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

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Presented at the 14th Congress of ECCO, March 2019, Copenhagen, Denmark.

Abstract

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. The aim was to report on whether cutaneous lesions associated with inflammatory bowel disease (IBD) and refractory to standard medical therapy including anti-TNFs, would respond to the newer biologic agents Ustekinumab (UST) or Vedolizumab (VDZ). This report includes 28 patients with cutaneous lesions form 14 centres, all of whom had failed immunomodulator and anti-TNF therapy. Metastatic Crohn's disease (MCD) was diagnosed in 10 patients: UST led to remission in 5 cases and partial response in 4 cases, with a single report of VDZ inducing remission. All cases of MCD treated with UST responded after the first or second dose, whilst the median time for the 5 cases that attained remission 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. In summary, UST appears to be useful for different cutaneous lesions including MCD, PG and EN, whilst VDZ does not appear to be useful for lesions that are independent of disease activity.

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), 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, occurring in 14.9% of a recent cohort when cutaenoues lesions due to nutrient deficiencies and medications were excluded. The most common cutaneous lesion in IBD is erythema nodosum (EN), which is a reactive lesion that closely parallels intestinal disease activity. [3] Pyoderma gangrenosum (PG) is the second most common cutaneous lesion and amongst the most debilitating. 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] It can occur independent of disease activity.

Cutaneous lesions such as these can be particularly distressing and are often difficult to treat even with anti-TNF agents. There are two new biologic agents, ustekinumab (UST) and vedolizumab (VDZ), 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. Theoretically there should be little activity on those EIMs that are independent of disease activity. A population-based study showed that VDZ was not useful for EIM prevention,[7] whilst a recent systematic review concluded VDZ was not useful for cutaneous lesions.[8] However, there have been reports of improvements in EIMs felt to be independent of disease activity such as PG, uveitis and ankylosing spondylitis. [9, 10]

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.

Case Report

This was a retrospective multicentre case series supported by the European Crohn's and Colitis Organisation (ECCO), and performed as part of the ECCO Collaborative Network for Exceptionally Rare case reports (CONFER) project. 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 including: demographics, Montreal classification, previous medications, location, type and morphology of cutaneous lesion, treatments for the lesion, and time to response or remission.

This study includes 28 patients with cutaneous lesions from 14 different centres, diagnosed with the help of dermatology specialists. 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 here.

Metastatic Crohn's disease (MCD) was diagnosed in 10 patients (see table 2), 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. Two of these cases had failed VDZ, whilst there was a single report of VDZ leading to 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, and a case of dissecting cellulitis of the scalp that did not respond to UST.

Discussion

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. Its limitations 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.

Ten patients with MCD were included, one of the largest case series of this rare cutaneous manifestation of CD to date. Although MCD can occur independent of disease activity, 7 of the 10 cases had active luminal disease. Morphology 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 [11], anti-TNF biologic agents [12, 13] and surgical debridement. [14] 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. [15, 16] 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. [17] 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. [18, 19] There have also been some case reports of the successful use of UST in PG not associated with IBD, [20] including one case which demonstrated high levels of IL-23 in the lesion. [21] 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.

Of the other inflammatory lesions, 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. [22, 23] 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. [24] In summary, UST appears to be useful for different cutaneous lesions including MCD, PG and EN, whilst VDZ does not appear to be useful for lesions that are independent of disease activity.

Acknowledgements

ECCO 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.

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Table 1: Treatments and outcomes of the different cutaneous lesion types

