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Short Report

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Anaplastic Large Cell T Cell Lymphoma in a Patient With Severe Therapy-refractory Crohn's Disease on Long-standing Immunosuppressive Medication During Ustekinumab Treatment: A Case Report and Review of the Literature

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Abstract

Use of ustekinumab in Crohn's disease was approved in 2016, and consequently data regarding its real-world safety are still limited. We here present a 29-year-old woman with severe therapy-refractory Crohn's disease, who developed an anaplastic large cell T cell lymphoma during treatment with ustekinumab.

Key Words: Ustekinumab; lymphoma; Crohn's disease

1. Introduction

Most patients with Crohn's disease [CD] have alternating periods of disease relapse and remission with need for maintenance therapy. Primary non-response to tumour necrosis factor [TNF] antagonists or immunomodulators, loss of response, and potential serious side effects warrant the development of novel medical options.[1]

Ustekinumab is a monoclonal antibody targeting the p40 subunit of interleukin [IL]-12 and IL-23. Binding of IL-12 and IL-23 to the IL-12Rβ1 receptor, expressed at the surface of T cells and natural killer cells, leads to enhancement of immune cell activation. IL-12 induces differentiation of naive CD4+ T cells into interferon [IFN]-Ɣ-producing Th-1 cells, and enhancement of cytotoxicity by natural killer cells and cytotoxic T cells. Moreover, IL-23 induces chronic inflammation by expansion of Th-17 cells with secretion of pro-inflammatory cytokines including IL-17, which activates various cell types [e.g., macrophages, endothelial cells, fibroblasts] with pro-inflammatory and destructive effects.[2] Binding of ustekinumab to the p40 subunit of IL-12 and IL-23 prevents binding of both interleukins to the IL-12Rβ1 target receptor which leads to attenuation of immune cell activation.

The UNITI-1 and -2 trials showed efficacy of ustekinumab for induction and maintenance of remission in moderate to severe CD.[3–5] Although the safety profile of ustekinumab in these trials seems favourable, long-term and real-life data are still scarce.[3]

2. Case Report

A 29-year-old female patient was diagnosed with ileocolic CD at the age of 17. Three years later, she had a flare with a small intestinal stenosis and perianal disease activity. She underwent a segmental resection of the small intestine, and received azathioprine and infliximab. Azathioprine and, later, methotrexate were discontinued

due to gastrointestinal intolerance. At the age of 22, she developed a rectovaginal fistula and underwent a rectum amputation with colostomy. In the following years, treatment was switched to adalimumab due to active luminal disease, and she developed a cheilitis granulomatosa which was treated with prednisolone. At the age of 27, she underwent a second segmental small intestinal resection with double loop ileostomy because of a stenosis, despite an adequate adalimumab titer and no identifiable antibodies. Treatment was switched to vedolizumab, but the patient developed then an extensive oesophageal localisation of CD [Figure 1]. After registration, ustekinumab was started and restoration of small intestinal continuity was achieved. For the oesophageal CD, the patient also used proton pump inhibitors and oral beclomethasone. Six months after ustekinumab initiation, an upper endoscopy and ileocolonoscopy were performed. Colonoscopy demonstrated no ileocolic disease activity, and upper endoscopy showed the previously described extensive oesophagitis with deep ulcers.

Four days after the endoscopies, the patient was admitted to the hospital because of fever and abdominal pain. Laboratory investigation demonstrated increased inflammatory parameters (C-reactive protein [CRP] 229 mg/l, leukocytes 15.1 × 10^9/l). Urinary analysis and chest X-ray were normal. Complications of the endoscopies and intra-abdominal abscesses were excluded by a thoracic and abdominal computed tomography [CT] scan. On the thoracic CT scan, an incipient pneumonia was suggested and consequently treatment with amoxicillin clavulanic acid was initiated. Fever persisted in the following days. Neurological and gynaecological examinations were normal. In addition, viral serology was negative for Epstein Barr virus [EBV], cytomegalovirus, and herpes simplex virus.

