Insect Bite–like Reaction in Patients With Hematologic Malignant Neoplasms

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Background: Exaggerated reaction to insect bites, mainly to mosquitoes, is infrequently described in patients with chronic lymphocytic leukemia. Skin lesions usually appear months to years after the diagnosis of leukemia and are unrelated to laboratory findings, disease course, or therapy.

Observations: We describe 8 patients with various hematologic disorders (chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute monocytic leukemia, mantle-cell lymphoma, large-cell lymphoma, and myelofibrosis) who developed insect bite–like reaction. Although the clinical picture and the histological characteristics of the lesions were typical for insect bites, none of the patients actually had a history, course, or response to treatment suggestive of arthropod assaults. In 2 patients, the eruption preceded the diagnosis of the malignant neoplasm. The rash persisted for months to years and was resistant to therapies other than systemic corticosteroids. The 3 patients with chronic lymphocytic leukemia seemed to have a worse prognosis than expected for their disease. In 1, the polymerase chain reaction detected leukemic cells in the infiltrate.

Conclusions: Insect bite–like reaction is an infrequent, disturbing, and difficult-to-treat nonspecific phenomenon in patients with hematologic malignant neoplasms. Since it may precede the hematologic disorder, oriented evaluation is warranted. We speculate that immunodeficiency plays a role in its pathogenesis; however, the exact pathogenesis and its prognostic implications await further studies.

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Skin eruptions are common in patients with hematologic malignant neoplasms. These can be due to either cutaneous involvement by malignant cells (specific lesion) or a nonmetastatic (paraneoplastic or nonspecific) phenomenon. Among lesions in the latter group, exaggerated reaction to insect bite is infrequently described in patients with chronic lymphocytic leukemia (CLL). We describe 8 patients with various hematologic diseases in whom insect bite–like reaction occurred and discuss this phenomenon.

RESULTS

Clinical features of the 8 patients are summarized in the Table. In all patients, the clinical appearance was that of red itchy papules or plaques. In 1 patient (patient 3), edematous, almost bullous, lesions developed. In another patient (patient 6), 1 of the lesions evolved to a persistent ulcer. Lesions were equally distributed on exposed and nonexposed areas, and there was no seasonal variation in their appearance. None of the patients reported or recalled either insect bites or outdoor activities. A single lesion persisted for about a week and then resolved, seldom leaving postinflammatory hyperpigmentation. Recurrent lesions were the rule. The maximal duration of the rash was 5 years (patients 5 and 6). None of the patients had peripheral eosinophilic leukocytosis.

Only 3 of the 8 patients had CLL. In all of them, the eruption appeared months to years after the diagnosis of leukemia. In 2 patients, 1 with mantle-cell lymphoma (patient 5) and 1 with acute monocytic leukemia (patient 7), the rash preceded the diagnosis of the hematologic disease by 24 and 6 months, respectively. All 3 patients with CLL seemed to have an accelerated course of their disease, more than expected; 1 patient (patient 3) died from transformation to Richter syndrome, and in 2 patients (patients 4 and 6) chemotherapy was initiated due to expansion of the malignant clone, which caused severe pancytopenia. In all pa-
PATIENTS AND METHODS

PATIENTS

From 1995 to 1998, 8 patients who had characteristic itchy papular or vesiculobullous eruption suggestive of insect bites were referred to our dermatologic clinic. In all patients, the diagnosis of the hematologic disease was based on peripheral blood findings (absolute lymphocytosis > 5 x 10^9 lymphocytes/L for patients with CLL) and on either bone marrow or lymph node biopsy results. All patients were followed up for the clinical course of their eruption and their disease.

