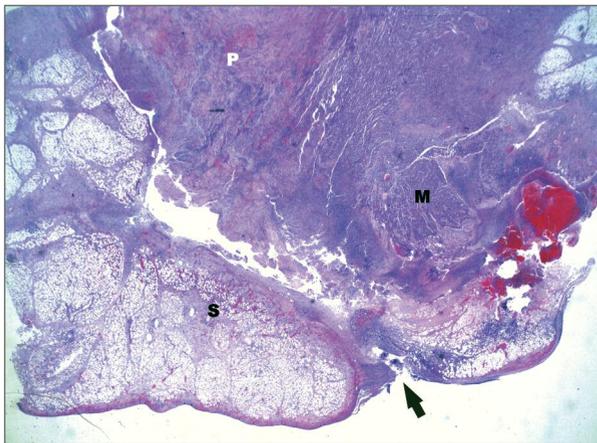


FIGURE 3. Histopathology of the surgical specimen corresponding to the perforated area (end marked with a black arrow) showing infiltration of the intestinal wall by tumor cells from the lung metastasis (M) with an area of necrotic tissue and acute inflammatory infiltrate in relation to the adjacent plastron formation (P). Acute inflammatory infiltrate in the surface of the serous layer (S) (hematoxylin & eosin, x10 magnification)

DISCUSSION

TNF- α is a cytokine that plays a central role in the pathogenesis of rheumatoid arthritis, ankylosing spondylitis and other inflammatory diseases. Over the past 10 years, anti-TNF drugs have emerged as effective treatment in NSAID refractory patients with ankylosing spondylitis. Anti-TNF drugs, including infliximab, etanercept, adalimumab and golimumab have been shown to reduce disease activity (measured by the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) in up to 50% of patients⁷. TNF- α is also involved in the control of tumor growth, so that theoretically anti-TNF- α drugs may affect the host defense mechanisms against the development of neoplasms. However, the relationship between continuous anti-TNF therapy and the overall risk of developing cancer is controversial⁸. In a systematic review and meta-analysis of rare harmful effects of infliximab and adalimumab in randomized controlled trials, there was evidence of a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis⁹, but this finding has not been confirmed in other studies. In a meta-analysis of 74 randomized controlled trials of adalimumab, etanercept and infliximab, the relative risk associated with all anti-TNF was 0.99². National registries also failed to show clear evidence of anti-TNF therapy and risk of solid tumors^{3,4}, although an increased risk of lympho-

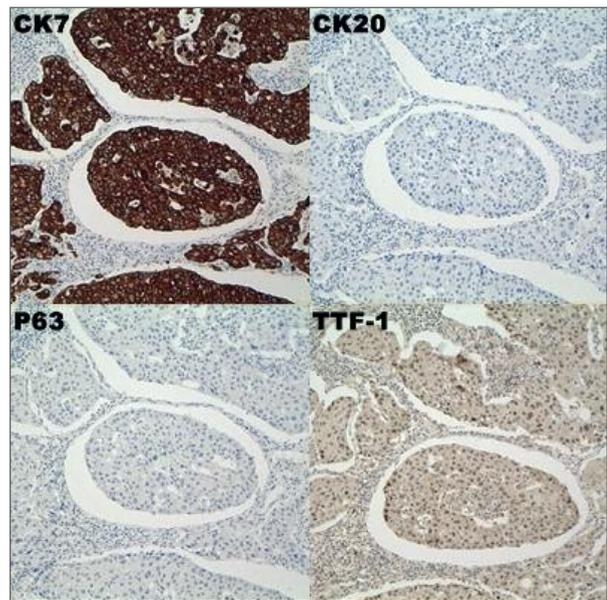


FIGURE 4. Immunohistochemical staining of the intestinal metastasis with nests of tumor cells with positivity for CK7 and TTF-1 and negativity for CK20 and p63, compatible with adenocarcinoma of the lung

ma for all anti-TNF- α drugs has been observed¹⁰⁻¹².