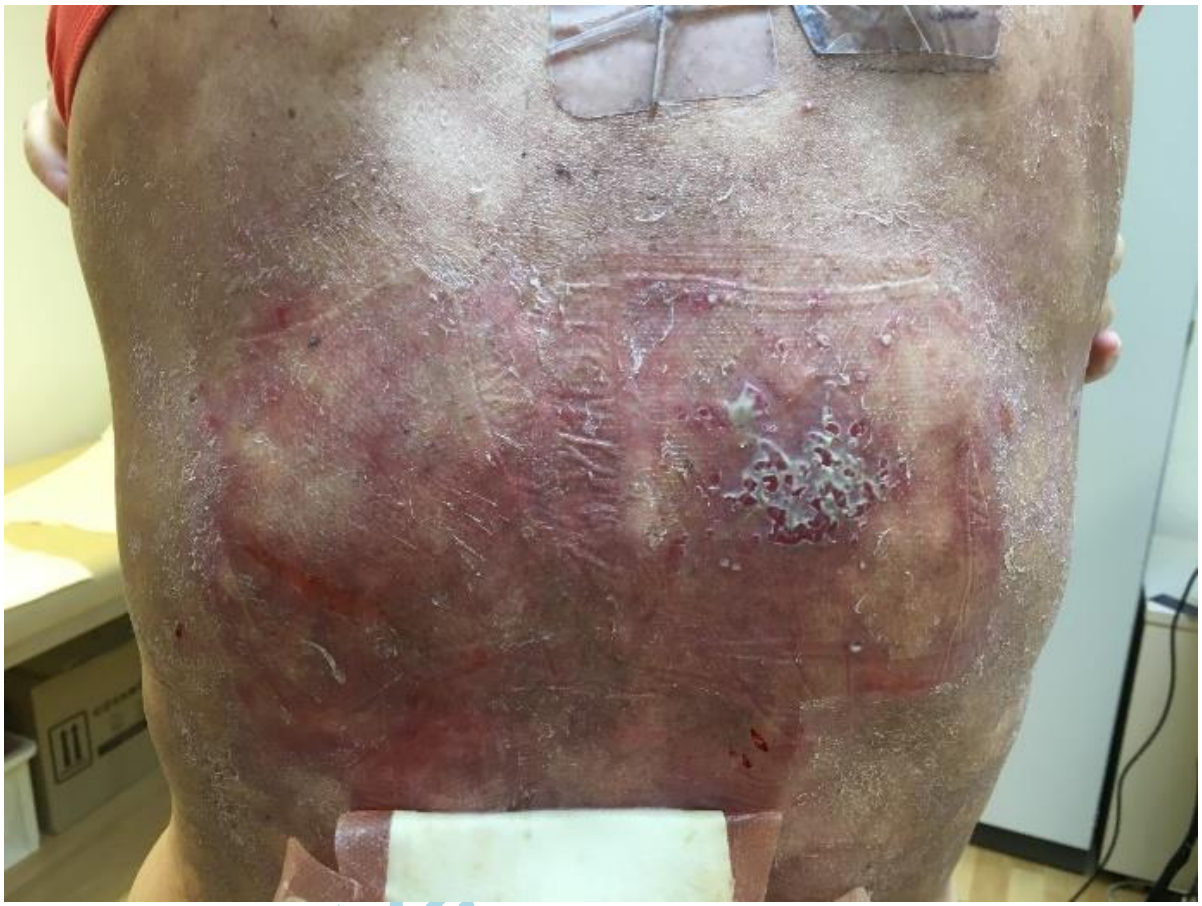
	N=	Luminal activity	Previous anti-TNF therapy	Mean duration of lesion prior to UST or VDZ starting	Concomitant therapy	Ustekinumab	Vedolizumab
Metastatic Crohn's disease	10	7	4 cases failed anti-TNF 6 cases had anti-TNF prior to lesion developing	10 months	Methotrexate in 6 cases Azathioprine in 1 case Topical therapy in 1 case	Remission in 5 cases Response in 4 cases	Remission in 1 case Non-response in 2 cases
Pyoderma gangrenosum	4	3	2 cases failed anti-TNF 2 cases had anti-TNF prior to lesion developing	5 months	Topical therapy in 3 cases	Remission in 3 case	Non-response in 1 case
Erythema nodosum	7	6	3 cases failed anti-TNF 4 cases had anti-TNF prior to lesion developing	8 months	Topical therapy in 2 cases Methotrexate in 1 case Azathioprine in 1 case	Remission in 4 cases Response in 1 case	Response in 2 cases Non-response in 2 cases
Leukocytoclastic vasculitis	1	1	Anti-TNF prior to lesion developing	4 months	Azathioprine		Remission in 1 case
Hidradenitis suppurativa	1	1	Failed anti-TNF for 2 months	2 months	Triamcinolone	Response in 1 case	
Dissecting cellulitis of the scalp	1	0	Failed anti-TNF for 2 months	2 months	None	Non-response in 1 case	
Unspecified inflammatory lesions	4	1	Failed anti-TNF for 1 month 2 cases already on VDZ when lesion appeared	<1 month	None in 3 cases Steroid in 1 case		Response in 2 cases Non-response in 2 cases