On the abdominal CT scan, novel and marked para-aortic, para-iliac, and retroperitoneal lymphadenopathy was noted [Figure 2], and an ultrasound-guided histological puncture of an inguinal lymph node was performed. Six days after admission, awaiting the results of the lymph node biopsy, a positron emission tomopraphy [PET]-CT scan was performed because of the novel lymphadenopathy and persisting fever. The PET-CT scan demonstrated extensive lymphadenopathy below the diaphragm, with strong bone marrow activation [Figure 3]. In addition, the PET-CT showed novel thoracic lymphadenopathy with extensive infiltrative intrapulmonary changes [Figure 4]. The differential diagnosis consisted of a pneumonia with secondary thoracic lymphadenopathy, or lymphoma.

Seven days after admission, clinical deterioration with respiratory insufficiency and marked leukocytosis [59.3 × 10^9/l] was noted. The patient was admitted to the intensive care unit and was intubated. In order to cover atypical pathogens and *Pneumocystis jiroveci*, treatment was extended with ciprofloxacin/cotrimoxazole. A broncho-alveolar lavage was performed but revealed no pathogens.

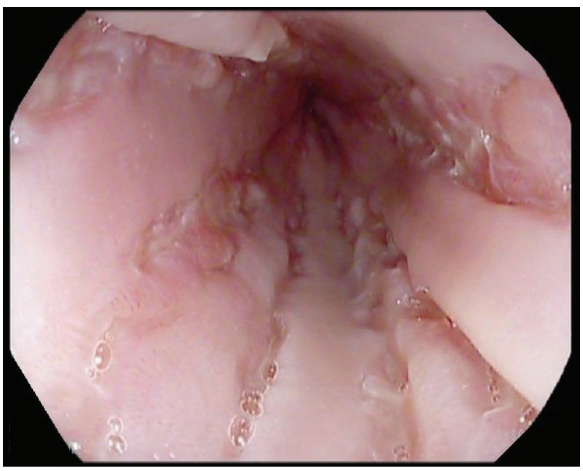

Figure 1. Upper gastrointestinal endoscopy demonstrating extensive oesophagitis with deep ulcers due to Crohn's disease [CD] during treatment with vedolizumab.

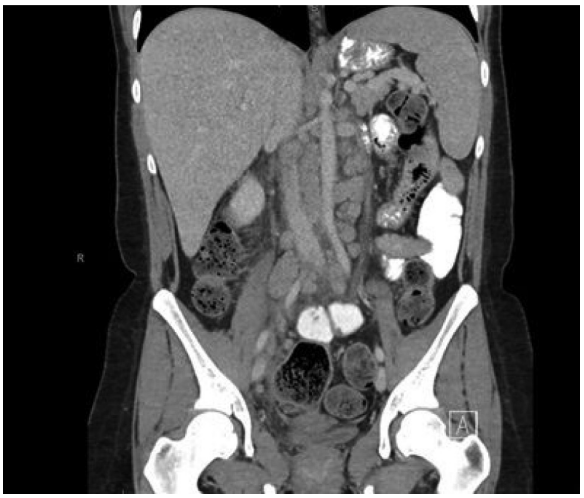

Figure 2. Extensive para-aortic and para-iliac lymphadenopathy on abdominal computed tomography [CT] scan.

