Exaggerated Delayed Hypersensitivity to Mosquito Bites in Chronic Lymphocytic Leukemia

By Robert I. Weed

It is the purpose of this report to describe the occurrence of unusual cutaneous hyper-reactivity phenomena in certain patients having chronic lymphocytic leukemia. These reactions are consistent with an exaggerated delayed hypersensitivity type of response to insect bites, inoculated mosquito antigen and to certain other delayed hypersensitivity antigens.

The mosquito is an example of certain insects whose bites are capable of evoking both immediate and delayed hypersensitivity types of cutaneous response.1-4 Exaggerated delayed response may occur after initial sensitization and it is occasionally seen in children, but repeated exposure to the antigen seems to moderate the response. Spontaneous development of exaggerated delayed hypersensitivity to the mosquito is exceedingly rare in individuals past middle age. However, out of 97 cases of chronic lymphocytic leukemia that were seen between 1950 and 1963 at Strong Memorial Hospital, there were 8 individuals who were found to have severe troublesome local reactions to insect bites, usually mosquito. Such reactions display features consistent both with delayed cutaneous hypersensitivity and with leukemia cutis. The enhanced delayed hypersensitivity has led to further evaluation of the immunologic competency of these individuals.

Clinical Features

Gross and Histologic Appearance of the Insect Bite Lesions

Each of these patients had the cutaneous reactions on several occasions, but only those reactions with a definite history of an observed antecedent insect bite and/or evidence of a puncture wound in the center of the lesion are reported here. All of the patients who were able to identify the insect reported a mosquito as the offender. The reactions to the bites developed slowly, reaching their peak in from 12 to 24 hours and they were characterized by induration, edema, erythema and intense pruritis. The most severe lesions progressed to the development of bulla, up to 10 cm. in diameter surrounding the puncture. Figure 1 illustrates such a severe reaction to a known mosquito bite, resulting in hemorrhagic bullous formations. Resolution occurs spontaneously within 2 to 14 days.
Histologically, these lesions are characterized by (1) preservation of the epidermis, (2) subepidermal edema with disruption of collagen bundles, (3) dense dermal infiltration with lymphocytes and eosinophils, as well as occasional histocytes. Figure 2A and B illustrate these features under low and high power respectively. Although the dense lymphocytic infiltration might be attributed to leukemic involvement of the skin alone, the edema and eosinophilia cannot be considered a feature of lymphocytic leukemia cutis nor can the spontaneous resolution of the gross lesion, often within 4 to 5 days. In addition, as pointed out by Allen in 1948, the histopathology of persistent reactions to insect bites in hematologically normal individuals may be mistaken for cutaneous involvement by lymphatic malignancy, illustrating the absolute necessity for a clinical history consistent with the histology in order to establish a diagnosis of lymphocytic leukemia cutis.

Incidence of Exaggerated Response to Insect Bites

Table 1 compares data on the incidence of this type of reaction in patients with chronic lymphocytic leukemia with three other groups. The records of 54 patients having chronic myelocytic leukemia were reviewed without any such patient being found. In a group of 45 Medical Center personnel, only one was found to have a history of reaction to mosquito bites greater than 20 mm. in diameter. None developed bullous lesions. In addition, patients under treatment in the Allergy Clinic were interviewed and out of 37 patients only one gave a history of hyper-reactivity to insect bites and that individual
had immediate anaphylactic reaction to mosquito bites rather than the delayed type seen in our patients. Thus, the occurrence of this abnormality seems distinctly more frequent in patients with chronic lymphocytic leukemia.

Table 2 summarizes the incidence of all cutaneous lesions diagnosed in the 97 patients surveyed in this investigation. Note that the exaggerated cutaneous reaction to insect bites is more frequent in this group of patients than any other abnormality of the skin, including herpes zoster, which had a lower incidence than expected. It is to be emphasized, however, that patients should be questioned specifically since many do not complain of even an exaggerated reaction to insect bites. In this regard, the retrospective review of patients with chronic myelocytic leukemia is of less value as a control than the allergy clinic patients who were questioned directly.

Occurrence in Affected Patients

Table 3 summarizes the course of the illness, the therapy for both the leukemia and the cutaneous reaction and levels of white blood count at the
Fig. 2.—(B) Same as figure 2A. High power, illustrating dense dermal infiltration with lymphocytes and eosinophils.

time of reaction, which characterized this group of patients with chronic lymphocytic leukemia. The cutaneous hyper-reactivity usually develops within 1 to 4 years after the clinically recognized onset of the disease. The lesions occur on exposed areas such as the face and extremities, and appear between May and September. The distribution, as well as the freedom from trouble of these patients during the cold months is predictable in relation to the site of the mosquito bites and the mosquito season in Rochester.

