

Paradoxical ulcerative colitis during adalimumab treatment of psoriasis resolved by switch to ustekinumab

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Linked Comment: Sticherling. *Br J Dermatol* 2018; **178**:333–334.

Summary

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Accepted for publication

29 April 2017

Funding sources

This study was supported by a grant from the Swiss National Science Foundation (grant 31003A-146940) to A.W.

Conflicts of interest

None declared.

A.G.A.K. and L.B. contributed equally to this work. All authors had full access to all data in the case. A.G.A.K., A.W. and L.B. take responsibility for the integrity of the data and the accuracy of the data analysis. A.G.A.K., A.W. and L.B. drafted the manuscript. A.C., J.M., A.A.N. and L.E.F. undertook critical revision of the manuscript for important intellectual content. L.E.F. supervised study.

DOI 10.1111/bjd.15631

Here we report the case of a patient with psoriasis who developed ulcerative colitis most likely caused by adalimumab. After cessation of adalimumab, colitis improved significantly. However, as psoriasis worsened, the patient was switched to ustekinumab, which resulted in complete cessation of colitis. During the 2 year follow up under ustekinumab therapy, no further gastrointestinal complaints occurred. Paradoxical psoriasis manifestations in inflammatory bowel disease (IBD) under tumour necrosis factor (TNF) inhibitor therapy have been reported and paradoxical IBD occurred rarely (mostly Crohn disease) in patients with rheumatological conditions treated with infliximab or etanercept. Due to the highly probable association of adalimumab with the onset of colitis in this case, we would like to suggest the term 'paradoxical ulcerative colitis' (PUC) for this as yet extremely rarely reported phenomenon. To the best of our knowledge this is the first description of PUC in a patient with psoriasis and in adalimumab treatment. Our observation suggests that ustekinumab is an effective treatment option in patients with paradoxical anti TNF driven inflammatory reactions like psoriasis or IBD.

What's already known about this topic?

- Paradoxical adverse events in tumour necrosis factor (TNF) inhibitors most commonly affect the skin, but also joints and lungs.
- Isolated cases of paradoxical ulcerative colitis (PUC) due to TNF inhibitors have been described.

What does this study add?

- This is the first case describing PUC in a patient with psoriasis treated with adalimumab completely controlled by ustekinumab.
- In addition to its effect in paradoxical skin reactions, ustekinumab might also be an effective treatment option in patients with psoriasis who develop PUC.

Case report

We present the case of a 56 year old white man with an 18 year history of plaque type psoriasis without joint involvement or comorbidities but a 30 pack year history of smoking (body weight 70 kg, height 173 cm, body mass index 23.4 kg m⁻²). There were no triggering factors. Upon first

presentation, the Psoriasis Area and Severity Index (PASI) score was 12.8 (Fig. 1) and the patient was included in a clinical trial with ponesimod for 6 months, after which the PASI score dropped to 7.1. During therapy the patient reported slight dyspnoea but pneumological work up, including drug related pathology, remained unsuspicious. Chest X ray was normal. Spirometry showed obstructive lung disease with normal

carbon monoxide diffusing capacity, which was interpreted as chronic obstructive pulmonary disease due to the 30 pack year history of smoking. An inhalative corticosteroid was prescribed and smoking cessation was highly recommended.

After study completion he was treated with methotrexate 15 mg subcutaneously once weekly with folic acid supplementation for 6 months, and his PASI further improved to 2.3. Due to dyspnoea (not as bad as with ponesimod), elevated transaminases and lymphopenia, the patient was switched to adalimumab 40 mg subcutaneously every other week (induction 80 mg followed by 40 mg beginning 1 week thereafter) with no further PASI improvement but cessation of side effects (month 0). About 8 months after initiation of adalimumab the patient developed abdominal pain and diarrhoea with daily stool frequencies of between 12 and 15 (Fig. 2) and intermittent bloody diarrhoea. Because the patient did not report these considerable abnormalities during initial dermatological consultations, gastroenterological work up with colonoscopy was delayed by 4 months (month 12). The patient had frequent work related travelling around the world but microbiological investigations remained negative. The patient did not report previous comparable gastrointestinal complaints. Histology showed highly active colitis with cryptitis, crypt abscesses, crypt architectural distortion and loss of crypts.