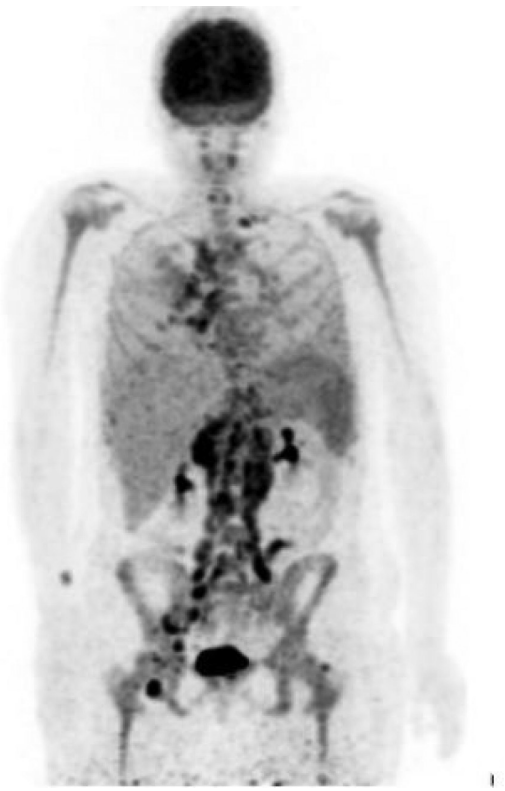

Figure 3. Extensive lymphadenopathy below the diaphragm with novel thoracic lymphadenopathy on positron emission tomography computed tomography [PET-CT] scan.

During the stay at the intensive care unit, histopathological analysis of the inguinal lymph node demonstrated an anaplastic large cell ALK-positive T cell lymphoma. Analysis for EBV was negative. On the same day, treatment with CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] was initiated. In the following days, respiratory improvement was observed and the patient was successfully detubated. Revision of the recent oesophageal biopsies and small intestine resection specimen of 1 year earlier showed no signs of lymphoma.

The patient was scheduled for a total number of eight CHOP treatments. Unfortunately, the patient had a refractory lymphoma after five CHOP treatments, and treatment was switched to second-line treatment with GDP [gemcitabine, dexamethasone, cisplatin] as preparation for an autologous stem cell transplantation. Although the patient initially responded with improvement of the thoracic and intra-abdominal lymphadenopathy, she presented with a novel enlarged lymph node in the right axilla after two of the three scheduled GDP treatments [Figure 5]. A lymph node extirpation was performed and histological examination showed lymphoma localisation, proving progressive disease during second-line treatment. Subsequently, she proceeded to allogeneic stem cell transplantation.

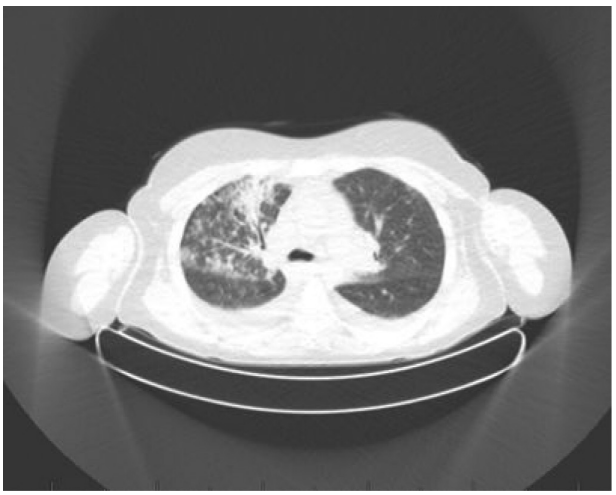

Figure 4. Extensive infiltrative intrapulmonary changes on low-dose positron emission tomography computed tomography [PET-CT].

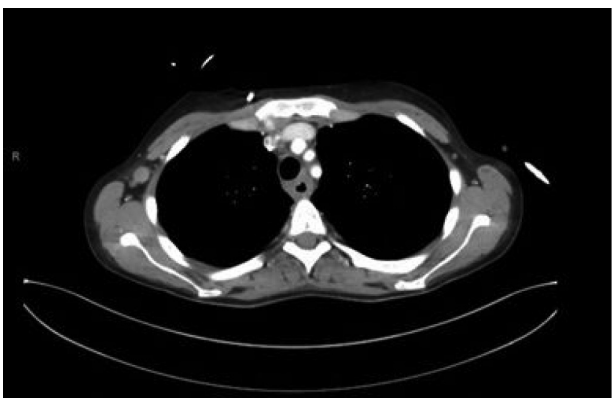

Figure 5. Enlarged lymph node in the right axilla after two second-line GDP [gemcitabine, dexamethasone, cisplatin] treatments on computed tomography [CT] scan.