LABORATORY METHODS

In total, 13 skin biopsies were performed in all patients. Sections (4 µm thick) from the formalin-fixed paraffin-embedded blocks were stained with hematoxylin-eosin. Sections were also stained with pan B-cell marker (CD20, mouse anti-human monoclonal L26), pan T-cell marker (CD45RO, mouse anti-human monoclonal UCHL1, and CD3, rabbit anti-human polyclonal antibody), and anti-Epstein-Barr viral (EBV) proteins (mouse monoclonal CS1-4) (all obtained from DAKO Ltd, Glostrup, Denmark) using the standard streptavidin-biotin immunoperoxidase technique. In 2 cases, parts of the biopsy specimens were frozen in liquid nitrogen. Direct immunofluorescence with antibodies against IgG, IgM, IgA, C3, and fibrinogen was performed. In all cases of B-cell lymphoma or leukemia, to detect malignant cells in the infiltrate, the polymerase chain reaction performed on the paraffin-embedded sections was used as previously described. In brief, DNA was extracted from 5-µm-thick sections of the paraffin-embedded blocks and was amplified using the seminested procedure with primers Fr3A and LlH in the first 30-cycle round and Fr3A and VLJH in the second 20-cycle round. Each reaction contained DNA, 1 µl; the selected primers, 10 pmol; each deoxynucleotide triphosphate, 200 µM; magnesium chloride, 4 or 5 mM; dimethyl sulfoxide, 10% vol/vol; and Taq polymerase and buffer, 0.2 U, supplied by the manufacturer (Bio-line, London, England). The first round of the polymerase chain reaction cycle consisted of annealing for 30 seconds at 56°C, extension for 1 minute at 72°C, and denaturation for 30 seconds at 94°C. The annealing temperature in the second round was 60°C. Before each round, the reaction was heated to 94°C for 4 minutes, and after each round, a final extension step of 6 minutes was performed. Polymerase chain reaction-amplified material was electrophoresed in 2% agarose gel in Tris-boric acid EDTA (TBE) buffer, 250 V, for 25 minutes.

doxorubicin hydrochloride, vincristine sulfate [Oncovin], and prednisone) had been initiated.

All patients were treated with antiscabies agents because when considering the clinical appearance in some patients, the histological characteristics, and that those patients were either immunosuppressed or hospitalized, scabies had to be excluded. Patients were also instructed to avoid outdoor activities and to use repellents and insecticides. All these measures were of no benefit, and the rash persisted. Treatment with topical antipruritic agents, topical corticosteroids, and systemic antihistamines caused no or only temporary relief. Only systemic corticosteroids in a dose equivalent to prednisone, 40 mg/d or more, were effective in suppressing the eruption. However, lesions recurred when corticosteroids were tapered. Improvement was also seen in 1 patient who received combined chemotherapy for his disease, but this is probably due to the fact that corticosteroids were included in the regimen used. In 1 patient (patient 1), the rash disappeared after natural phototherapy at the Dead Sea, and in another 2 patients (patients 5 and 8), 3 months of UV-B phototherapy was either not or only partially beneficial. Low-dose chlorambucil alone was also ineffective in 1 of these patients. Interferon alfa caused only temporary relief in 1 patient (patient 3). In another patient, who was cured from her acute lymphoblastic leukemia (patient 2), the eruption resolved spontaneously.

All biopsy specimens showed a superficial and deep perivascular and interstitial infiltrate composed of small lymphocytes and eosinophils (Figure 3). The density of the infiltrate varied among cases. A biopsy specimen of 1 of the bullous lesions obtained from patient 3 revealed massive subepidermal edema, reminiscent of that seen in Sweet syndrome. Most of the lymphocytes stained with the T-lymphocyte markers. Both T-lymphocyte markers (CD45RO and CD3) stained approximately the same percentage of cells in the infiltrate. In 7 of the 8 patients, T lymphocytes constituted more than 90% of the infiltrate. In 1 patient with CLL (patient 6), B cells exceeded 30% of the infiltrate. Only in this patient, the polymerase chain reaction detected monoclonality, implicating the presence of leukemic cells in the infiltrate. Epstein-Barr viral proteins were not detected in any biopsy specimen. The results of direct immunofluorescence were negative in both cases in which it was tested.

