B-Cell Lymphoma Associated With Eosinophilia

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B-Cell Lymphoma Associated With Eosinophilia

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A case of non-Hodgkin's lymphoma associated with eosinophilia is reported. The lymphoma was of the diffuse, large-cell type and was of B-cell origin. The number of eosinophils decreased with combination chemotherapy, along with a reduction in the size of the lymph nodes. Eosinophilia reappeared with the regrowth of lymphoma. The relationship between B-cell lymphoma and eosinophilia is discussed.
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IT HAS BEEN SHOWN that malignant diseases,[1] including lymphoma, are occasionally associated with eosinophilia. Hodgkin's disease is known to present with eosinophilia.[2–4] Recently, non-Hodgkin's lymphoma with eosinophilia has been reported, with all of the cases being T-cell lymphoma.[5–9] We report a case of malignant lymphoma of B-cell origin with eosinophilia.

Case Report

A 53-year-old man was admitted to our hospital with swelling of the cervical lymph nodes of 3 months duration. There were no B symptoms. The patient's medical history included cholecystomy and viral hepatitis 3 years before admission. A physical examination showed swelling of the lymph nodes in the Waldeyer's ring, bilateral cervical chains, bilateral axillae, and left inguinal region. The lungs were clear and the heart was normal. No organomegaly or masses were palpated. Laboratory data showed mild leukocytosis (10,900/μl) with eosinophilia (3500/μl). The eosinophils appeared normal morphologically.

The hematocrit was 44.5% and the platelet count was 342,000/μl. The chemistries were within normal ranges. A bone marrow aspirate showed increased numbers of eosinophils (17.2%), but no evidence of leukemia or lymphoma infiltration. The immunoglobulin (Ig) A, M, and G levels were normal. However, the IgE level was slightly increased (341 ng/dl) once, but was persistently normal later. Both anti-human T-cell lymphotrophic virus type I (HTLV-I) antibody and anti-human immunodeficiency virus (HIV) antibody were negative. Abdominal ultrasonography, computed tomography, lymphangiography, and a gallium scan showed paraaortic lymphadenopathy.

Exhaustive studies to identify the cause of the eosinophilia were undertaken with negative results.

The lymph node biopsy specimen showed effacement of normal lymph node architecture and proliferation of large, atypical mononuclear cells with multiple nucleoli (Fig. 1). There was no invasion of eosinophils. Immunohistochemical studies showed that the tumor cells were stained with CD20, CD22 (Fig. 2), HLA-DR (Becton Dickinson, Sunnyvale, CA), LN1, LN2 (Techniclone Int., Santa Ana, CA), and Ig heavy chain μ and light chain κ (Dakopatts, Copenhagen, Denmark). They were not stained with CD3, CD4, CD8, or CD21 (Becton Dickinson). This indicates that the tumor cells were of B-cell origin.

The patient was treated with methotrexate, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B).[10] An absolute count of eosinophils disappeared as soon as the treatment was started. At the completion of chemotherapy, the cervical lymph nodes had disappeared completely but the paraaortic lymph nodes still remained, although they were greatly reduced in size. Two months later, the patient complained of abdominal fullness. Abdominal sonography disclosed further enlargement of the paraaortic lymph nodes. The laboratory data again showed marked eosinophilia (5000/μl). Combination chemotherapy with cyclophosphamide, Adriamycin (Adria Laboratories), prednisone, vincristine, and etoposide (VP-16) was started, with reduction of the eosinophil counts (0/μl). Three months later, the patient experienced a relapse with hilar and abdominal paraaortic lymphadenopathy. The eosinophil count was elevated to 6400/μl. The patient received cisplatin (CDDP), VP-16, and prednisone, with a decrease in the eosinophil count. However, the patient's disease did not go into remission thereafter. He died of pneumonia 3 months later. Figure 3 shows the entire clinical course. At autopsy, there were a few large lymph nodes ranging from 2 to 5 cm along the abdominal aorta. There was a slight invasion of lymphoma cells into the liver and spleen. There was no eosinophil infiltration into the lymph nodes or the visceral organs.

