Inflammatory Cutaneous Lesions in Inflammatory Bowel Disease Treated With Vedolizumab or Ustekinumab: An ECCO CONFER Multicentre Case Series

Inflammatory cutaneous lesions in inflammatory bowel disease treated with Vedolizumab or Ustekinumab: an ECCO CONFER multicentre case series

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Abstract

Background

Inflammatory cutaneous lesions are a common extraintestinal manifestation of inflammatory bowel disease (IBD). However, it is unknown whether such lesions, which may be refractory to standard medical therapy including anti-TNFs, would respond to the newer biologic agents ustekinumab (UST) or vedolizumab (VDZ).

Methods

This was a multicentre case series supported by the European Crohn's and Colitis Organisation (ECCO) and, performed as part of the Collaborative Network of Exceptionally Rare case reports (CONFER) project. A call to all ECCO members was made to report on cutaneous lesions in IBD treated by UST or VDZ, excluding psoriasiform lesions. Clinical data were recorded in a standardised data collection form.

Results

This report includes 28 patients with cutaneous lesions form 14 centres; 23 had Crohn's disease and 5 had ulcerative colitis whilst 19 were treated with UST and 11 with VDZ (2 patients were treated with both). All had failed immunomodulators and anti-TNF therapy. Metastatic Crohn's disease (MCD) was diagnosed in 10 patients and UST therapy led to remission in 5 cases and partial response in 4 cases, with a single report of VDZ inducing remission. All cases of MCD that were treated with UST responded after the first or second dose, whilst for the 5 cases that attained remission, the median time for this was 5 months. Pyoderma gangrenosum (PG) was diagnosed in 4 cases: 3 of these attained remission with UST (median time to remission 4 months) whilst one case did not respond to VDZ. There were 7 cases of erythema nodosum (EN): UST led to remission in 4 cases and partial response in 1 case whilst VDZ had partial response in 2 cases and non-response in 2 cases. There were 7 single cases of other inflammatory lesions, which included: a case of leukoclastic vasculitis that attained remission with VDZ, a case of hidradenitis suppurotiva (HS) with partial response to UST, a case of dissecting cellulitis of the scalp that did not respond to UST; 2 unspecified cases with partial response to VDZ and another two unspecified cases with no response to VDZ.

Conclusion

This is the first case series to describe the efficacy of UST and VDZ in the treatment of cutaneous lesions related to IBD. UST appears to be useful for different cutaneous lesions, with remission or a partial response achieved in all cases of MCD, PG, HS and EN. VDZ caused a partial response or non-response in EN and other inflammatory lesions, as well as a single case of remission in MCD.

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), are chronic idiopathic inflammatory conditions of the intestines of a relapsing and remitting nature. They are often associated with extraintestinal manifestations, occurring in 43% of patients with CD and 31% with UC in one large population study. [1] These can be just as or more debilitating than the underlying intestinal inflammation.

The skin is one of the most common extraintestinal organ systems involved. A useful method of classification for cutaneous lesions in IBD is based on pathogenesis, with four groups being described: [2]

1) Granulomatous lesions share the same histological features as the underlying intestinal disease.
2) Reactive lesions are believed to stem from common immuno-pathogenic mechanisms, which may be related to common antigens shared by gut bacteria and skin.
3) Associated lesions occur with increased frequency in IBD compared to the general population but are completely independent of intestinal disease activity.
4) Secondary lesions occur as a result of either micronutrient deficiencies or drug reactions.

The most common cutaneous lesion in IBD is erythema nodosum (EN), which is an example of a reactive lesion that closely parallels intestinal disease activity. [3] It presents as painful, warm palpable nodules or raised reddish-blue subcutaneous lesions or plaques, located on the extensor surfaces of the extremities. Pyoderma gangrenosum (PG) is the second most common cutaneous lesion and amongst the most debilitating. It begins as non-infectious nodules and pustules that expand outward and develop into painful deep ulcers with sharply demarcated and undermined borders. Both can usually be diagnosed clinically without the need for biopsy. Whilst treatment for EN focuses on treating the underlying intestinal disease, PG often occurs independently of disease activity and requires systemic immunosuppression.