3. Discussion

Ustekinumab has been approved for treatment of moderate to severe CD since 2016. Consequently, data regarding the safety and occurrence of malignancies in CD patients treated with ustekinumab are scarce. Recently, Sandborn *et al*. published long-term data of CD patients treated with ustekinumab, and found no increased malignancy rate for ustekinumab compared with placebo [i.e., 0.37/100 patient-years for ustekinumab vs 2.60/100 patient-years for placebo]. In total, two patients developed a malignancy during ustekinumab maintenance therapy: a testicular seminoma and a basal cell carcinoma.[5] Malignancies described by previous trials with short-term follow-up in inflammatory bowel disease [IBD] patients were non-melanoma skin cancers and one case of prostate cancer [with increased prostate-specific antigen levels before study entry].[6,7]

More extensive information about the risk of malignancy is available from clinical trials in psoriasis patients. In a long-term prospective observational cohort of patients with moderate to severe psoriasis treated with immunosuppressants, 252 malignancies were identified among 12 090 patients. Lymphoma was the fifth most common malignancy with an incidence rate of 0.03/100 patient-years [n = 14]. However, no increased risk for malignancy in general or specifically for lymphoma was observed for ustekinumab-treated patients compared with patients without ustekinumab use, regardless of treatment duration.[8] Moreover, malignancy rates were comparable between ustekinumab-treated patients [0.3%] and placebo-treated patients [0.4%] in clinical trials.[9] In addition, Papp *et al*. evaluated the long-term safety of ustekinumab in the largest cohort of psoriasis patients over 5 years, and the observed malignancy rates were compared with those expected in the general US population; 54 patients developed a malignancy [other than non-melanoma skin cancer] during 5 years, and this observed rate was comparable with that expected in the general population. Two patients developed a lymphoma: one patient with pre-existing cutaneous T cell lymphoma which had been misdiagnosed as psoriasis at study entry; and one possible case of Hodgkin disease based on autopsy findings.[10]

According to these results, use of ustekinumab seems to be associated neither with an overall increased risk of malignancy nor with lymphoma. However, long-term real-world safety data are necessary to evaluate whether ustekinumab is associated with increased malignancy rates in CD patients, especially as previously performed murine studies demonstrated that depletion of both IL-12 and IL-23 was associated with a significantly increased tumour incidence.[11]

Awaiting these long-term follow-up data, it is important to report on malignancies during treatment with novel biologicals, including ustekinumab, especially as several other immunosuppressive agents are associated with an increased risk of [non-Hodgkin] lymphomas in IBD patients.[12–14] Previously, Humme *et al*. described an anaplastic large cell T cell lymphoma in a patient with pityriasis rubra pilaris consecutively treated with psoralen and ultraviolet A [PUVA] therapy, corticosteroids, cyclosporine, infliximab, methotrexate, and finally ustekinumab. The patient was treated with chemotherapeutics but died because of infectious complications.[15] Another subtype of non-Hodgkin lymphoma, a mucosa-associated lymphoid tissue [MALT] lymphoma, was found in a patient with psoriasis treated with ustekinumab.[16]

We here describe for the first time the development of an anaplastic large cell T cell lymphoma, a subtype of non-Hodgkin lymphoma, in a young patient with severe therapy-refractory CD during treatment with ustekinumab. However, we have to explicitly mention that we cannot define a causal link between the anaplastic large cell T cell lymphoma and treatment with ustekinumab, as

several other factors might have contributed. First, patients with [insufficiently controlled] chronic inflammatory disorders including CD might have an increased baseline risk for development of [non-Hodgkin] lymphomas irrespective of the use of immunosuppressive medication.[17–20] Second, our patient had a long-standing severe therapy-refractory CD and she was exposed to a multitude of immunosuppressive agents, including TNF antagonists and thiopurines, for years before introduction of ustekinumab. The influence of the immunosuppressive agents, especially thiopurines, used before treatment with ustekinumab is unknown.[12–14,21]

In conclusion, we report the first case of an anaplastic large cell T cell lymphoma during treatment with ustekinumab in a young patient with severe therapy-refractory CD. Although we cannot define a causal link between the lymphoma and ustekinumab treatment in our patient, reporting on potential severe adverse events of novel immunosuppressive agents is important while awaiting safety results of studies with long-term follow-up.