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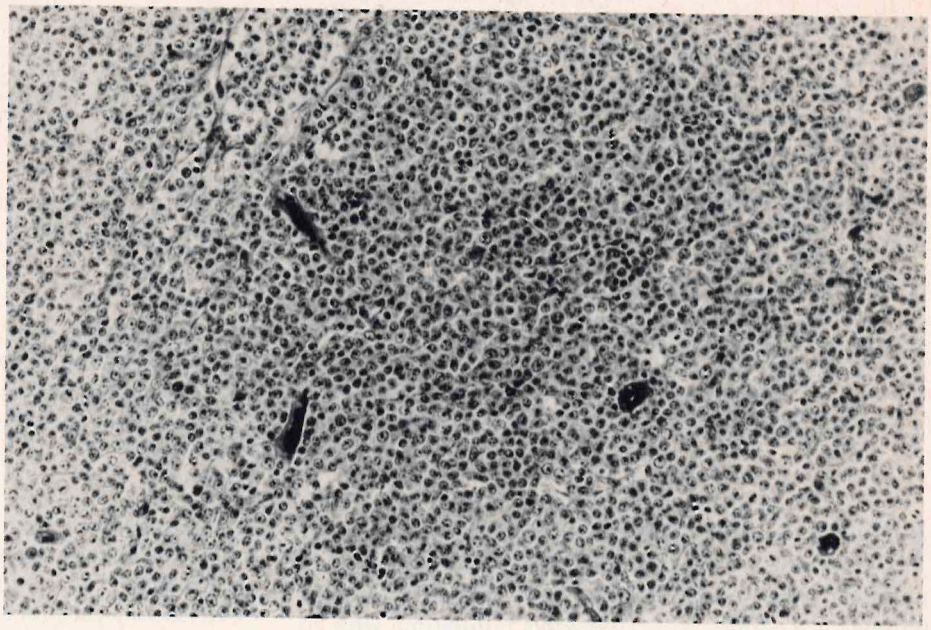

FIG. 1. Histologic features of the inguinal lymph node. Large, noncleaved cells were diffusely occupied with round to oval nuclei and multiple nucleoli (H & E, ×200).

Discussion

Eosinophilia is known to associate with a variety of diseases including allergic diseases, parasitic infestations, skin diseases, hypereosinophilic syndrome, topical eosinophilia, and malignant diseases,[1] especially with tumor necrosis[11] or dissemination.[12] The mechanism of eosinophilia remains obscure.

Isaacson and Rapoport[11] reported that 0.5% of cases of all types of malignancy exhibited eosinophilia. Hodgkin's disease is known to be associated with eosinophilia among lymphomas.[2–4] In recent years, some investigators have described the presence of eosinophilia in non-Hodgkin's lymphomas.[5–9] Immunohistologic examinations showed that all of the cases were T-cell lymphomas. In the current case, the tumor cells were stained with CD20, CD22, LN1, LN2, and IgM(κ). Therefore, this lymphoma originated from B-cells. To our knowledge, there is no previous report

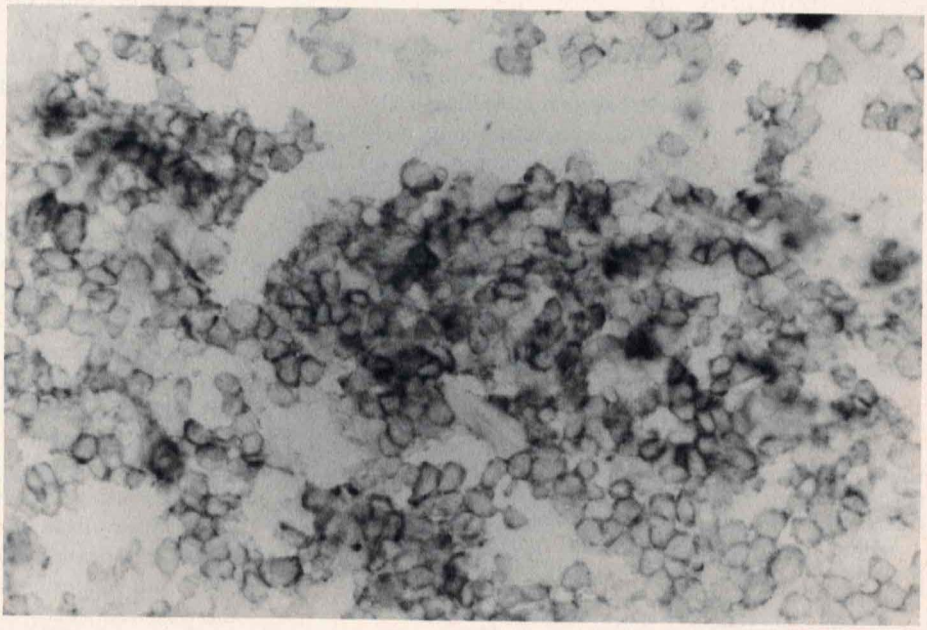

FIG. 2. Immunoperoxidase staining for Leu-14 (CD22) showing intense membrane staining of atypical lymphocytes (×400).