One of the rarest cutaneous lesions in IBD is metastatic Crohn disease (MCD), also known as cutaneous Crohn disease. This is characterised by non-caseating granulomas with similar histology to intestinal Crohn's disease but at sites anatomically distinct from the gastrointestinal tract. [4] Histological examination distinguishes it from other granulomatous lesions such as cutaneous sarcoidosis, hidradenitis suppurativa (HS) and PG.

Cutaneous lesions such as these can be particularly distressing and are often difficult to treat. It is not uncommon for lesions to be refractory to standard medical therapy, including anti-TNF agents. Two new biologic agents, ustekinumab (UST) and vedolizumab (VDZ), are now used widely in the treatment of IBD.

UST is a humanised monoclonal antibody that targets the common p40 subunit of IL-12 and IL-23 cytokines. The phase III UNITI trials established UST as an effective treatment for CD, [5] whilst the recently published phase III UNIFI trials show it is also an effective treatment for UC too. [6]

VDZ is a humanised monoclonal antibody that targets α4β7 integrin, which is expressed by a subset of gastrointestinal-homing T-lymphocytes. Lymphocyte trafficking from the blood vessels to the intestines is blocked, and results in its gut-selective action. Theoretically there should be little

activity on those EIMs that are independent of disease activity. However, there have been reports of improvements in EIMs such as pyoderma gangrenosum, uveitis and ankylosing spondylitis. [7] The GETAID OBSERV-IBD cohort followed 294 patients with IBD treated with VDZ and showed an improvement in inflammatory joint disease and cutaneous lesions, although this may be related to improvement of the underlying GI disease. [8] On the other hand, a population-based study showed that adult IBD patients receiving VDZ had higher rates of EIMs than those on anti-TNF therapies, indicating the limitations of VDZ for EIM prevention. [9]

This collaborative case series looks at the efficacy of both UST and VDZ to treat different types of anti-TNF refractory cutaneous lesions in IBD.

Methods

This was a retrospective multicentre case series supported by the European Crohn's and Colitis Organisation (ECCO). The ECCO Collaborative Network for Exceptionally Rare case reports (CONFER) projects are based on an initiative introduced by ECCO to support individual investigators in developing rare case series by collecting enough similar cases among the IBD Community. This support includes dissemination of a call for similar cases, as well as assessment of the feasibility of the cases by the ECCO CONFER Steering Committee. It does not include any financial support nor any input in the scientific collection of the data, the analysis or the publication of the data collected. ECCO, and/or any of its staff members, may not be held liable for any information published in good faith in the ECCO CONFER articles.

A call to all ECCO members was made to report on cutaneous lesions in IBD treated with UST or VDZ. This excluded psoriasiform lesions, oral lesions and perianal lesions. Clinical data was recorded in a standardized data collection form. Key data recorded included: demographics, Montreal classification, previous medications, location, type and morphology of cutaneous lesion, treatments for the lesion, and time to response or remission.

Several different types of cutaneous lesions were included in this study, diagnosed with the help of dermatology specialists.

Results

This study includes 28 patients with cutaneous lesions from 14 different centres; 20 patients were female and the median age range was 37 years old; 23 had CD and 5 had UC whilst 19 were treated with UST and 11 with VDZ (2 patients were treated with both). As far as we are aware, all patients were treated with UST and VDZ according to the manufacturer's recommendations. All patients had failed both immunomodulator and anti-TNF therapy, whilst the use of topical therapies was ongoing in some cases. The results are summarised in table 1 and figures 1-6 show cases included in this series.