Lung cancer during treatment with infliximab in smokers, such as the case here described, has been reported. In a clinical series of 500 patients with Chron's disease collected at the Mayo Clinic, two cases of lung cancer in elderly smokers possibly related to infliximab were found⁵. Rennar et al.⁶ in a 24-week clinical trial of 157 patients with chronic obstructive pulmonary disease (COPD) treated with infliximab, found 12 cases of cancer (6 of which were lung cancers). In the BIOBADASER Spanish national registry, the standardized incidence rate of lung cancer was 1.19% in patients with rheumatoid arthritis and 1.66% in patients with ankylosing spondylitis treated with anti-TNF- α drugs, without an increase in the total cancer risk as compared with the general population³. In the Anti-Rheumatic Therapy in Sweden (ARTIS) clinical registry, a more favourable distribution of lung cancer stages in patients treated with biologics than in biologics-naïve patients was observed, and this finding was attributed to a more frequent indication of control chest radiographs after starting anti-TNF therapy which may increase lung cancer detection at earlier stages; moreover, the relative risk of death following cancer associated with exposure to anti-TNF was 1.1¹³.

Treatment with methotrexate is another factor that may have influenced the development of lung cancer

in our patient. Buchbinder et al.¹⁴ evaluated cancer risk in a cohort of 459 rheumatoid arthritis patients treated with methotrexate in community practice and found a 3-fold increase for lung cancer. However, given that patients with rheumatoid arthritis have an increased risk of this neoplasm which is even higher when active smoking is present, the authors could not conclude that this increase was specifically related to the use of methotrexate. A similar increase in the risk of lung cancer during treatment with methotrexate in patients with ankylosing spondylitis has not been reported.

Bowel perforation during treatment with infliximab is a very rare adverse event. Only one case of a heart transplant patient who presented with an ileal perforation after infliximab treatment for Chron's disease has been reported, but this patient also received an immunosuppressive regimen with corticoids, mycophenolate mofetil and cyclosporine A¹⁵. Some cases of intestinal perforation in patients treated with etanercept for psoriatic arthritis and rheumatoid arthritis have been described^{16,17} and also a case of oligosymptomatic bowel perforation in a patient with Chron's disease treated with adalimumab¹⁸. There is some biologic plausibility to the association of intestinal perforation and the use of anti-TNF drugs. Given that TNF- α is a key mediator of inflammation, its blockade could interfere with the ability to mount an inflammatory response against infection, mainly due to intracellular organisms such as Salmonella, Listeria or Mycobacterium tuberculosis. Moreover, some clinical trials and post-marketing surveillance studies have been shown an increased risk for serious infections in patients receiving anti-TNF drugs¹⁹. It has been hypothesized that if these patients are affected by inflammatory bowel conditions such as diverticulitis, the impairment in antibacterial host mechanisms could conceivably predispose to losing the integrity of the bowel wall, leading finally to perforation¹⁶. Another hypothesis is that anti-TNF drugs may cause vasculitis and necrosis of the intestinal mucosa facilitating the passage of bacteria into the peritoneal cavity²⁰. Although in some cases of anti-TNF therapy and bowel perforation, a temporal association between initiation of treatment and intestinal perforation was observed, other risk factors were also present in these patients, such as older age, history of diverticulitis/diverticulosis, oral intake of NSAID, treatment with corticoids and other immunosuppressants, vasculitis and inflammatory bowel disease^{13,16-18}.

Approximately 40% of patients with lung cancer have metastatic disease, involving the gastrointestinal tract in 4.7% to 12.2% of the cases^{21,22}, being symptomatic in only 0.4-0.5% of them^{22,24}. Intestinal perfora-

tion secondary to metastatic disease is very rare accounting for 0.1% of cases and has been usually described as a complication of advanced disease. In the present case, thickening at the sigmoid colon initially observed in the CT scan corresponded to a metastasis of the lung tumor on the area that previously had diverticula, which in association with radiological description of an apparent benign condition, lead us to assume that the patient presented a perforated diverticulitis as there was no evidence of metastatic disease. Post-mortem examination was not performed. The immunohistochemical pattern of the tumor cells was consistent with adenocarcinoma of the lung. Berger et al.²³ in a series of 1544 patients collected between 1984 and 1996, seven patients developed symptomatic small bowel metastases, two of which presented with peritonitis secondary to intestinal perforation at the site of the metastasis. Our patient presented large bowel perforation from metastatic lung cancer, an even rarer complication than metastatic disease to the small intestine. Garwood et al.²⁵ carried out a search to identify all cases of gastrointestinal tract perforation secondary to metastatic lung cancer published between 1960 and 2004, and identified 98 cases of perforated lung cancer metastasis to the small intestine but only three colonic perforations and one appendiceal perforation.