Based on the chronicity of abdominal symptoms, lack of evidence for differential diagnoses (especially infection or ischaemic colitis), and suggestive endoscopic and histological characteristics, the diagnosis of left sided ulcerative colitis

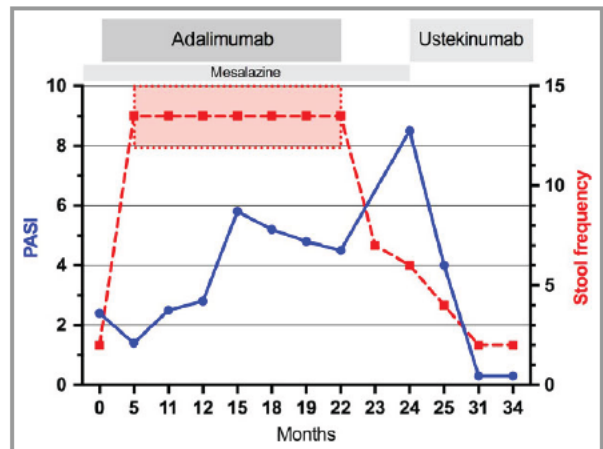


Fig 2. Psoriasis Area and Severity Index (PASI) (blue solid line) and daily stool frequency (red dotted line, red bar indicating 12–15 per day) during treatment with mesalazine, adalimumab and ustekinumab.

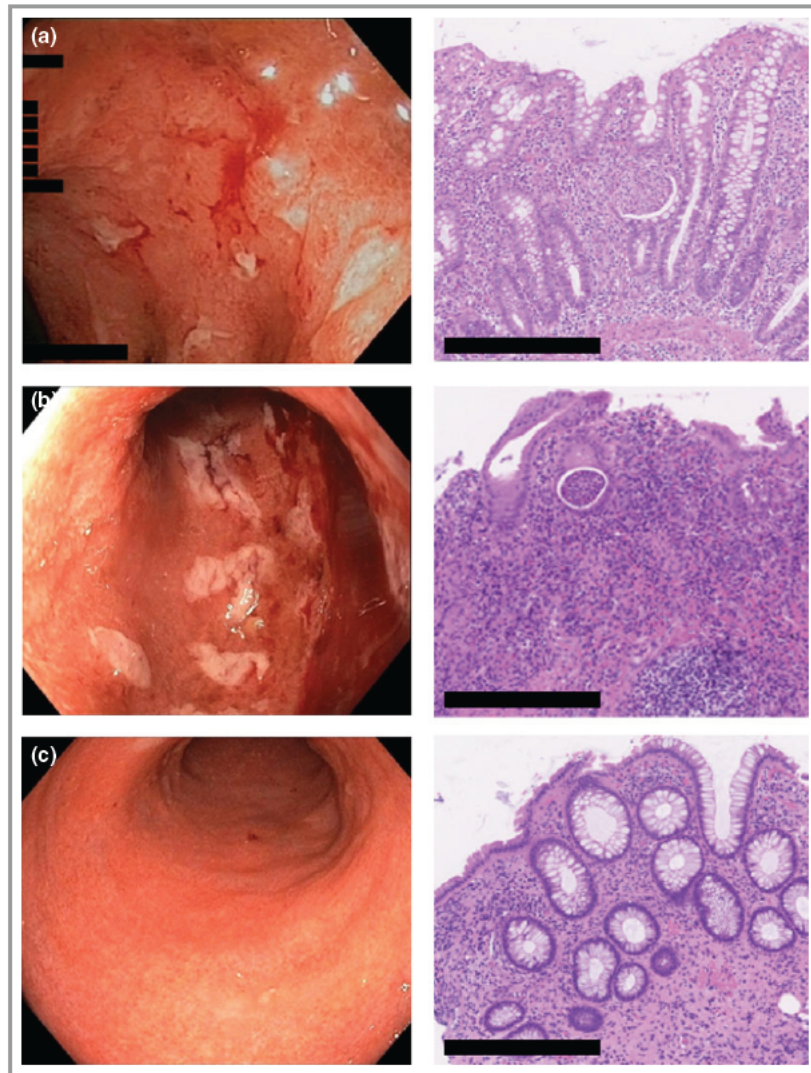
(UC) (Fig. 3a) was made. The patient received treatment with oral mesalazine 1.5 g twice daily but intestinal symptoms did not improve. Three months later (month 15) diarrhoea persisted and psoriasis worsened to PASI 5–8. The patient received additional adalimumab intensification with 80 mg on one occasion and 40 mg 1 week later ('reintroduction') followed by 40 mg every other week, as well as an intensified topical regimen.