Table 1

	N=	**Active luminal disease**	**Ustekinumab**	**Vedolizumab**
Metastatic Crohn's disease	10	7	Remission in 5 cases Response in 4 cases	Remission in 1 case
Pyoderma gangrenosum	4	3	Remission in 3 case	Non-response in 1 case
Erythema nodosum	9	8	Remission in 4 cases Response in 1 case	Response in 2 cases Non-response in 2 cases
Leukocytoclastic vasculitis	1	0		Remission in 1 case
Hidradenitis suppurativa	1	1	Response in 1 case	
Dissecting cellulitis of the scalp	1	0	Non-response in 1 case	
Unspecified inflammatory lesions	4	1		Response in 2 cases Non-response in 2 cases

Metastatic Crohn's disease (MCD) was diagnosed in 10 patients, 9 confirmed by histology and the other diagnosed clinically by an experienced dermatologist. UST therapy led to remission in 5 cases and partial response in 4 cases. There was also a single report of VDZ inducing remission in MCD. All the cases of MCD treated with UST responded after either the first or second dose, whilst for the 5 cases that attained remission, the median time for this was 5 months. The distribution of CD was ileocolonic in 8 cases and colonic in 2 cases. Luminal Crohn's disease was active in 7 cases and quiescent in the other 3 cases. The location of the MCD lesion was truncal in 3 cases, genital in 4 cases, groin in 2 cases, and groin and genitals in one case. The morphology of the MCD lesions was ulcerative in 4 cases, papular in 3 cases and plaque-like in 3 cases.

Pyoderma gangrenosum (PG) was diagnosed in 4 cases: 3 of these attained remission with UST (median time to remission 4 months) whilst the other case did not respond to VDZ. Erythema nodosum (ED) was diagnosed in 7 cases: 2 cases had non-response to VDZ with subsequent remission to UST; UST led to remission in a further 2 cases and partial response in 1 case; VDZ had partial response in a further 2 cases.

In addition, there were 7 single cases of other inflammatory lesions, which included: a case of leukocytoclastic vasculitis that attained remission with VDZ, a case of HS with partial response to UST, a case of dissecting cellulitis of the scalp that did not respond to UST; 2 unspecified cases without histology with a partial response to VDZ and another two unspecified cases without histology with no response to VDZ.

Discussion

Inflammatory cutaneous lesions are common extraintestinal manifestations of IBD and their management can often be challenging. This case series describes the efficacy of the newer biologic agents for a series of cutaneous lesions refractory to standard immunomodulator and anti-TNF therapy.

Ten patients with MCD were included, one of the largest case series of this rare cutaneous manifestation of CD to date. The morphology of MCD is variable, [4] which is reflected in our cases with approximately equal numbers of ulcers, plaques and nodules. Location is also variable with a predilection for moist skin creases such as the perineal, inguinal, abdominal and sub-mammary areas. Seven of our cases were located to the groin or genitals, and 3 to the trunk, which may represent a predilection for these areas or difficulties in treating lesions in the groin and genital areas. It has previously been reported that MCD is more common in patients with CD colitis, and this is reflected in this study, with all 10 patients having colonic involvement.

Experience of the treatment of MCD mainly comes from case reports with various treatment modalities having been used, including steroids, immunomodulators, antibiotics, hyperbaric oxygen [10] and anti-TNF biologic agents [11, 12]. Surgical debridement has also been used for cases refractory to medical therapy. [13] More recently, there have been two case reports of ustekinumab being used for MCD affecting the groin and genitals, one of which is included in this series. [14, 15] Given the rarity of MCD and the prominence in this study, it perhaps reflects the difficulties in treating this condition with standard medical therapy. It is therefore significant that all 9 patients with MCD treated with UST in this series responded after the first or second dose, with 5 of these patients attaining complete remission in a median time of 5 months. This indicates a potentially strong signal for the efficacy of ustekinumab in MCD.

EN occurs in up to 15% of CD and 10% of UC. [16] There were 7 cases in this series, with UST leading to response or remission in all 5 of its cases. Two of these patients had failed VDZ prior to UST, and another two had a partial response to VDZ. Given that EN lesions parallel disease activity, the response of UST and VDZ likely reflected the response to the underlying IBD activity.