Table 2: Individual cases of metastatic Crohn's disease

Age/gender	Lesion location	Lesion type	Diagnosis	Luminal activity	VDZ or UST use	Concomitant medications	Response	Remission
52/F	Genitals	Plaque-like	Biopsy	Quiescent	UST	Methotrexate	Month 2	Month 4
57/F	Genitals & groin	Papular	Biopsy	Active	UST	Methotrexate	Month 2	Month 6
17/M	Genitals	Papular	Biopsy	Active	UST	Methotrexate	Month 3	Not achieved
47/F	Trunk	Plaque-like	Biopsy	Quiescent	UST	Methotrexate	Month 2	Not achieved
62/M	Trunk	Ulcer	Biopsy	Active	UST	Methotrexate	Month 3	Month 5
60/F	Genitals	Ulcer	Biopsy	Quiescent	UST	Methotrexate	Month 12	Not achieved
68/F	Genitals	Plaque-like	Biopsy	Active	VDZ	None	Month 6	Month 12
35/F	Groin	Papular	Biopsy	Active	UST	None	Month 1	Month 4
24/M	Groin	Ulcer	Biopsy	Active	UST	Topical therapy	Month 2	Month 12
47/F	Trunk	Ulcer	Clinically	Active	UST	Azathioprine	Month 2	Not achieved

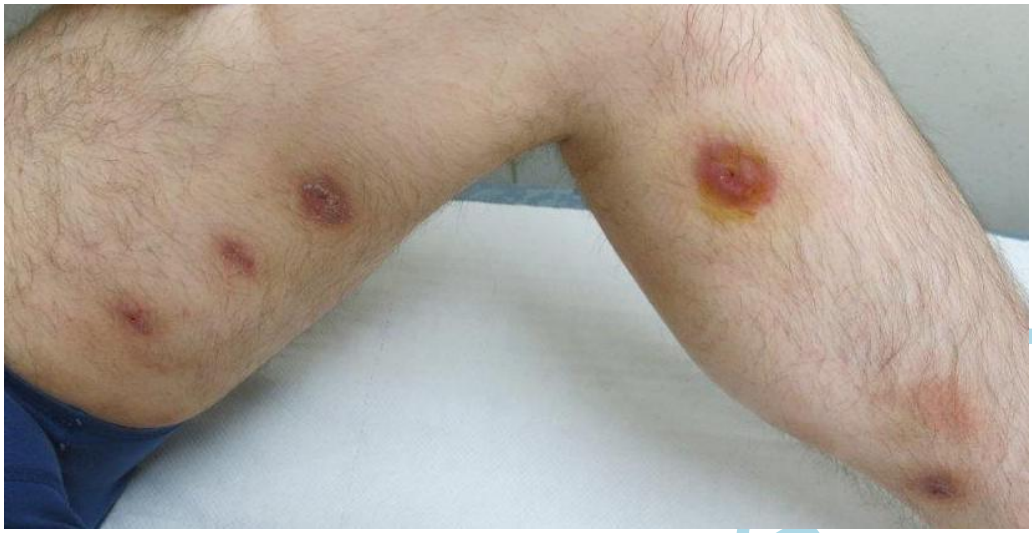
Case of metastatic Crohn disease: partial resolution with UST

