Eosinophilic Folliculitis

Before and After the Introduction of Antiretroviral Therapy

Priya M. Rajendran, BS; Jacqueline C. Dolev, MD; Michael R. Heaphy, Jr, MD; Toby Maurer, MD

Objective: To characterize the relationship of new eosinophilic folliculitis (EF) cases between June 30, 1994, and January 5, 2000, and antiretroviral therapy (ART) status and immune reconstitution.

Design: Retrospective cohort analysis.

Setting: Dermatology clinics at a county hospital.

Subjects: Fifty-seven consecutive subjects with biopsy-proved EF from the pathology database. Subject groups were as follows: naïve to ART, receiving ART without protease inhibitors/nucleoside reverse transcriptase inhibitors, and receiving ART containing protease inhibitors/nucleoside reverse transcriptase inhibitors.

Main Outcome Measures: Onset of EF, CD4 cell count and nadir at EF onset, and time of ART initiation.

Results: Among the 3 groups previously described, mean CD4 cell counts (86.26/µL vs 113.82/µL vs 145.65/µL, respectively [Kruskal-Wallis rank sum test, \( P = .15 \)]) and nadir (68.43/µL vs 66.18/µL vs 64.17/µL, respectively [Kruskal-Wallis rank sum test, \( P = .41 \)]) at EF diagnosis were not statistically different. Fifty-two subjects (91%), regardless of treatment group, had a nadir below 200/µL. Of the subjects undergoing ART, 28 (82%) developed EF within 6 months of initiating ART; their average CD4 cell count increase was 108/µL. Of the 23 subjects receiving protease inhibitor/nucleoside reverse transcriptase inhibitor–containing ART regimens, 17 (74%) were diagnosed as having EF within 3 months, with 4 additional subjects diagnosed as having EF within 6 months (a total of 21 [91%] of the 23 subjects). This is not significantly different from the 7 (64%) of 11 subjects diagnosed as having EF at 3 and 6 months of starting ART without protease inhibitors/nucleoside reverse transcriptase inhibitors (\( P = .07 \)) (odds ratio, 0.18; 95% confidence interval, 0.01-1.54).

Conclusions: Our study shows an association between low nadir (66.28/µL) and low CD4 cell count (115.54/µL) and the development of EF, regardless of subjects’ ART status. However, most subjects receiving ART were diagnosed as having EF within 3 to 6 months of ART initiation, regardless of the regimen.

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Human immunodeficiency virus (HIV)–associated eosinophilic folliculitis (EF) classically presents as recurrent, pruritic, erythematous, or urticarial follicular papules located on the upper body (Figure 1). Eosinophilic folliculitis develops in the setting of abnormal host immunity, in individuals with late-stage HIV, and/or in those with CD4 cell counts lower than 300/µL. This has been documented in case reports and in a previous study that described 10 of 12 subjects with CD4 cell counts lower than 250/µL. EF may be a marker for subjects who have a high risk of developing opportunistic infections. It has been anecdotally observed that during the initial phases of immune reconstitution with antiretroviral therapy (ART), there is a flare of EF. This phenomenon of immune restoration diseases, occurring after the initiation of ART, has been noted in the first 2 to 6 months of therapy. Paradoxically, case reports and anecdotal evidence have suggested that ART, by reconstituting the immune system to a CD4 cell count of greater than 250/µL, has resulted in improvement of EF. Apart from ART, multiple treatment modalities have been recommended for EF, although, to our knowledge there are no studies to support a gold standard of treatment. Treatments have included topical corticosteroids, antihistamines, clotrimazole, metronidazole, oral retinoids, and UV light therapy. In clinical practice, if immune reconstitution is implicated in the development of EF lesions, subjects are given these medications for an 8- to 12-week period while immune restoration stabilizes.

This study will examine the onset of EF after the initiation of ART, the CD4
We also describe the different modalities of treatment and the frequency of their use.

