IDCases 26 (2021) e01324

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

# Immune recovery folliculitis: Case reports in HIV naïve and experienced patients

Marta Camici[a,*], Alessandra Scarabello[b], Franca Del Nonno[c], Daniele Colombo[c], Roberta Gagliardini[a], Andrea Antinori[a]

[a] HIV/AIDS Clinical Unit, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy
[b] Dermatological Clinical Unit, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy
[c] Histology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy

ARTICLE INFO

*Article history:*
Received 14 September 2021
Received in revised form 26 October 2021
Accepted 26 October 2021
Available online xxxx

*Keywords:*
HIV infection
Immune recovery folliculitis
Immune reconstitution inflammatory syndrome
Therapy simplification
Case report

ABSTRACT

Immune recovery folliculitis (IRF) is defined as the development of an inflammatory disorder of the facial pilo-sebaceous unit due to the immune reconstitution inflammatory syndrome (IRIS). Skin lesions can be related to an immune response against skin saprophyte bacteria (e.g. *Demodex folliculorum, Cutibacterium acnes).* The rapid reconstitution of T lymphocyte, with a CD8+ predominance, is considered a key pathogenic factor for this phenomenon. IRF is clinically similar to acne vulgaris and can be challenging to treat. Patients with facial pustules can experience social discomfort. Here we report two cases of IRF diagnosed at the human immunodeficiency virus (HIV) clinic of the National Institute of Infectious Diseases L. Spallanzani, in Rome, Italy. The first case occurred in an antiretroviral therapy (ART)-experienced patient, after a treatment simplification; the second one was registered in an ART-naïve patient, diagnosed with acute HIV infection shortly, after ART initiation. To date, an IRF secondary to an ART switch, has not been described yet. IRF should be ruled out and considered in differential diagnosis from antiretroviral drug-related skin effects.


## Background

With the development of more effective antiretroviral therapies (ARTs), the clinical manifestations related to the rapid immunological recovery are gaining more and more importance during HIV infection. In the recent years, new manifestations of immune reconstitution inflammatory syndrome (IRIS) are emerging [1]. In that contest, the role of CD8 cells is getting clearer. In fact, several studies have pointed out the relevant part of CD8 in the development of IRIS (e.g. PML-IRIS, TB-IRIS and herpes zoster-IRIS) [2–4].

Immune recovery folliculitis (IRF) is defined as the development of an inflammatory disorder of the facial pilo-sebaceous unit caused by cutaneous IRIS. The clinical picture of IRF resembles to that of acne vulgaris [5], which is a common cutaneous disorder characterized by the presence of papules, pustules, or nodules on the face, neck, trunk, or proximal upper extremities. Acne vulgaris is the effect of the interaction of multiple factors such as *Cutibacterium acnes* infection, a follicular hyperkeratinisation and an increased sebum production by sebaceous glands [6]. IRF seems to be related to the rapid reconstitution of T lymphocyte, with a relevant role of CD8 phenotype, against skin saprophyte bacteria (e.g. *Demodex folliculorum, Cutibacterium acnes*) [7,8].

Two cases of IRF are here reported. The first occurred in an ART-experienced patient after a therapy switch and the second one in an ART-naïve patient, right after ART initiation for an acute HIV infection. As far as we know, this is the firs reported case of IRF as a consequence of an ART switch in a virological suppressed subject with still a proper CD4 cells count.

## Cases presentation

### *Case report 1*

A 26-year-old Latin female was diagnosed with HIV-1 infection on July 2016, after 8 weeks of pregnancy. At the time of the diagnosis she was in charge to an Argentinian hospital; CD4 cells count was 1045

*Abbreviations:* IRF, Immune Recovery Folliculitis; IRIS, Immune Reconstitution Inflammatory Syndrome; HIV, Human Immunodeficiency Virus; ART, Antiretroviral Therapy; VL, Viral Load; CDC, Centers for Disease Control; TDF/FTC, Tenofovir disoproxil fumarate/Emtricitabine; LPV/r, Lopinavir/ritonavir; TAF/FTC, Tenofovir alafenamide fumarate/Emtricitabina; DRV/c, Darunavir/cobicistat; RAL, Raltegravir; E/C/F/TAF, Elvitegravir/cobicistat/Emtricitabina/Tenofovir alafenamide fumarate; BIC/F/TAF, Bictegravir/Emtricitabina/Tenofovir alafenamide fumarate

* Corresponding author.
*E-mail address:* marta.camici@inmi.it (M. Camici).

https://doi.org/10.1016/j.idcr.2021.e01324
2214-2509/

cells/μL and a viral load (VL) 1,620,000 cp/mL. ART with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) + lopinavir/ritonavir (LPV/r) was quickly initiated. On March 2018 she moved to Italy and, since then, she has been receiving treatment at our clinic. So, therapy was changed to tenofovir alafenamide fumarate/emtricitabina (TAF /FTC) + darunavir/cobicistat (DRV/c) to improve safety.