The relationship of PG to IBD activity is not entirely clear and treatment of intestinal disease does not always help with PG. The mainstay of treatment is with systemic steroids, with or without topical treatments. Anti-TNF agents have also been used successfully in refractory cases. [17, 18] There have also been some case reports of the successful use of UST in PG not associated with IBD, [19] including one case which demonstrated high levels of IL-23 in the lesion. [20] Our study included 4 patients with IBD-associated PG, 3 of whom attained remission with UST and the other did not respond to VDZ. This indicates the potential usefulness of UST for IBD-associated PG.

There were 6 cases of other inflammatory lesions in this series showing mixed responses to UST and VDZ. Of note, there was one case of leukocytoclastic vasculitis showing complete response to VDZ, which correlates with experience that shows most cases resolve with treatment of the underlying IBD. [21, 22] There was a single case of response of HS to UST. A small open label study of UST for HS has previously indicated its potential usefulness. [23] There was a further case of dissecting cellulitis of the scalp that did not respond to UST.

The limitations of this study are that reporting is retrospective and histology was not available in all cases, although it is common for dermatological diagnoses and assessment of response or remission to be made on clinical grounds.

Conclusion

This is the first case series to describe the efficacy of UST and VDZ in the treatment of cutaneous lesions related to IBD. It also includes one of the largest series of patients with MCD. There were a mix of lesions and all were refractory to standard immunotherapy and anti-TNF therapy.

UST appears useful for cutaneous lesions, with remission or a partial response in all 9 cases of MCD, all 5 cases of EN and all 3 cases of PG. Given its gut selectivity, VDZ is predictably less useful and caused a partial response or non-response in EN and other inflammatory lesions, although there was a single case of remission in MCD.