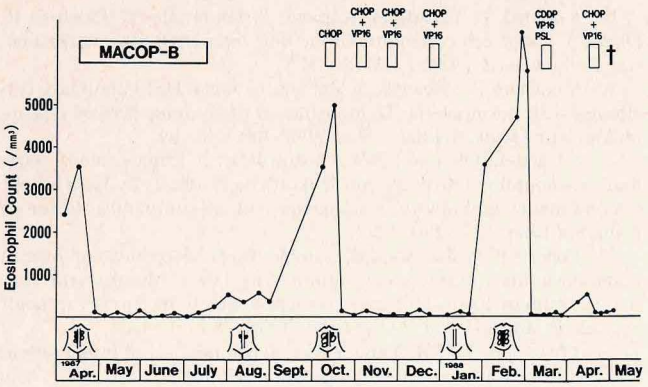

FIG. 3. Clinical course.

of B-cell lymphoma with eosinophils, although a case of lymphoma and eosinophilia reported by Reddy *et al.*[13] was thought to be of B-cell origin (nodular histocytic lymphoma).

In our case, eosinophilia served as a marker of the disease activity and eosinophil counts were correlated with the size of the paraaortic lymph nodes. Although extensive investigations were made, there was no evidence of any other causes of eosinophilia. In our case, eosinophilia may have been due to lymphoma.

One can postulate the following: (1) that lymphoma cells can produce and secrete a humoral eosinophil chemotactic factor; (2) that normal T-lymphocytes activated by tumor antigen, regional inflammation, or tumor necrosis produce and secrete a humoral eosinophil colony-stimulating factor; and (3) that the lymphoma cells produce and secrete a humoral factor that acts on the bone marrow to stimulate and promote differentiation of the eosinophil precursors.

Wassermann *et al.*[14] extracted a peptide, preferentially chemotactic for eosinophils, from a large-cell anaplastic carcinoma of the lung. This peptide was indistinguishable from the eosinophil chemotactic factor of anaphylaxis (ECF-A).

Goetzl *et al.*[15,16] demonstrated eosinophil chemotactic substances and demonstrated that they were different from ECF-A.

Basten *et al.*[17,18] showed that *Trichinella*-induced eosinophilia in mice required circulating T-lymphocytes and that passively transferred, sensitized T lymphocytes could promote eosinophilia in nonsensitized recipients. These findings suggest that carcinomas indirectly promote the growth of eosinophil colonies *in vitro* by activated T-cells.

Another speculation of eosinophilia in cases of malignant tumor is that the tumor itself promotes and secretes a substance that stimulates eosinophil colony formation in the bone marrow. Kodama *et al.*[19] reported a case of large-cell carcinoma of the lung associated with eosinophilia and they demonstrated that the tumor produced eosinophil colony-stimulating factor. Slungaard *et al.*[20] demonstrated the presence of eosinophil colony-stimulating factor in anaplastic carcinoma of the lung and in patient serum.

Granulocyte/macrophage colony-stimulating factor (GM-CSF)[21,22] and interleukin-3 (IL-3)[23] have been shown to stimulate the production of eosinophils. They are multilineage regulators that also promote the differentiation of neutrophil, macrophage, and mixed neutrophil/macrophage colonies. In addition, a third eosinophil colony-stimulating factor, interleukin-5 (IL-5), has been reported and its amino acid sequence has been determined. It is specific for the eosinophil lineage.[24,25]

In our patient, eosinophils did not infiltrate the interiors of the lymph nodes. If eosinophil chemotactic factor had played a role in the eosinophilia in our case, this factor might have been expected to elicit infiltration of eosinophils into the lymph nodes. Furthermore, it is unclear how a chemotactic factor would increase the marrow eosinophil count without evidence of lymphoma involvement, as was noticed in our patient.

Because eosinophilia was demonstrated in the peripheral blood and bone marrow, and other leukocytes were within normal ranges, it was hypothesized that the tumor was producing and secreting IL-5. However, we were unable to demonstrate mRNA of IL-5 in the tumor by northern blotting.

We have reported a case of eosinophilia associated with B-cell lymphoma. The mechanism of eosinophilia in our case was speculated to be due to an eosinophilopoietic factor produced by lymphoma.

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