It is apparent from table 2 that the hyper-reactivity to insects was not related to the level of peripheral white blood count. Also it was unassociated with any elevation of serum uric acid levels in six patients and with levels of 7.8 and 8.0 mg. per cent in two others. The occurrence of these reactions appears unrelated to alkylated or x-ray therapy. They have also occurred while individuals were under treatment with prednisone although possibly the reaction might have been more severe in the absence of steroid therapy. In fact, both the current evidence that corticosteroids will modify delayed hypersensitivity in normals⁵,⁷ and the benefit seen from prednisone therapy in Case No. 8 support such a suggestion.

Immunologic Responsiveness

Only 1 of these patients had distinctly low γ-globulin levels (patient No. 4—0.3 Gm. per cent.), indicating that this concomitant of immunologic hyporesponsiveness was not more common in this group and possibly less common...
MOSQUITO HYPERSENSITIVITY IN LEUKEMIA

Table 1.—Incidence of Local Hyper-reaction to Insect Bites (Lesion > 20 mm. in Diameter)

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. Pts. Affected</th>
<th>Total No.</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>8</td>
<td>97</td>
<td>8.3</td>
</tr>
<tr>
<td>Chronic myelocytic leukemia</td>
<td>0</td>
<td>54</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical center personnel</td>
<td>1</td>
<td>45</td>
<td>2.2</td>
</tr>
<tr>
<td>Allergy clinic patients</td>
<td>1</td>
<td>37</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Table 2.—Cutaneous Abnormalities in 97 Patients with Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Condition</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis medicamentosa</td>
<td>2</td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
<td>1</td>
</tr>
<tr>
<td>Erythroderma (± pruritus)</td>
<td>4</td>
</tr>
<tr>
<td>Erythema multiforme bullosum</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>3</td>
</tr>
<tr>
<td>Hives</td>
<td>5</td>
</tr>
<tr>
<td>Insect bite hyper-reactivity</td>
<td>8</td>
</tr>
<tr>
<td>Leukemia cutis</td>
<td>4</td>
</tr>
</tbody>
</table>

than the 30–38 per cent incidence found by Ultman, Fish, Osserman, and Gellhorn* and by Hudson and Wilson9 among all patients with chronic lymphocytic leukemia. Although "autosensitization" of red cells with or without hemolytic anemia was relatively common in the overall group (16.9 per cent of 71 patients tested between 1950 and 1963), none of the patients described in this report had a persistently positive Coombs test. Two had transiently positive non-γ-Coombs tests1 and one a transiently positive γ-Coombs. Thus no correlation is apparent between autosensitization of red cells and cutaneous hyper-reactivity.

Because the usual response to a mosquito bite in healthy adults is a mild delayed type of hypersensitivity response14 it was felt essential to evaluate the cutaneous reactivity of these patients. Table 4 indicates the results of skin test studies conducted on patients still alive when this investigation was begun. In order to exclude alteration in local cutaneous reactivity unrelated to immune processes, a Prausnitz-Küstner reaction was produced by passive transfer of .05 cc. of serum hyperimmune to ragweed, followed in 24 hours by an intradermal challenge with ragweed antigen. None of these patients demonstrated any initial sensitivity but following the passive transfer of antibody, all developed normal cutaneous reactions with edema, erythema and pseudopod formation upon challenge with ragweed antigen. These reactions subsided in minutes to a few hours. This evidence suggests that the exaggerated local delayed reaction to mosquito bites cannot be accounted for by nonspecific cutaneous alterations or reactivity. Testing with a 1/100 dilution of standard mosquito antigen* revealed that all of these tested had markedly positive (3-4+) skin tests at 24 hours, in contrast to twelve normal individuals who had 24 hour reactions to the antigen ranging from 0–2+, with one 3+