METHODS

This is a retrospective medical record review describing subjects diagnosed as having EF before and after protease inhibitors (PIs)/nonnucleoside reverse transcriptase inhibitors (NNRTIs) were introduced into clinical practice. We chose June 30, 1996, to reflect the time when PIs were standardly used in ART regimens. By using the San Francisco General Hospital, San Francisco, Calif, pathology database, we identified the first 30 subjects with biopsy-proved diagnoses of EF on and before June 30, 1996, and the first 30 subjects after June 30, 1996. Our dates included EF cases between June 30, 1994, and January 5, 2000. A total of 7 cases, 1 from each study year, were randomly selected and reviewed by a dermatopathologist (M.R.H.) to confirm the EF diagnosis (Figure 2 and Figure 3). We then defined the following groups: naïve subjects (those not receiving any form of ART), subjects receiving ART without PIs/NNRTIs, and subjects receiving ART containing PIs/NNRTIs. We obtained demographic and immunologic laboratory data and treatment choices from patient records. We specifically obtained the following information: date of onset of EF lesions (defined as the first date of appearance of a lesion identified by a physician, then confirmed by a dermatologist and examined by biopsy); date of initiation of any antiretroviral regimen; nadir before onset of disease; closest CD4 cell count available before, on, or after the date of EF onset; EF treatments; compliance with therapy; and clinical outcome. We defined nadir as the lowest CD4 cell count before the onset of EF, and current CD4 cell count as the closest CD4 cell count reported within 80 days of EF onset. Two subjects with limited clinical data available and 1 patient who was not HIV infected were excluded from analysis. We used univariate analysis to describe demographic characteristics and treatments. We used \( t \), Wilcoxon rank sum, and Kruskal-Wallis tests to analyze differences in CD4 cell count, nadir, and treatments. Immune reconstitution was defined as 3 to 6 months after the initiation of ART.

RESULTS

Of the total 60 subjects identified, 57 were eligible for analysis. The following demographics were noted: 51 (89%) were men, and 6 (11%) were women; and 14 (25%) were African American, 30 (53%) were white, 8 (14%) were Latin American, and 5 (9%) were Asian or Pacific Islander (percentages do not total 100 because of rounding). These demographics reflected the general HIV outpatient population at San Francisco General
Hospital from January 1, 2002, to December 31, 2003: 79% were men and 21% were women; and 31% were African American, 48% were white, 15% were Latin American, and 5% were Asian (percentages do not total 100 because of rounding). All subjects in our study were diagnosed as having HIV before developing EF.

Thirty-four (60%) of the 57 subjects were receiving ART: 11 (32%) were receiving regimens without PIs/NNRTIs, and 23 (68%) were receiving PI/NNRTI-containing regimens. Of the 23 subjects taking PI/NNRTI-containing ART regimens, 17 (74%) were diagnosed as having EF within 3 months and 21 (91%) were diagnosed as having EF within 6 months of starting therapy. Of the 11 subjects receiving ART regimens without PIs/NNRTIs, 7 (64%) were diagnosed as having EF within 3 and 6 months of starting ART. There was no significant difference between the ART without PIs/NNRTIs group and the ART with PIs/NNRTIs group in the percentage of subjects diagnosed as having EF within 3 and 6 months of ART initiation ($P = .69$ [odds ratio, 0.63; 95% confidence interval, 0.10-4.0] and $P = .07$ [95% confidence interval, 0.01-1.54], respectively). The antiretroviral treatment groups had a higher CD4 cell count increase than the naïve group. The CD4 cell count increase, measured from nadir to 3 months and from nadir to 6 months after the diagnosis of EF, was higher in the ART-treated groups compared with the naïve group (89.78/µL vs 48.08/µL [Wilcoxon rank sum test, $P = .04$] [95% confidence interval for difference in the rise between groups at 3 months, 88.0 to 1.0] and 107.53/µL vs 2.07/µL [Wilcoxon rank sum test, $P = .01$] [95% confidence interval for difference in the rise between groups at 6 months, 181.0 to 11.0, respectively]). The mean CD4 cell count at EF diagnosis for all cases included in the study was 115.54/µL. The mean nadir before EF diagnosis was 66.28/µL. There was no statistically significant difference in the mean CD4 cell count at diagnosis between the 3 groups (86.26/µL vs 113.82/µL vs 145.65/µL for the naïve group vs the ART without PIs/NNRTIs vs the ART with PIs/NNRTIs group, respectively; Kruskal-Wallis test, $P = .15$), although a trend was observed. There was also no significant difference in nadir before diagnosis (68.43/µL vs 66.18/µL vs 64.17/µL for the 3 described groups, respectively; Kruskal-Wallis test, $P = .41$). Of the 57 subjects, 52 (91%), regardless of treatment group, had a nadir below 200/µL.

Irrespective of treatment groups, the same treatment algorithms were used. The topical treatments used included topical corticosteroids (n = 43) and permethrin (n = 22). The oral agents used, listed from most frequent to least frequent, include antihistamine (n = 36), itraconazole (n = 16), and indomethacin (n = 2). Three patients received UV-B therapy, and none received psoralen–UV-A therapy. The frequency of use of these treatments did not differ by ART status ($P = .77$, $P = .72$, $P = .16$, $P = .66$, $P = .33$, and $P = .38$, respectively).

