Eosinophilia in Patients Infected with Human Immunodeficiency Virus

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Patients infected with human immunodeficiency virus (HIV) frequently are said to have eosinophilia. To evaluate this assumption, the differential blood cell counts of 855 HIV-infected patients were examined over 4 years. All differential cell lines in the HIV-infected population were less than those in a noninfected control group, but the difference was much less pronounced for eosinophils than for the other blood cell components. For HIV-infected patients, the eosinophil count increased and the other blood cell components decreased as the CD4 cell count decreased. The increase in eosinophils was the result of eosinophilia in a subgroup of patients and a preservation of that cell line for the other patients. No etiologic agent was associated with eosinophilia; hence, HIV infection itself may induce proliferation of eosinophils while other cell components are declining.

Eosinophilia has been described in patients with AIDS [1–5]. Most of these descriptions have been case reports concerning patients with eosinophilic pustular folliculitis, and therefore the frequency and true prevalence of this finding is unclear. Smith et al. [5] described a patient population with an increase in the percent eosinophils that positively correlated with an increasing stage (Walter Reed stages) of illness; however, they did not indicate if this represented an increase in the absolute eosinophil count.

The purposes of this investigation were to determine if eosinophilia was more prevalent in human immunodeficiency virus (HIV)–infected patients than in noninfected controls, how eosinophil counts of an HIV-infected population with lower CD4 cell counts compared with those of a group with higher CD4 cell counts, how the eosinophil counts compared with those of other complete blood cell count (CBC) components, and what the clinical characteristics were of those patients who presented with eosinophilic episodes.

Materials and Methods

The study was retrospective and involved patients seen at the University Medical Center at Stony Brook. Pertinent information was taken from a computer database containing CBC data collected from 855 HIV-infected patients seen from 1 January 1990 to 31 December 1993 and from 2988 control patients seen between 1 January 1991 and 31 December 1991 [6]. The control population consisted of patients who were not known to be HIV infected. The prevalence of HIV infection in the study area is <1:1000; therefore, it is estimated that very few, if any, members of the control group had HIV infection. All specimens were analyzed within 3 h of being collected. Percentages of eosinophils, neutrophils, lymphocytes, basophils, and monocytes were derived from the database. Absolute counts of each cell type were calculated. De-
Results

The normal eosinophil count is generally considered to be <400/μL [1]. The proportion of patients with eosinophilia is dependent on the definition of eosinophilia used: At a threshold of 1500 eosinophils/μL, 2.5% (24/855) of our HIV-infected population had episodes of eosinophilia, compared with 0.7% (21/2988) of the control population. At a threshold of 1000 eosinophils/μL, 5.5% (47/855) of the HIV-infected population and 2.1% (64/2988) of the control population had eosinophilic episodes. In both instances, the difference between the 2 groups was significant ($\chi^2$, $P < .001$ in both cases). These rates correspond to those for 1991 for the control population and for 1990–1993 for the HIV-infected population. The corresponding 1991 rates for the HIV-infected population were almost identical to the 4-year rates.

The HIV-infected patients were, on average, tested more frequently over a longer period of time than were controls (13.5 measurements over 286 days vs. 3.3 measurements over 21 days, respectively; $P < .001$ for differences between measurements and days in both cases). This probably occurred because the HIV-infected population was sicker and, hence, had CBCs done more often. To determine if this was responsible for the different prevalences of eosinophilia among the HIV and the control groups, the control patients were case matched with HIV-infected patients such that each group averaged 4.3 measurements over 65 days ($n = 400$). When compared in this manner, 1.5% of HIV-infected patients versus 1.0% of controls had eosinophilic episodes at a threshold of 1500 cells/μL, and 2.75% of HIV-infected versus 3.0% of control subjects had eosinophilic episodes at a threshold of 1000 cells/μL (no significant difference in any case). Similar values were obtained when the patients were matched for only the number of measurements or for only the period of time. Hence, it is possible that the increased number of episodes of eosinophilia in the HIV patients was partly related to their increased number of measurements and the severity of their illnesses.