Courtesy of Oliver Bachman



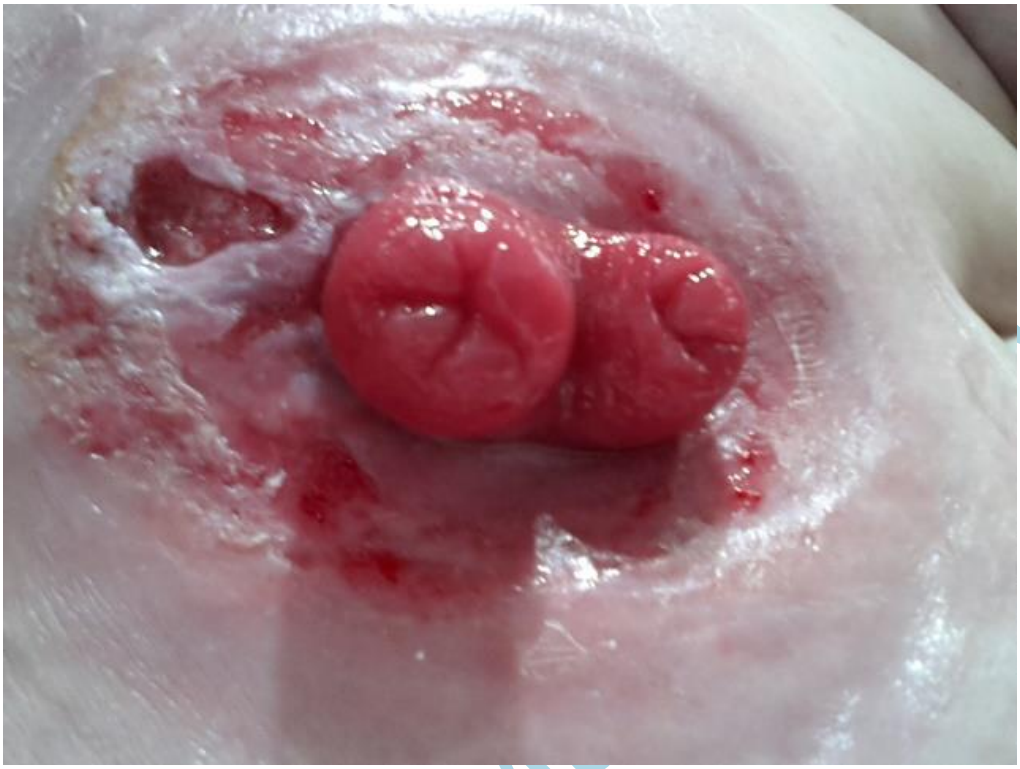
Pyoderma gangrenosum: complete remission with UST

Courtesy of Bram Verstockt



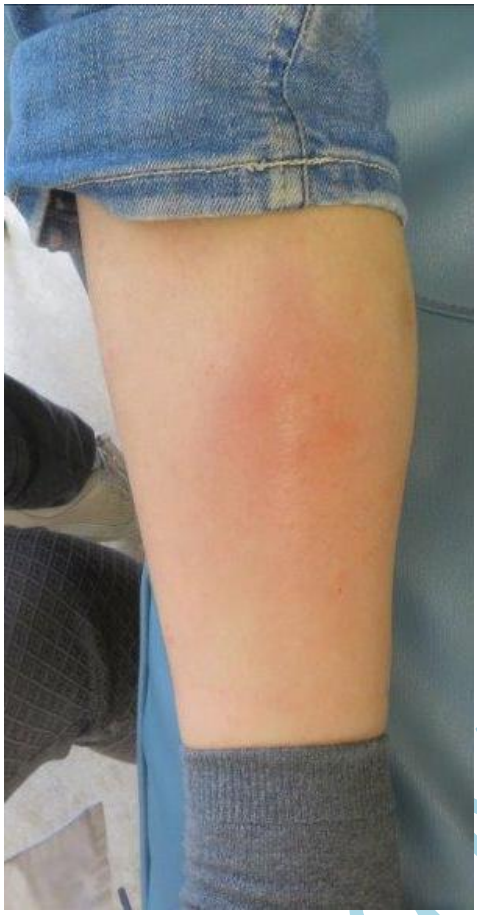
Case of peristomal pyoderma gangrenosum: complete remission with UST