12 weeks after the switch, a pruritic papular-pustular facial eruption appeared, and she received clinical diagnosis of acne vulgaris. Molluscum contagiusum dermatitis were clinically excluded for the absence of typical lesions with shiny surface and central indentation or umbilication. Bacterial folliculitis was excluded for the localization of lesions, that moreover did not present the characteristic aspect of the pustule with the hair piercing the central part.

She was treated with oral doxycycline 100 mg daily plus a topical retinoid, once daily (at bedtime) for one month, without clinical improvement. Patient had emotional distress, given also that she did not recall previous history of acne vulgaris. Subsequently, oral contraceptive pills were started by the gynecologist and a reduction of skin lesions was observed with mood deflection appearance. Oral contraceptive was hence interrupted after three months, without the complete resolution of IRF. Considering immunological and virological parameters, when TAF/FTC + DRV/c was started, her CD4 cells count was 1151 cells/μL, CD8 was 630 cells/μL and CD4/CD8 was 1.82. 20 weeks after the ART simplification, CD8 cells count increased to 1006 cells/μL (+ 376 cells/μL) and ratio CD4/CD8 decreased to 1.00. 1 year after the ART switch, CD4 reached 1272 cells/μL (+ 121 cells/μL); CD8 961 cells/μL (+ 331 cells/μL) and CD4/CD8 1.32. The skin lesions slightly improved spontaneously after two years, without completely disappear.

*Case report 2*

A 24-year-old Caucasian man was diagnosed with acute HIV infection on February 2018. He was enrolled in a clinical trial studying the efficacy of a rapid 4-drug regimen with DRV/c+ raltegravir (RAL) +TDF/FTC in acute infection. At diagnostic time, CD4 cells count was 324 cells/μL, CD8 440 cells/μL, CD4/CD8 ratio 0.73 and VL 6889 cp/mL. Three weeks post ART, few facial comedones, papules and pustules appeared (Fig. 1).

At that time, immunological parameters revealed CD4 cells count of 635 cells/μL (+ 311 cells/μL), CD8 cells 827 cells/μL (+ 387 cells/μL), CD4/CD8 ratio 0.76. After 8 weeks, virological suppression was achieved and ART was simplified to elvitegravir/cobicistat/emtricitabina/tenofovir afenamide fumarate (E/C/F/TAF), after reviewing genotype, as for study procedure, with the persistence of skin lesions. The patient had a previous history of acne. Clinical diagnosis of acne vulgaris was made and treatment with topical retinoid once a day for 4 months plus oral doxycycline 100 mg daily during 40 days was started, with only a mild reduction of the lesions. Therefore, on June 2020 a skin biopsy was performed and IRF was histologically confirmed. In this period, CD4/CD8 ratio was 1.08 and decreased until 0.68 at December 2020.

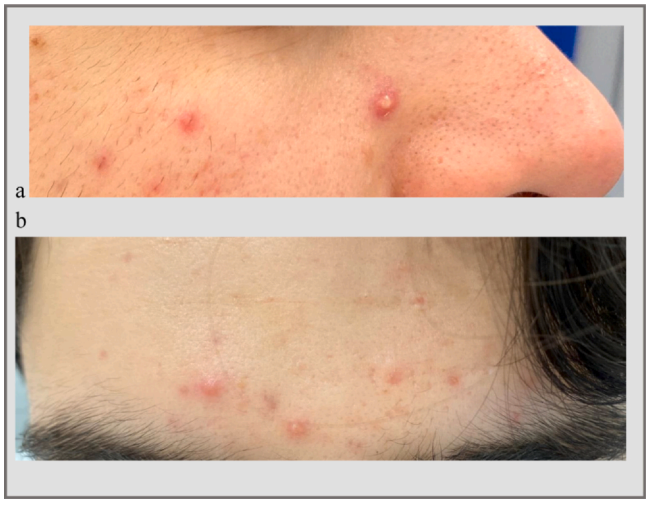


**Fig. 1.** Macroscopic lesions: facial pustules (a) and front papules (b). Macroscopic facial lesions appear similar to Acne vulgaris lesions.