Colonoscopy again showed active colitis corresponding to an endoscopic Mayo Score of 3, which was confirmed by



Fig 1. Skin involvement on first presentation and before systemic therapy (Psoriasis Area and Severity Index score 12.8).

Fig 3. Endoscopy (left) and histology (right) images are depicted at first gastroenterological evaluation: (a) 12 months after beginning adalimumab; (b) at the end of adalimumab therapy (month 22); and (c) after the initiation of ustekinumab therapy (month 24). (a) Sigmoid colon with diffuse active inflammation, significant mucosal oedema and erythema, increased friability and several ulcers, corresponding to an endoscopic Mayo Score of 3. Histology shows cryptitis, crypt abscesses, crypt architectural distortion and loss of crypts. (b) Sigmoid colonic mucosa with comparable mucosal abnormalities as in (a). Significant amounts of blood are also due to prior biopsy. Histology shows crypts, crypt abscesses, crypt architectural distortion and loss of crypts. (c) Marked improvement of endoscopic activity with only mild residual mucosal erythema and oedema but complete absence of erosions or ulcerations, corresponding to an endoscopic Mayo Score of 1. Histology shows almost normal colon mucosa with minimal distortion of crypt architecture. Scale bars = 250 μ m.



histology (month 22) (Fig. 3b). As the patient developed *de novo* colitis harbouring typical clinical, endoscopic and histological features of UC in the course of treatment with adalimumab, the diagnosis of paradoxical UC to adalimumab was considered and reported to pharmacovigilance. Adalimumab was withdrawn (month 23) while mesalazine was continued. The patient experienced an immediate improvement of his gastrointestinal symptoms and stool frequency halved within 4 weeks. However, with the cessation of adalimumab therapy the patient's psoriasis worsened, reaching a PASI score of 8.5 (month 24). Given the burden of disease, ustekinumab was initiated at 45 mg subcutaneously every 12 weeks (induction at weeks 0 and 4, followed by every 12 weeks). A colonoscopy 1 month after beginning ustekinumab therapy (month 25) showed almost normal intestinal mucosa with only minimal residual mucosal oedema and erythema; histology revealed no significant inflammation (Fig. 3c) and stool frequency normalized. During a follow up period of 2 years under ustekinumab, complete resolution of psoriasis without further complaints was achieved (Figs 2 and 4).

Discussion

Psoriasis is a chronic autoimmune skin disease and is associated with various comorbidities including UC (0.5–1.4% in psoriasis).^{1–3} If refractory to topical and conventional systemic therapy, tumour necrosis factor (TNF) inhibitors such as adalimumab and the interleukin 12/23 blocker ustekinumab are indicated in moderate to severe psoriasis, and adalimumab but not ustekinumab is indicated for UC.^{4,5} Ustekinumab has shown efficacy in refractory Crohn disease (CD), and got approval also for CD in Switzerland since 2017.^{6,7} A phase III study assessing its efficacy in UC is currently ongoing.