However, the percentage of eosinophils in the HIV-infected group was 1.5 times higher than that in the matched control group. The absolute mean number of eosinophils in the HIV-infected group was 77% of that of the control group, while the absolute mean numbers of granulocytes and lymphocytes were 44% and 52% of those for the control group, respectively, and the absolute mean white blood cell count for the HIV group was 48% of that for the control group. Hence, there was at least a relative preservation of eosinophils in the HIV-infected population compared with other CBC components (table 1, left columns).

Figure 1. Average absolute granulocyte, lymphocyte, and eosinophil count distributions of HIV-infected patients in relation to CD4 cell counts of ≤200 and >200 cells/μL. $n = 92$ in each group.
Complete blood cell count

Table 1. Average values for differential blood cell counts in HIV-infected and control populations.

<table>
<thead>
<tr>
<th>Component</th>
<th>Case-matched patients</th>
<th>Case-matched HIV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-infected (n = 400)</td>
<td>Control (n = 400)</td>
</tr>
<tr>
<td>Granulocytes/μL</td>
<td>3315 (3064–3565)</td>
<td>7495* (7110–7881)</td>
</tr>
<tr>
<td>Lymphocytes/μL</td>
<td>1167 (1048–1285)</td>
<td>2251* (1900–2136)</td>
</tr>
<tr>
<td>Eosinophils/μL</td>
<td>123 (101–144)</td>
<td>159* (144–174)</td>
</tr>
<tr>
<td>% eosinophils</td>
<td>2.7 (2.2–3.1)</td>
<td>1.8* (1.6–1.9)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>5.0 (4.7–5.3)</td>
<td>10.4* (9.7–11.1)</td>
</tr>
</tbody>
</table>

**NOTE.** Ranges in parentheses are 95% confidence intervals. P derived using t test.
* P < .001, † = .03, ‡ = .02, § < .01.

The relationship between eosinophilia and CD4 cell count and, by implication, progression of disease was investigated next. A CD4 cell count of 200 cells/μL was used as a predetermined break point to divide patients into subgroups. Using a threshold of 1500 cells/μL, there were 5 patients with eosinophilic episodes among those with ≤200 CD4 cells/μL and no patients with episodes among those with >200 CD4 cells/μL (n = 223). At a 1000 cells/μL threshold, there were 14 and 0 episodes among the 2 groups, respectively.

Most striking was a decrease in each CBC cell component, except for eosinophils, as the CD4 cell count declined to ≤200 cells/μL. However, as with the comparison between the control and HIV-infected populations, there were different numbers of measurements between the 2 groups (2.6 measurements over 97 days for the high CD4 cell count group; 9.8 measurements over 184 days for the low CD4 cell count group).

The groups were matched as before, and 92 patients were culled from each group (6.2 measurements over 92 days for the lower CD4 cell count group; 6.2 measurements over 100 days for the higher CD4 cell count group). The frequency of eosinophilic episodes for the 2 subgroups was similar to that for the unmatched groups, with a greater number of episodes of eosinophilia in those with ≤200 CD4 cells/μL. No patient from the higher CD4 cell count subgroup had eosinophilic episodes at either threshold. The absolute mean eosinophil count was 62% higher (P < .01) in patients with ≤200 CD4 cells/μL than in those with >200 CD4 cells/μL. In contrast, the other CBC components were significantly lower in the group with ≤200 CD4 cells/μL. The mean absolute lymphocyte and granulocyte counts were 59% and 81%, respectively, of those in the higher CD4 cell count group (table 1, right columns).

For all CBC components except eosinophils, the decrease in mean absolute counts was due to a downward population shift for the group of patients with ≤200 CD4 cells/μL (figure 1). In sharp contrast, there was no population shift to fewer eosinophils at lower CD4 cell counts; hence, the eosinophils were preserved as other cell components declined.