The histological microscopic examination showed an epidermal infundibular cyst with peripheral ulcer, associated to an acute and chronic inflammatory infiltrates into the dermal layer (Fig. 2). The immune-phenotype study, revealed a large amount of T lymphocytes cells (CD3) with a majority of CD4 phenotype with respect to CD8 phenotype (Fig. 3).

In March 2020 ART was simplified to bictegravir/emtricitabina/tenofovir alafenamide fumarate (BIC/F/TAF), to reduce pills burden. 2 years later, the patient refers a spontaneous remission of the facial comedones.

## Discussion

Patient 1 is the first documented case of IRF occurred after a therapeutic switch in an ART-experienced person with good immune status and a stable virological suppression. She was diagnosed with acne vulgaris shortly after the ART switch from TDF/FTC + LPV/r to TAF/FTC + DRV/c. Patient 1 has been previously on ART for almost two years, with good efficacy and adherence. Interestingly, after the ART simplification, an absolute increase of CD8 lymphocyte was observed not followed by a CD4 increment. CD4/CD8 ratio decreased from 1.82 to 1.00 in 5 months. So, we suppose that IRF was driven by a CD8 lymphocyte upregulation. Interestingly, the patient did not recall a previous history of acne vulgaris, as formerly documented in most cases of IRF.

The second patient was enrolled in a clinical trial on rapid 4-drug regimen for acute HIV infection and DRV/c+RAL+TDF/FTC was started within 4 days of diagnosis. Soon after ART start, facial comedones, papules and pustules appeared. During that time, T lymphocyte cells count doubled with a stable CD4/CD8 ratio. VL at diagnosis was low and resulted undetectable within less than 8 weeks. In contrast with the previous one, he recalled a history of acne vulgaris during puberty.

In both of cases CD8 reconstitution was evident during lesions progression: in patient 1 CD4 reconstitution was poor, while, in patient 2 happened simultaneously with the CD8 immune reconstitution. Accordingly, skin biopsy documented T CD3 lymphocyte inflammatory with both CD4 and CD8 phenotypes (Fig. 3). Bacterial folliculitis and Molluscum contagiusum dermatitis were clinically excluded for both patients. According to our experience and to the limited literature data available, IRF is often self-limiting within few months. The effect of oral antibiotics combined with retinoid cream are controversial. In some cases, the cure was achieved with topical corticosteroid (betamethasone dipropionate, 0.05% cream) [5] or low-dose oral prednisone [2]. In our two clinical reports, dermatological lesions were only mitigated by the treatment. Indeed, patients with acne can experience significant psychological morbidity that may impact social lives and employment of the affected individuals.

The strength of our case report was the histological examination with the immuno-phenotype study. This showed the presence of inflammatory infiltrate within the epidermal layer. Further studies are needed to deeply understand the complex manifestations of IRIS and to define its treatment.

With the improvement of ART efficacy and the rapid immunological recovery, we are assisting to a rising incidence of atypical IRIS pictures, that can be misdiagnosed by clinicians [1]. The skin manifestations caused by IRIS should be ruled out, and considered in differential diagnosis from antiretroviral drug-related skin effects. IRF is defined as the development of inflammatory disorder