To our knowledge, this study is the first to document EF as part of ART-associated immune reconstitution. We found a close association between the initiation of ART and the onset of EF. Clinicians should be aware that subjects who are about to initiate ART, regardless of regimen, may develop EF during the 3- to 6-month period after initiating ART. This places EF into a family of other diseases that have been reported during ART-associated immune reconstitution; these include herpesviruses, cytomegalovirus, mycobacteria, cryptococci, inflamed cutaneous warts, molluscum contagiosum, and sarcoidosis.8-10,24-34 These paradoxical flares do not indicate a failure of ART but rather are complications of a rejuvenile immune response with increased levels of circulating immune cells and accessibility of immune cells to sites of infection.35,36

There was a trend, although not statistically significant, of increasing CD4 cell count at EF onset by group, suggesting that subjects receiving ART develop EF at increasing CD4 cell counts. However, even with this increasing trend, the CD4 cell count at EF diagnosis was still below 200/µL. The nadir before EF onset was not different among the 3 groups, and most subjects had nadirs well below 200/µL. Previous studies37-39 suggest that CD4 cell count nadir plays a significant role in long-term immunologic recovery, and that the degree of damage may be different in those subjects with low nadirs. Thus, a low CD4 cell count and a low nadir seem to be important determinants in the development of EF, regardless of ART status. Previous studies40-42 have outlined the importance of CD4 cell counts in the onset of cutaneous manifestations of HIV. Although there may be differences in CD4 cell counts at EF onset between groups with different ART status, subjects still developed EF at low CD4 cell counts (<200/µL).

Moreover, ART alone may not be sufficient to cause EF. In the period studied (June 30, 1994, through January 5, 2000), the recommendation was to initiate ART in patients with CD4 cell counts of less than 500/µL.43-48 Although historically patients with higher CD4 cell counts (>200/µL) were receiving ART during this time, most of our subjects receiving ART had low CD4 cell counts and nadirs (<200/µL for both), further highlighting that EF development after ART initiation may be dependent on concomitant low CD4 cell counts.

We analyzed CD4 cell counts from nadir to 3 months after therapy, showing that the subjects were indeed responding to their ART. As expected, both treatment groups had a higher increase than the naïve group.49-51 The level of increase in CD4 cell count in response to treatment with ART is consistent with levels reported in previous literature.52,53 In some disease processes, such as oral candidiasis and Kaposi sarcoma, PIs/NNRTIs are thought to have a beneficial effect independent of their increase in CD4 cell count.53-57 However, our study subjects receiving PI/NNRTI-containing regimens still developed EF at the same frequency as those receiving non-PI/NNRTI-containing regimens, suggesting that PIs/NNRTIs do not have any independent protective effects against EF.

Paradoxically, although we demonstrate that the onset of EF is associated with initiation of ART, EF has been thought to respond favorably to treatment with antiretroviral regimens.54 When ART gradually restores the T lymphocytes depleted by HIV infection, it may also re-
store the T helper cell 1 response, accounting for anecdotal reports of improvement of EF with ART. Moreover, treatments that were previously unsuccessful, such as metronidazole, may become effective. A prospective study documenting treatment outcomes would be needed to provide conclusive information on the effectiveness of ART in the treatment of EF.

The onset of EF was previously associated with male sex. In 1996, the first cases of women with HIV-associated EF were reported. Since then, a total of 6 female subjects with EF have been described in the literature. Hayes et al point out that EF is not a disease found solely in homosexual men with AIDS, and our data support this, with an additional 6 cases of women observed. Physicians should be careful not to overlook the diagnostic possibility of EF in women. Although there have been reports of EF as a presenting feature of HIV, all of our 57 patients investigated had been diagnosed as having HIV before EF diagnosis.

Accepted for Publication: May 17, 2005. Correspondence: Toby Maurer, MD, Department of Dermatology, University of California, San Francisco, 1001 Potrero Ave, Bldg 90, Ward 92, San Francisco, CA 94110 (tmaurer@itsa.ucsf.edu). Author Contributions: Study concept and design: Rajendran, Dolev, and Maurer. Acquisition of data: Rajendran and Heaphy. Analysis and interpretation of data: Rajendran, Dolev, Heaphy, and Maurer. Drafting of the manuscript: Rajendran. Critical revision of the manuscript for important intellectual content: Rajendran, Dolev, Heaphy, and Maurer. Statistical analysis: Rajendran, Dolev, and Maurer. Administrative, technical, and material support: Dolev and Maurer. Study supervision: Maurer. Financial Disclosure: None. Funding/Support: This study was supported by the University of California, San Francisco, School of Medicine Dean’s Fund for Research; and the Doris Duke Charitable Foundation, New York, NY. Disclaimer: All authors had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Acknowledgment: We thank Ru-Fang Yeh, PhD, Department of Biostatistics, University of California, San Francisco, for her statistical contribution.

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