Paradoxical adverse events to TNF inhibitors affect most commonly the skin (20–25%), joints and lungs.⁸ Typical psoriasis form reactions appear in 5–30% of patients treated with TNF inhibitors and occur in 3–5% of patients with inflammatory bowel disease (IBD).^{9–11} Paradoxical lung disease includes interstitial lung disease, sarcoidosis and pulmonary granulomatous disease.^{8,12} Disease exacerbation in IBD due to TNF inhibitors is reported in one case of CD during infliximab.¹³ A few cases with



Fig 4. Skin involvement after 1 year of ustekinumab therapy (Psoriasis Area and Severity Index score 0.5).

paradoxical appearance of mostly CD have been reported in rheumatoid arthritis or ankylosing spondylitis after treatment with etanercept or infliximab.^{12,14} Paradoxical UC in rheumatoid arthritis has been described in the literature either during infliximab alone or during etanercept persisting despite switching to adalimumab or infliximab.^{15,16} As reported in paradoxical psoriasis, suspicion for a class effect of TNF inhibitor is suggested by the previous cases.¹⁷ There is increasing evidence for the efficacy of ustekinumab in paradoxical psoriasiform reactions in patients with IBD (including our own experience).⁹

To the best of our knowledge this is the first case of UC occurring in a patient with psoriasis and on adalimumab treatment. Although UC could be a comorbidity of psoriasis, the immediate improvement after adalimumab cessation suggests a paradoxical reaction. By analogy to the above cases, we would like to propose the term 'paradoxical ulcerative colitis' (PUC) for this entity.¹² Due to a presumable class effect and after switching to ustekinumab, complete remission of UC and psoriasis occurred for up to 2 years of follow up (Fig. 4). Similarities to the abovementioned cases were the nonresponse to topical steroids and the delayed onset after months of TNF inhibitor treatment. For paradoxical psoriasis an interquartile range of 0.5–3.9 years (median 1.9) between onset of therapy and paradoxical disease has been described.¹⁰ Thus, PUC adds to the list of known TNF inhibitor induced gastrointestinal adverse reactions such as apoptotic enteropathy.¹⁸

Blocking TNF α leads to interferon (IFN) α release in lupus or increased transcription of IFN α regulated genes.¹⁹ Upregulation of alpha 4/beta 7 integrin on CD4⁺ T cells leading to

increased gut homing has been described in infliximab treated patients with CD, which could be an explanation in our case.¹⁶

There are to date no reports of ustekinumab induced IBD. As our patient's symptoms had already significantly improved after cessation of adalimumab, we cannot conclude cessation alone of adalimumab would have been sufficient, or if ustekinumab was necessary to resolve PUC completely. Due to the worsening of psoriasis we started ustekinumab before we could have addressed this question completely. A limitation of this report is that faecal calprotectin levels were not measured before or during adalimumab treatment. However, stool calprotectin 1 month after cessation of adalimumab was only 217 $\mu\text{g g}^{-1}$ (reference < 50) and further decreased to 67 $\mu\text{g g}^{-1}$ 8 weeks after cessation.

Here we report a case of adalimumab induced PUC in a patient with psoriasis, beginning 8 months after adalimumab induction. After cessation, gastrointestinal problems resolved significantly; as we suspected a possible class effect of TNF inhibitors, we changed to ustekinumab to control the psoriasis exacerbation without further complaints for a 2 year follow up. There is increasing evidence that ustekinumab is an effective treatment option for paradoxical inflammatory reactions such as psoriasis and IBD in patients treated with TNF inhibitors.

Acknowledgments

We thank Mr Markus Bär for the high quality photographs.

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