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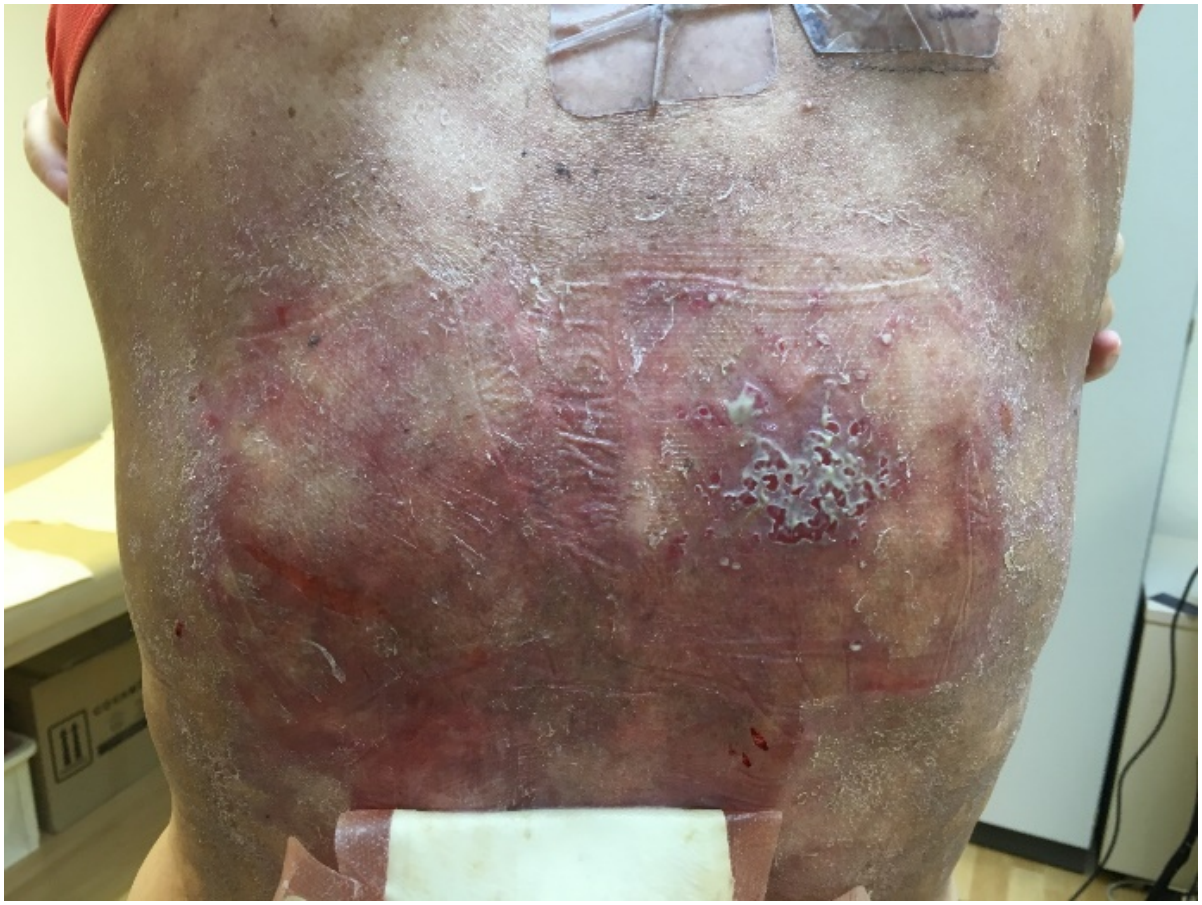
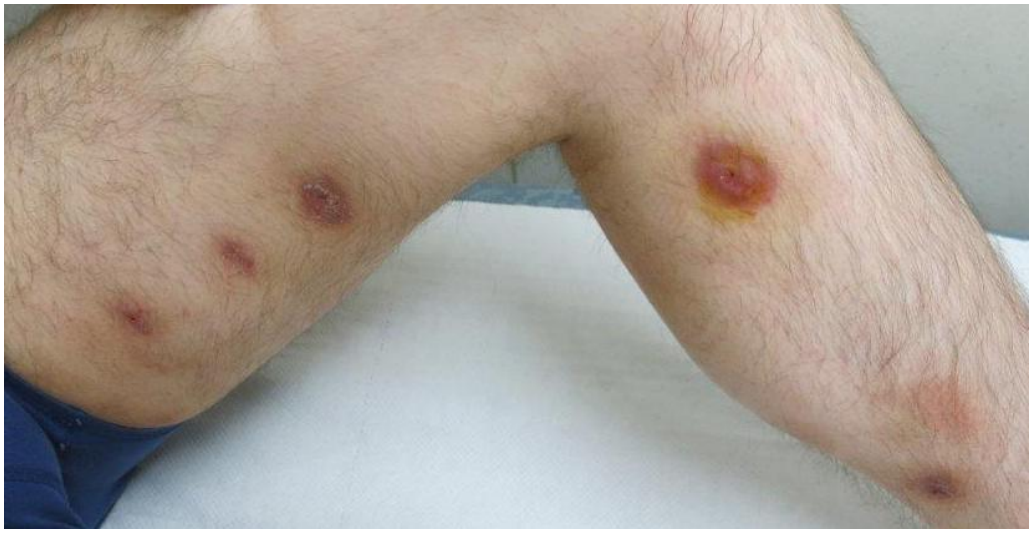
Case of metastatic Crohn disease: partial resolution with UST