To examine for possible associations with eosinophilia, we reviewed 24 randomly selected charts of HIV-infected patients who had had eosinophilic episodes and 20 patients without eosinophilia but with similarly low CD4 cell counts. The review revealed that eosinophilia was associated with the proximate initiation of drugs in 2 patients (neupogen and dilantin, 1 case each) or illness (possibly adrenal insufficiency) in 1; however, in 19 of 22 cases, no cause could be found. There was no difference between those with eosinophilia and CD4 cell counts >200 cells/μL and those with eosinophilia and CD4 cell counts ≤200 cells/μL.

The relationship between eosinophilia and CD4 cell count was assessed using a linear regression model, which showed that eosinophilia increased as CD4 cell counts declined. The relationship was significant for eosinophils, granulocytes, and lymphocytes, but not for eosinophils.

Discussion

Eosinophils are bilobed granule-containing cells that circulate in the blood with a half-life of ~18 h on the way to their primary site in tissue. Eosinophilopoiesis is controlled by T cells and T cell products, as initially shown by Beeson and Bass [7]. Eosinophilia is associated with infections, particularly those caused by helminths, allergic reactions to many stimuli (including inhaled material, drugs, and foods), neoplasms, and skin diseases. Since it has been suggested that HIV infection is associated with eosinophilia and since the infection causes dysfunction of T lymphocytes, we determined the prevalence of eosinophilia in our HIV-infected patient population and examined its relation to CD4 cell counts and other cell CBC components and attempted to identify characteristics that are associated with eosinophilia in this population.

We found a preservation of eosinophils, in contrast to the loss of other cell components, and a trend toward an absolute increase in eosinophils in our HIV-infected patients. These findings were still observed when we controlled for the greater number of measurements made in the HIV groups compared with the control population. In addition, we observed an increase in eosinophilia as the patients’ CD4 cell counts declined to <200 cells/μL, a point at which the number of polymorpho-
nuclear leukocytes and lymphocytes was decreasing. The increase in eosinophils observed in the entire group of patients was accompanied by markedly elevated eosinophil counts in a subgroup.

Eosinophil development and differentiation is controlled by at least three T cell–derived cytokines [8]: Granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-3 stimulate the development of eosinophils, while IL-5 promotes the development and terminal differentiation of eosinophils. IL-5 and GM-CSF are products of the Th2 subset of T lymphocytes, while IL-3 is produced by both Th1 and Th2 cells. T cells with a Th2 profile of cytokine production are found in association with allergic reactions, and elevated levels of IL-5 have been detected in blood of patients with eosinophilia of various etiologies [9], with idiopathic hypereosinophilia syndrome [10], and with infections caused by helminths [11].

We did not find any consistent condition in our patient population that could explain the eosinophilia or the increase in eosinophilia among those with lower CD4 cell counts. The observations and the suggestion that with advancing HIV disease there is shift from a predominantly Th1 response (with production of IL-2 and interferon-γ) to a Th2 type of response (with production of IL-4 and IL-5) may be relevant to the increase in eosinophils in advancing HIV disease. On the basis of data from murine models of AIDS and HIV-infected patients, Clerici and colleagues [12, 13] have suggested that with progression to AIDS there is a shift from a Th1 to Th2 response upon antigenic stimulation. The shift in cytokine profile need not be from one clone of cells to another but by the same subset of cells with differing cytokine production, depending upon the type of stimulus they encounter. Therefore, it is possible that with advancing HIV-induced immunologic dysfunction or phenotypically changing HIV there is a greater stimulus to production of Th2-associated cytokines, including IL-4 and IL-5, and a decrease in production of IL-2 and interferon-γ. A consequence of this would be eosinophilia, as described in this report.

Eosinophils can secrete many regulatory factors, including lipid mediators, proteases, products of the oxygen burst, and cytokines (IL-1, GM-CSF, IL-3, IL-5, IL-6, transforming growth factor-α [TGF-α], TGF-β, and IL-8). These products of eosinophils are toxic to a number of cells, including respiratory epithelial cells, myocardial cells, and neuronal cells. Furthermore, IL-5, in addition to its role in maturation and differentiation of eosinophils, stimulates eosinophil functions, including cytotoxicity [14]. Hence, eosinophils may not only be a consequence of progressive HIV infection but may also contribute to AIDS pathogenesis, as has been suggested by Harris [15].

References