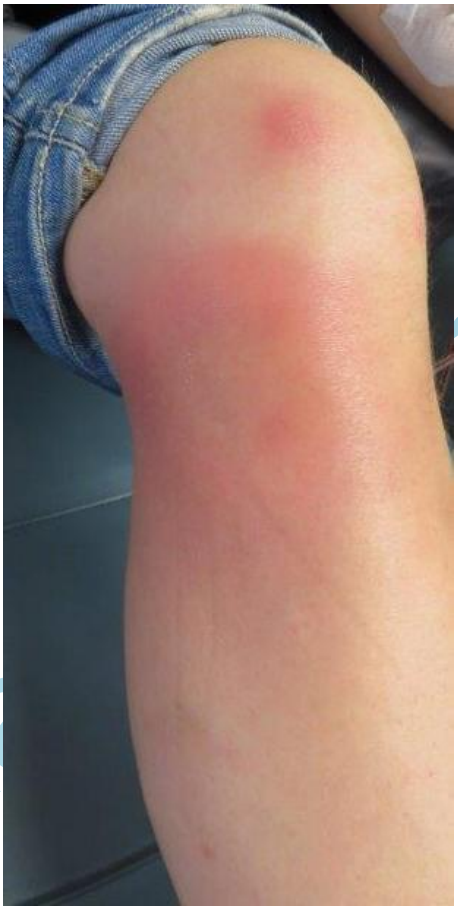
Courtesy of Nicolas de Suray



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

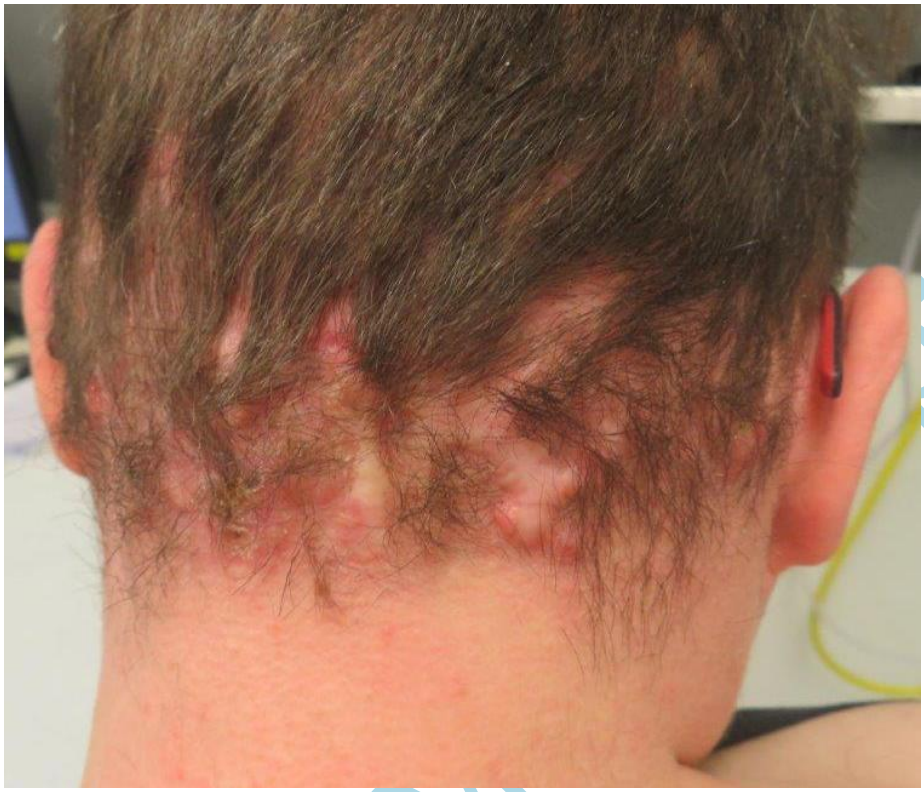
Courtesy of Bram Verstockt





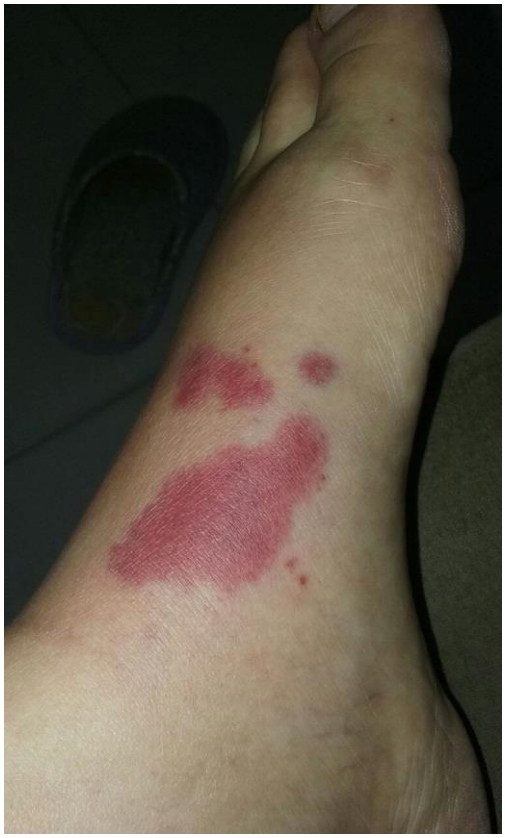
Case of dissecting cellulitis of the scalp: no response to UST