Patients with CLL may present an exaggerated reaction to insect bites. One case is also reported in a patient with lymphocytic lymphoma. In all cases but 1, skin lesions appeared months to years after the diagnosis of leukemia or lymphoma and were unrelated to laboratory findings, disease course, or therapy given. The term “exaggerated reaction to insect bites” was coined by Weed and adopted by others because the lesions either were large or developed bullae.

The diagnosis of insect bites in all reports, including ours, was based on the morphologic and histological characteristics of the lesions. However, from the 31 patients with this phenomenon described in the English-
language literature, only 11 recalled arthropod assaults, mainly mosquitoes.3-7,9 Weed3 also found a marked positive cutaneous reaction to mosquito antigen in 5 of his 8 patients. In all patients in the present study, neither the history nor the distribution, course, or efficacy of the preventive measures and treatment supported the assumption of exaggerated reaction to arthropod assault. In 1 patient, it may be related to the chemotherapy, and in another, it may represent leukemia cutis. Therefore, it might be that insect bites are not necessary to initiate the eruption, and terms like “insect bite–like reaction” or “eosinophilic eruption of hematoproliferative disease” should be preferred. Furthermore, the insect bite–like reaction in these patients shares features or may be even identical to the papular rash described in patients with human immunodeficiency virus infection.10,11 Therefore, immunodeficiency combined with various immunologic stimuli (insect bites, drugs, or viral infections) may play a role in the pathogenesis of both eruptions. It is also likely that Wells syndrome, which has been described in patients with malignant hematologic disorders,12 is nothing but a variant of this insect bite–like reaction.13,14

The present series further elucidates aspects of this response. First, the phenomenon occurred not only in patients with CLL but also in patients with other hematoproliferative diseases, thus emphasizing its generality as a “nonspecific” phenomenon in these diseases. Second, the rash may precede the diagnosis of the hematologic disorder, and an oriented evaluation is recommended when lesions persist. Interestingly, most of the hematologic diseases in our patients originated from B cells (3 cases of CLL, mantle-cell and large-cell lymphomas, and acute lymphoblastic leukemia). One may, therefore, speculate that a common mechanism (cytokine imbalance with excess of interleukin 4 and interleukin 5) leads to proliferation of malignant B cells and altered immune response characterized by eosinophilic infiltrate.15 Alternatively, the neoplastic B cells may be responsible for the skin hypersensitivity reaction.

In Japan, hypersensitivity to mosquito bites was associated with natural killer (NK)–cell lymphocytosis.16 Most of these patients developed malignant histiocytosis years later. In 1 report,17 a patient who was hypersensitive to mosquito bites and had EBV infection developed NK-cell lymphoma. Recently, a relation between hypersensitivity to mosquito bites and clonal proliferation of EBV DNA–positive NK cells was found.18 The researchers suggest that this may be responsible for the hypersensitivity and for a leukemic transformation. Marker CD45RO stains T lymphocytes and NK cells. Marker CD3 stains only T lymphocytes. Since we did not find a notable difference between these stains in the biopsy specimens from patients with an insect bite–like reaction, only a small percentage of NK cells was present. Therefore, it may be inferred that NK cells did not play a major role in the development of this reaction. Our findings also do not support a role for EBV in the evolution of the insect bite–like reaction. Although these observations may reflect the different epidem.