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Conflict of Interest

None.

Author Contributions

FS: drafting the article and final approval. PL: revising the article for important intellectual content and final approval. MP: revising the article for important intellectual content and final approval. RM: revising the article for important intellectual content and final approval. AM: revising the article for important intellectual content and final approval. MP: revising the article for important intellectual content and final approval.

References

1. Jiménez-Pérez M, Olmedo-Martín RV, Amo-Trillo VM, González-Gande R. Inflammatory bowel disease: new therapeutic options in the post Anti-TNFα era. *Curr Drug Metab* 2017;**18**:666–79.
2. Toussirot E, Michel F, Béreau M, Binda D. Ustekinumab in chronic immune-mediated diseases: a review of long term safety and patient improvement. *Patient Prefer Adherence* 2013;**7**:369–77.
3. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;**11**:CD007572.
4. Feagan BG, Sandborn WJ, Gasink C, *et al.*; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946–60.
5. Sandborn WJ, Rutgeerts P, Gasink C, *et al.* Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther* 2018;**48**:65–77.
6. Sandborn WJ, Gasink C, Gao LL, *et al.*; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;**367**:1519–28.
7. Sandborn WJ, Feagan BG, Fedorak RN, *et al.*; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;**135**:1130–41.
8. Fiorentino D, Ho V, Lebwohl MG, *et al.* Risk of malignancy with systemic psoriasis treatment in the psoriasis longitudinal assessment registry. *J Am Acad Dermatol* 2017;**77**:845–54.e5.
9. Gordon KB, Papp KA, Langley RG, *et al.* Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis [Part II of II]: results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol* 2012;**66**:742–51.
10. Papp KA, Griffiths CE, Gordon K, *et al.*; PHOENIX 1 Investigators; PHOENIX 2 Investigators; ACCEPT Investigators. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol* 2013;**168**:844–54.
11. Langowski JL, Zhang X, Wu L, *et al.* IL-23 promotes tumour incidence and growth. *Nature* 2006;**442**:461–5.
12. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.
13. Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol* 2011;**106**:2146–53.
14. Kotlyar DS, Lewis JD, Beaugerie L, *et al.* Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol* 2015;**13**:847–58.e4; quiz e48–50.
15. Humme D, Beyer M, Röwert-Huber HJ, Sterry W, Philipp S. [CD30-positive anaplastic large cell T cell lymphoma developing during immunosuppressive therapy of pityriasis rubra pilaris with ustekinumab]. *Hautarzt* 2013;**64**:190–4.
16. González-Ramos MLA-PJ, Mayor-Ibarguren A, Herranz-Pinto P. Gastric mucosa-associated lymphoid tissue lymphoma in a patient with severe psoriasis receiving Ustekinumab. *Actas Dermosifiliogr* 2015;**106**:326–7.
17. Annese V, Beaugerie L, Egan L, *et al.*; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;**9**:945–65.
18. Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. *Ann Oncol* 2014;**25**:2025–30.
19. von Roon AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The risk of cancer in patients with Crohn's disease. *Dis Colon Rectum* 2007;**50**:839–55.
20. Jess T, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. *Am J Gastroenterol* 2013;**108**:1869–76.
21. van den Heuvel TR, Wintjens DS, Jeuring SF, *et al.* Inflammatory bowel disease, cancer and medication: cancer risk in the Dutch population-based IBDSL cohort. *Int J Cancer* 2016;**139**:1270–80.