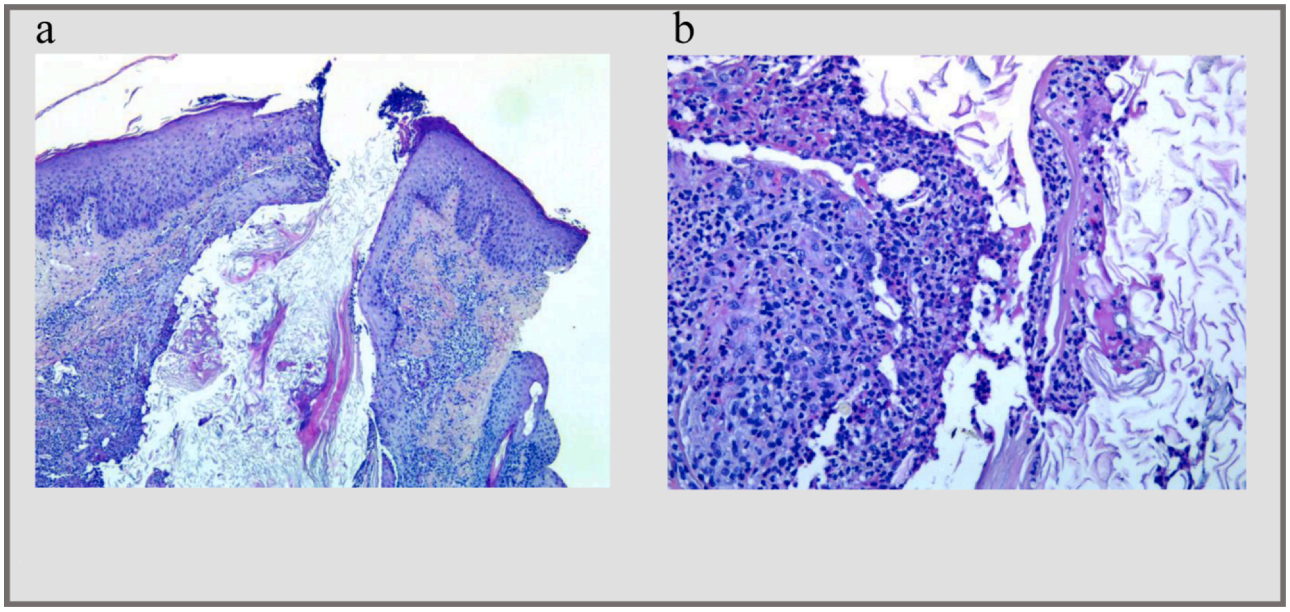


**Fig. 2.** Microscopic aspect of the facial pustule (a, b). Haematoxylin and eosin staining magnification. (a) Ruptured infundibular epidermal cyst, with severe acute and chronic inflammation, 5X. (b) Mixed inflammation, mostly composed by granulocyte cells, surrounding the epidermal cyst, 20X.