In conclusion, we present a patient with colonic perforation secondary to metastatic lung adenocarcinoma during treatment with infliximab for ankylosing spondylitis. Concomitant risk factors for intestinal perforation were also present in our patient (advanced age, history of diverticulosis and treatment with NSAIDs and corticoids), and although a definitive causal relationship could not be established, treatment with infliximab could be a facilitating factor for the development of the events that led to the final clinical outcome. No previous case of large bowel perforation from metastatic lung cancer without evidence of disseminated disease during treatment with infliximab has been previously reported in the literature. Although metastases are a rare cause of intestinal perforation, this possibility should be included in the differential diagnosis of acute abdomen in patients with lung cancer. On the other hand, a strong association between carcinogenesis and anti-TNF- α therapy has not been established but clinicians should be aware of this infrequent possibility in patients with concurrent risk factors.

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REFERENCES

1. Askling J, Klareskog L, Blomqvist P, Fored M, Feltelius N. Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study. *Ann Rheum Dis* 2006; 65: 1184-1187.
2. Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf* 2011; 20: 119-130.
3. Carmona L, Abasolo L, Descalzo MA, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. *Semin Arthritis Rheum* 2010; 41: 71-80.
4. Watson KD, Dixon WG, Hyrich KL, Lunt M, Symmons DPM, Silman AJ. Influence of anti-TNF therapy and previous malignancy on cancer incidence in patients with rheumatoid arthritis (RA): results from the BSR Biologics Register (BSRBR). *Rheumatology* 2006; 45:110-12.
5. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004; 126:19-31.
6. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 926-934.
7. Haibel H, Sieper J. Editorial review: how early should ankylosing spondylitis be treated with a tumor necrosis factor-blocker? *Curr Opin Rheumatol* 2010; 22: 388-92.
8. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med* 2006; 355: 704-712.
9. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295: 2275-2285.
10. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; 50: 1740-1751.
11. van Vollenhoven RF. Benefits and risks of biological agents: lymphomas. *Clin Exp Rheumatol* 2004; 22: S122-125.
12. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64: 1414-1420.
13. Raaschou P, Simard JF, Neovius M, Askling J. Does cancer that occurs during or after anti-tumor necrosis factor therapy have a worse prognosis? A national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents. *Arthritis Rheum* 2011; 63:1812-1822.
14. Buchbinder R, Barber M, Heuzenroeder L, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 2008; 59: 794-799.
15. Yamashita K, Oka Y, Okumura H, et al. An ileal perforation after infliximab treatment for Crohn's disease in a heart transplant patient: a case report. *Kawasaki Medical Journal* 2009; 35: 63-65.
16. Mohan AK. Safety update on TNF- antagonists: infliximab and etanercept, Food and Drugs Administration, Center for Biologic Evaluation and Research, 2001 http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2_01_cber_safety%20_revision2.pdf . Accessed 2012, Jan 10.
17. Corsi F, Previde P, Colombo F, Cellerino P, Donati M, Trabucchi E. Two cases of intestinal perforation in patients on anti-rheumatic treatment with etanercept. *Clin Exp Rheumatol* 2006; 24:113.
18. Jalocho Ł, Wojtu S, Wojtkowiak M, Błaszak A, Dyrła P, Gil J. Oligosymptomatic alimentary tract perforation in course of Crohn's disease in patient treated with anti-TNF alfa antibodies. *Pol Merkur Lekarski* 2009; 26: 491-582.
19. Tuccantu Z, Arthur K. Anticytokine Therapies. In: Firestein GS, Budd RC, Harris ED, McInnes IB, Ruddy S, Sargent JS, editors. *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia, PA: Saunders – Elsevier; 2009. p. 929-946.
20. Roberts L, McColl GJ. Tumour necrosis factor inhibitors: risks and benefits in patients with rheumatoid arthritis. *Intern Med J* 2004; 34: 687-692.
21. Stenbygaard LE, Sørensen JB, Larsen H, Dombernowsky P. Metastatic pattern in non-resectable non-small cell lung cancer. *Acta Oncol* 1999; 38: 993-998.
22. McNeill PM, Wagman LD, Neifeld JP. Small bowel metastases from primary carcinoma of the lung. *Cancer* 1987; 59: 1486-1489.
23. Berger A, Cellier C, Daniel C, et al. Small bowel metastases from primary carcinoma of the lung: clinical findings and outcome. *Am J Gastroenterol* 1999; 94: 1884-1887.
24. Galsky M, Darling M, Hecht J, Salgia R. Small bowel obstruction due to metastatic lung cancer. *J Clin Oncol* 2000; 18: 227-228.
25. Garwood RA, Sawyer MD, Ledesma EJ, Foley E, Claridge JA. A case and review of bowel perforation secondary to metastatic lung cancer. *Am Surg* 2005; 71: 110-116.