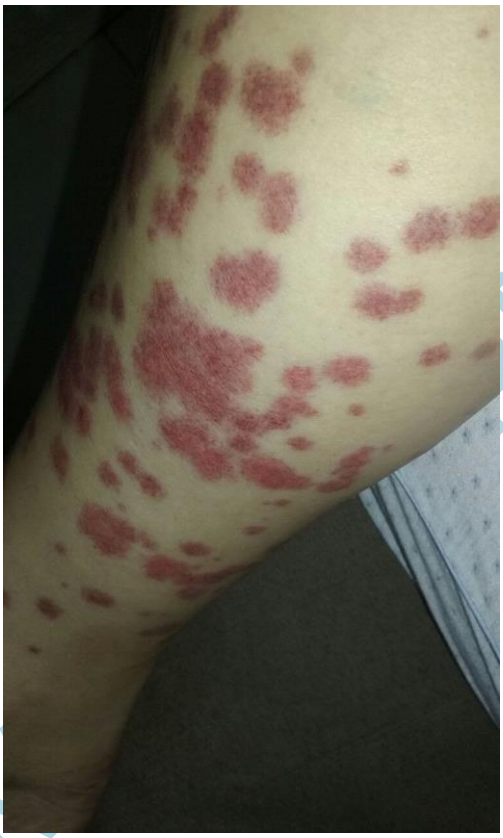
Courtesy of Bram Verstockt



Case of leucocytoclastic vasculitis: complete remission with VDZ

Courtesy of Cristina Flores





Consent

Patient consent was obtained for the publication of all photographs.

Authors contributions:

FP: Principle Investigator for the study, conceived the study idea, contributed 1 case and prepared the manuscript. BV: contributed 7 cases and critiqued the manuscript. SS: contributed 6 cases and critiqued the manuscript. DR: contributed 3 cases and critiqued the manuscript. SV: contributed 2 cases and critiqued the manuscript. KK: contributed 2 cases and critiqued the manuscript. ES: contributed 1 case and critiqued the manuscript. NdS: contributed 1 case and critiqued the manuscript. CF: contributed 1 case and critiqued the manuscript. WF: contributed 1 case and critiqued the manuscript. FV: contributed 1 case and critiqued the manuscript. EC: contributed 1 case and critiqued the manuscript. OB: contributed 1 case and critiqued the manuscript. UK: Case Manager for the study, supervised the project and critiqued the manuscript. All authors approved the final version

Conflicts of interest

FP: none. BV: financial support for research from Pfizer; lecture fees from Abbvie, Ferring, Takeda Pharmaceuticals, Janssen and R Biopharm; consultancy fees from Janssen and Sandoz. SS: research grants from Takeda, AbbVie, Biogen, Pfizer, Warner Chilcott, Ferring, MSD, Biohit and Celgene; serves on the advisory boards of Takeda, AbbVie, Merck, Ferring, Pharmacocosmos, Warner Chilcott, Janssen, Falk Pharma, Biohit, TriGenix, Cellgene and Tillots Pharma; received speaker fees from Abbvie, Jaansen, Merck, Warner Chilcott and Falk Pharma. DR: none. SV: none. KK: none. ES: none. NdS: advisory board member for Takeda and Janssen; speaker fees from Takeda. CF: none. WF: none. FV: none. EC: none. OB: personal fees from Takeda Pharma, Shield Therapeutics, Ferring Pharmaceuticals, Pfizer, CED Service GmbH, Janssen Pharmaceutica, Merck Sharp & Dohme, Abbvie, Astellas Pharma, Biogen, Falk Pharma GmbH, Bristol-Myers Squibb, Tillotts; grants from German Center for Infection Research. UK: research support from Takeda, Janssen, Medtronic; lecture/ advisory fees from Abbvie, Takeda, Janssen, MSD Medtronic

Funding

No specific funding has been received for this project.