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Hematologic Disease/Course</th>
<th>Clinical Appearance</th>
<th>Relation to Disease</th>
<th>Maximal Duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/68</td>
<td>Myelofibrosis/E</td>
<td>Red itchy papules</td>
<td>A</td>
<td>24</td>
</tr>
<tr>
<td>2/F/47</td>
<td>ALL/E</td>
<td>Red itchy papules</td>
<td>A</td>
<td>24</td>
</tr>
<tr>
<td>3/F/64</td>
<td>CLL/P</td>
<td>Red itchy papules and edematous plaques</td>
<td>A</td>
<td>30</td>
</tr>
<tr>
<td>4/M/47</td>
<td>CLL/P</td>
<td>Red itchy papules and plaques</td>
<td>A</td>
<td>10</td>
</tr>
<tr>
<td>5/M/42</td>
<td>Mantel-cell lymphoma/E</td>
<td>Red itchy papules and plaques</td>
<td>B</td>
<td>60</td>
</tr>
<tr>
<td>6/F/68</td>
<td>CLL/P</td>
<td>Red plaques, persistent ulcer</td>
<td>A</td>
<td>60, 18</td>
</tr>
<tr>
<td>7/F/72</td>
<td>AMOL/E</td>
<td>Red itchy papules</td>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>8/M/65</td>
<td>LCL/E</td>
<td>Red itchy papules</td>
<td>A</td>
<td>6</td>
</tr>
</tbody>
</table>

*E indicates expected for the disease; A, after hematologic disease was diagnosed; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; P, progression (more than expected); B, before it was diagnosed; AMOL, acute monocytic leukemia; and LCL, large-cell lymphoma.
The demiological characteristics of EBV infection between East Asia and western countries, the 2 hypersensitivity reactions may be totally different phenomena, for which the molecular mechanism requires further investigation.

Our cases further support the evidence that this rash is unrelated to bullous pemphigoid. However, since there are reports of bullous pemphigoid associated with malignant neoplasms, it is mandatory to perform direct immunofluorescence whenever pemphigoid is clinically suspected as histological features alone are not sufficient to rule out pemphigoid.

Specific lesions as traditionally defined, ie, leukemia cutis or lymphomatous infiltration of the skin, can be ruled out based on the immunophenotype and the molecular biology assays. In 1 patient with CLL who developed a persistent ulcer, the infiltrate contained malignant B cells; thus, it may actually represent leukemia cutis. However, this can merely be a reflection of the distribution of neoplastic cells in the blood and their capability to respond to immunologic stimuli.

In all the published cases of insect bite–like reaction, the eruption was unrelated to laboratory findings, disease course, or therapy given. This is also the trend in the present series. However, the observation on the 3 patients with CLL who showed progression of their disease in a relatively short period merits special attention. Fatal complications also developed in 3 of the 8 patients with CLL described by Davis et al. Larger series are required to establish whether this reaction has prognostic implications for patients with CLL, especially in light of the recent observation that prognosis is not affected by specific skin infiltrates in patients with CLL.

The insect bite–like reaction in these patients seems to pose a therapeutic challenge. Davis et al reported variable improvement in some of their patients who underwent chemotherapy for the CLL. Oral glucocorticoids and intravenous immunoglobulin seemed to work better, while antibiotics were not helpful at all. None of the patients in the present series responded sufficiently to most measures (topical treatment with antipruritics and corticosteroids, systemic antihistamine therapy, UV-B phototherapy, isolated chemotherapy, and interferon therapy). Only prednisone, 40 mg/d or more, was effective in suppressing the rash. The observation of 1 patient who responded to Dead Sea phototherapy may implicate that psoralen–UV-A may be beneficial. Disappearance of the eruption in the patient who was cured from her leukemia further stresses the interrelation between the 2 situations.

In summary, insect bite–like reaction should be included in the various nonspecific rashes accompanying hematoproliferative disorders. Clinicians should be aware of the fact that this phenomenon may precede the diagnosis of the hematologic disorder; thus, an oriented investigation is recommended. Beside corticosteroids, therapy for this disturbing eruption awaits further studies; its pathogenesis requires further study as well.

Figure 3. Left, A biopsy specimen shows a superficial, deep, and interstitial perivascular infiltrate involving also the subcutaneous fat (original magnification ×20). Right, The infiltrate is composed of lymphocytes and eosinophils (original magnification ×200).
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