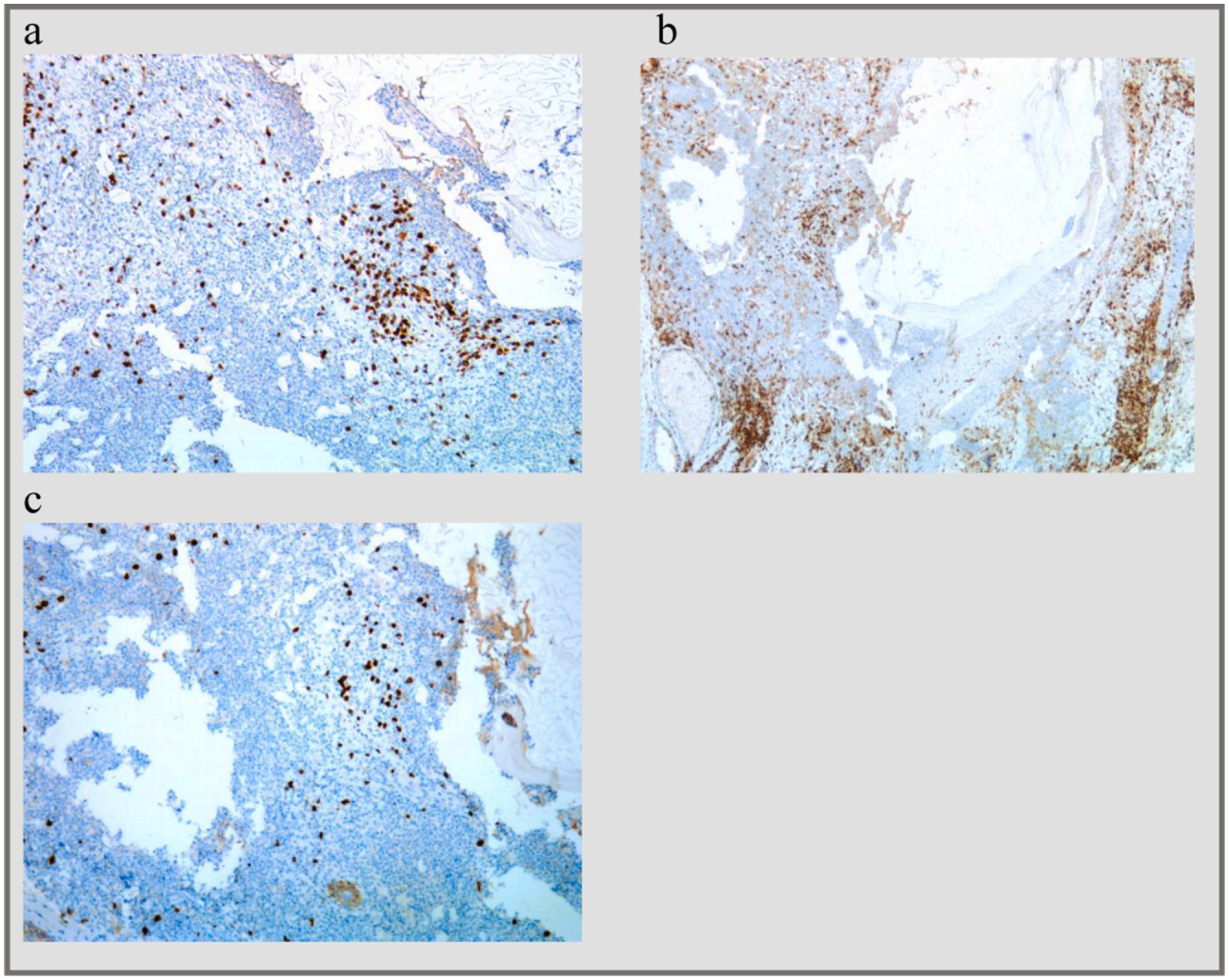


**Fig. 3.** Immunohistochemistry of the facial pustule. (a) A large amount of T CD3 lymphocyte cells, 10X (b) with a majority of T helper CD4 phenotype, 10X (c) with respect to T cytotoxic CD8 phenotype, 10X.

of the pilo-sebaceous unit due to the IRIS, in which CD8 reconstitution plays a key role. The first case report, reinforces the concept that an ART switch can modify the immunological balance of HIV-infected patients and could potentially trigger an IRIS, regardless of the viral load. Further studies are necessary on pathogenic, diagnostic and treatment of uncommon IRIS manifestations.

## Funding

No funding has been used for this work.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

The patients described in the case report gave their written consent to use their data. Written informed consent to publish this information was obtained from study participants. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Author contribution

MC and RG analyzed and interpreted the patient data regarding the occurrence of acne vulgaris-like lesions and the concomitant emergence of immunological CD3 lymphocyte reconstitution. AS performed the skin biopsy and the dermatological consultations for patient number 2, FDN and DC performed the histological examinations with the immunohistochemistry test and prepared the pictures of the skin tissue. MC was a major contributor in writing the manuscript. RG and AA revisited the draft. All authors read and approved the final manuscript.

## Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

## Competing interests

MC, AS, FDN, DC have not any potential competing interests. RG received speakers's honoraria from ViiV Healthcare, MSD and Gilead; grants for advisory board from ViiV Healthcare and Janssen. AA has served as a paid consultant to Gilead, Janssen, Merck, and ViiV Healthcare and received research funding from Gilead, Janssen, and ViiV Healthcare.

## Acknowledgements

Not applicable.

## References

[1] Nelson AM, Manabe YC, Lucas SB. Immune Reconstitution Inflammatory Syndrome (IRIS): what pathologists should know. Semin Diagn Pathol 2017;34(4):340–51. https://doi.org/10.1053/j.semdp.2017.04.010. Epub 2017 Apr 26. PMID: 28552210.

[2] Fearfield LA, Rowe A, Francis N, Bunker CB, Staughton RC. Itchy folliculitis and human immunodeficiency virus infection: clinicopathological and immunological features, pathogenesis and treatment. Br J Dermatol 1999;141(1):3–11. https://doi.org/10.1046/j.1365-2133.1999.02914.x

[3] Martin-Blondel G, Bauer J, Cuvinciuc V, Uro-Coste E, Debard A, Massip P, et al. In situ evidence of JC virus control by CD8+ T cells in PML-IRIS during HIV infection. Neurology 2013;81(11):964–70. https://doi.org/10.1212/WNL.0b013e3182a43e6d. Epub 2013 Aug 9. PMID: 23935178.

[4] Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. Am J Med 2001;110(8):605–9. https://doi.org/10.1016/s0002-9343(01)00703-3

[5] Bouscarat F, Maubec E, Matheron S, Descamps V. Immune recovery inflammatory folliculitis. AIDS 2000;14(5):617–8. https://doi.org/10.1097/00002030-200003310-00019

[6] Bojar RA, Holland KT. Acne and propionibacterium acnes. Clin Dermatol 2004;22(5):375–9. https://doi.org/10.1016/j.clindermatol.2004.03.005. PMID: 15556721.Scott C et al. International journal of STD & AIDS 2008.

[7] Kreuter A, Schlottmann R, Altmeyer P, Brockmeyer NH. Acne vulgaris as an immune reconstitution syndrome in a patient with AIDS after initiation of antiretroviral therapy. J Eur Acad Dermatol Venereol 2002;16(6):638. https://doi.org/10.1046/j.1468-3083.2002.00653_1.x

[8] Goovaerts O, Massinga-Loembé M, Ondoa P, Ceulemans A, Worodria W, Mayanja-Kizza H, et al. TB-IRIS Study Group. Increased KLRG1 and PD-1 expression on CD8 T lymphocytes in TB-IRIS. PLoS One 2019;14(4):e0215991https://doi.org/10.1371/journal.pone.0215991