Courtesy of Oliver Bachman



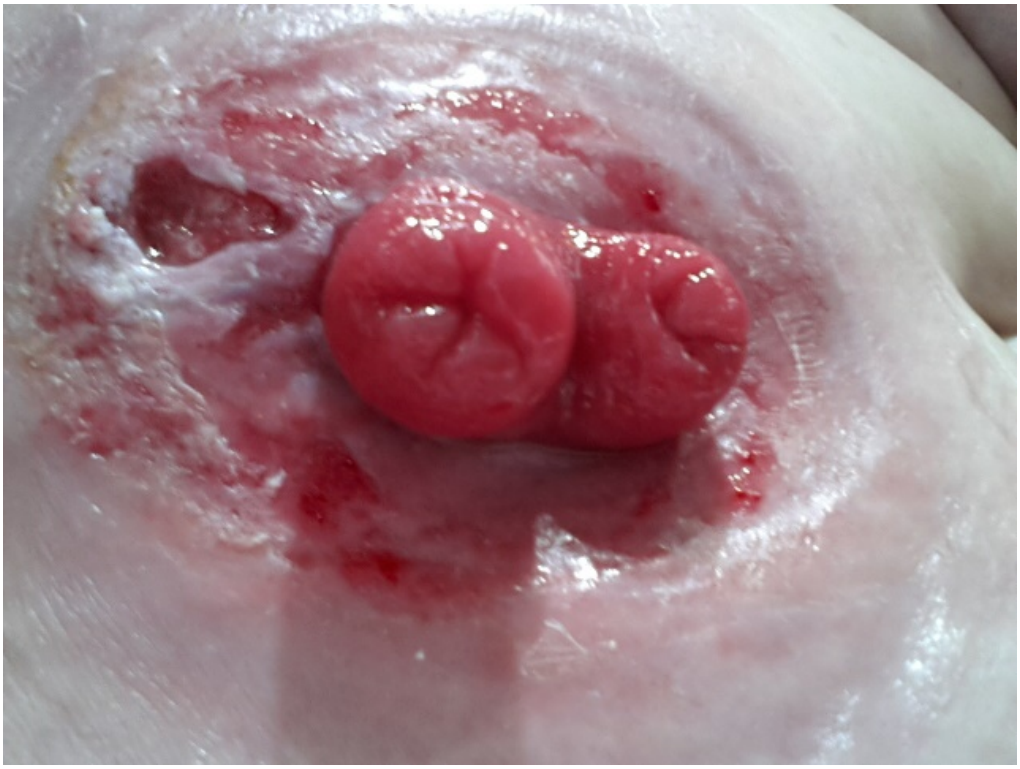
Pyoderma gangrenosum: complete remission with UST

Courtesy of Bram Verstockt



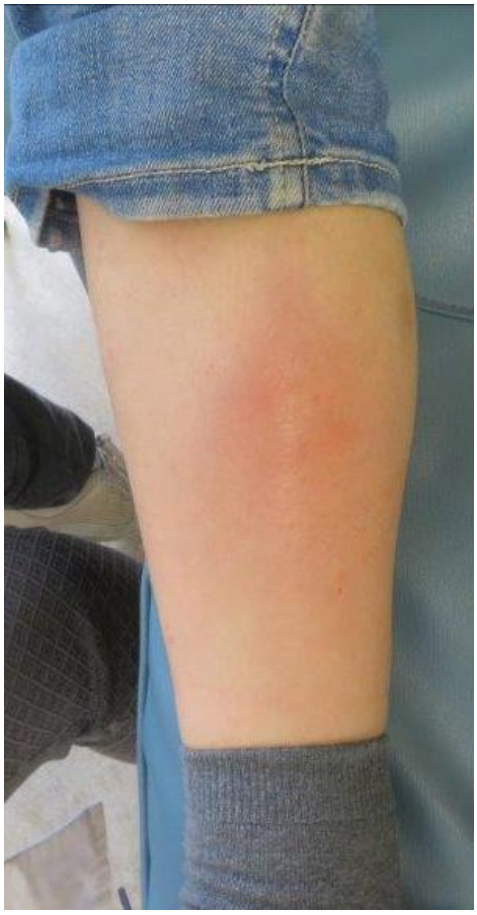
Case of peristomal pyoderma gangrenosum: complete remission with UST

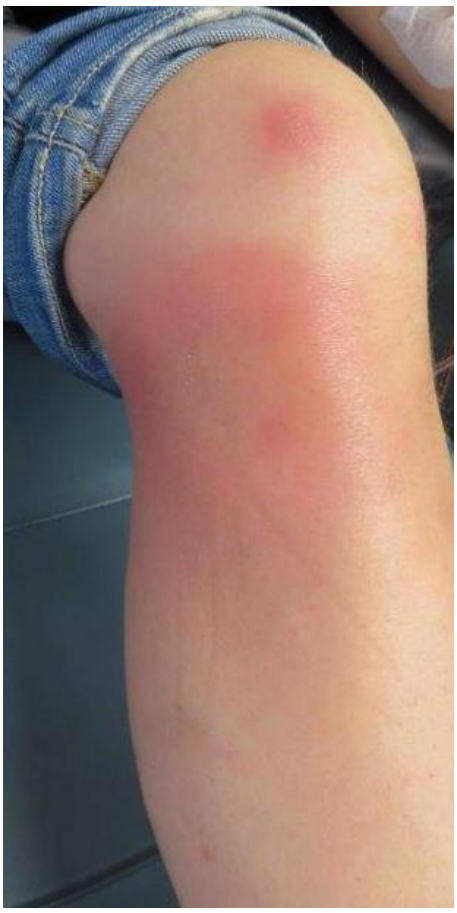
Courtesy of Nicolas de Suray



Case of erythema nodosum: no response to VDZ but subsequent remission with UST

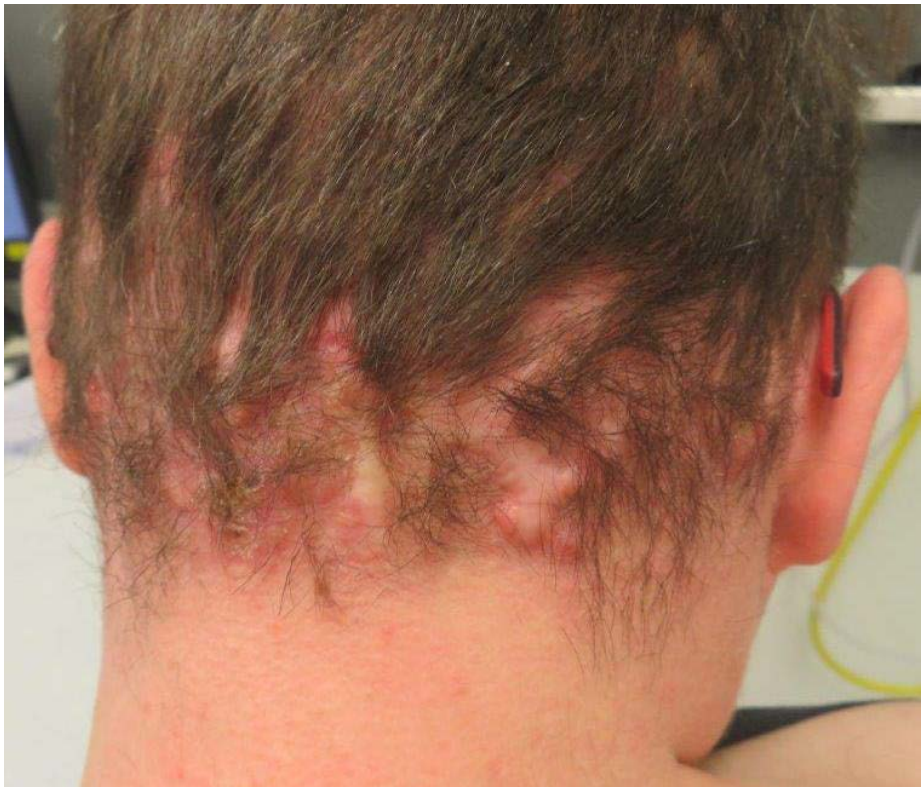
Courtesy of Bram Verstockt





Case of dissecting cellulitis of the scalp: no response to UST

Courtesy of Bram Verstockt



Case of leucocytoclastic vasculitis: complete remission with VDZ

Courtesy of Cristina Flores