*Mosquito antigen obtained from Hollester-Stier Laboratory, Yeadon, Penna.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Duration of Disease</th>
<th>Therapy of Leukemia</th>
<th>Occurrence of Cutaneous Reaction</th>
<th>WBC at Time of Skin Reaction</th>
<th>Therapy of Cutaneous Reactions</th>
<th>Coombs Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) H. D.</td>
<td>48</td>
<td>1947-51 lost to follow-up</td>
<td>12/48 abdominal x-ray</td>
<td>7/51</td>
<td>70,000</td>
<td>Irradiation</td>
<td>Improved</td>
</tr>
<tr>
<td>(2) P. C.</td>
<td>64</td>
<td>1957-61 (died – pulmonary edema)</td>
<td>12/60 – Prednisone</td>
<td>8/59</td>
<td>19,000</td>
<td>Benadryl</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12/58 – chlorambucil</td>
<td>7/60</td>
<td>178,000</td>
<td></td>
<td>neg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/60 – TEM and Prednisone</td>
<td>9/60</td>
<td>127,000</td>
<td></td>
<td>neg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11/60 – chlorambucil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) M. S.</td>
<td>71</td>
<td>1955-61 (died – broncho pneumonia)</td>
<td>4/56 – x-ray to nodes</td>
<td>8/56</td>
<td>79,000</td>
<td>Benadryl</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12/58 – TEM</td>
<td>7/57</td>
<td>162,000</td>
<td></td>
<td>neg.</td>
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<td></td>
<td></td>
<td></td>
<td>4/61 – chlorambucil</td>
<td>8/58</td>
<td>39,000</td>
<td>Pyribenzamine</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/59</td>
<td>181,000</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>8/60</td>
<td>76,000</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>8/61</td>
<td></td>
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</tr>
<tr>
<td>(4) I. J.</td>
<td>60</td>
<td>1951-63 (died – interstitial pneumonia and pulmonary fibrosis)</td>
<td>51 – x-ray to nodes</td>
<td>6/54</td>
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<td></td>
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<td>pos.</td>
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<td></td>
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<td>4/57 – TEM</td>
<td>8/57</td>
<td>100,000</td>
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<td></td>
<td></td>
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<td>8/58 – Prednisone</td>
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<td></td>
<td></td>
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<td>59 – 4/60 Prednisone</td>
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<td></td>
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<td>4/60 – TEM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(Leukemia and Addison’s Disease)</td>
<td>9/61</td>
<td>87,000</td>
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<td>neg.</td>
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<td></td>
<td></td>
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<td>6/60 – Chlorambucil</td>
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<td></td>
<td></td>
<td>neg.</td>
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<tr>
<td>No.</td>
<td>Name</td>
<td>Age</td>
<td>Year</td>
<td>Date(s)</td>
<td>Treatment(s)</td>
<td>Symptoms</td>
<td>Outcome</td>
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<tr>
<td>(7)</td>
<td>S. C.</td>
<td>40</td>
<td>1939-</td>
<td>6/59 and 11/60</td>
<td>x-ray therapy to nodes</td>
<td>Developed while on steroid - summer 1963</td>
<td>neg. neg.</td>
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<td>(8)</td>
<td>S. Y.</td>
<td>78</td>
<td>1954-</td>
<td>5/54</td>
<td>local x-ray to regional</td>
<td>Pyribenzamine</td>
<td>± neg.</td>
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<td>6/56</td>
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<td>Improved</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>local x-ray to tongue</td>
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<td></td>
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<td>1/64</td>
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Table 4.—Skin Tests in Patients with Hyper-reactivity to Insect Bites

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Prednisone When Tested</th>
<th>Ragweed 15 min.</th>
<th>P-K Transfer of Ragweed Immune Serum</th>
<th>1/100</th>
<th>1/100</th>
<th>Monilia</th>
<th>Hormodendron</th>
<th>Cottonseed</th>
<th>Tobacco</th>
<th>Other</th>
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<td>L.J. 4</td>
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<td>+++</td>
<td>0</td>
<td>+++</td>
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<td></td>
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<td>H.B. 5</td>
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<td>++</td>
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<td>+++</td>
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<td>H.K. 6</td>
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<td>S.C. 7</td>
<td>yes</td>
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<td>+++</td>
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<td>+</td>
<td>+</td>
<td>0</td>
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</tr>
<tr>
<td>S.Y. 8</td>
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<td>0</td>
<td>+++</td>
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<td>+</td>
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</table>

Had inactive tuberculosis

Immediate hypersensitivity (Ragweed) was read at 15 minutes and graded 1+ for erythema and edema confined to area of injection, 2+ for extension beyond area of injection and 3+ if pseudopods were identifiable. Delayed hypersensitivity reactions were read at 24 and 48 hours, with the more positive being reported: 1+, 5-10 mm. induration; 2+, 10-20 mm. induration; 3+, greater than 20 mm. induration, and 4+, necrosis.
reaction. Figure 3 illustrates a strongly positive skin test to 1:100 dilution of mosquito antigen. Five other patients with chronic lymphocytic leukemia but without any history of severe reaction to insect bites, had reactions to a 1/100 dilution of mosquito antigen from 1–3+. Only one of these individuals had a 3+ reaction and it is of interest that he also has a history of a 4+ histoplasmin skin test, with necrosis. The limited information in table 4 on reactivity to other delayed hypersensitivity antigens indicates that these individuals are certainly not anergic.

**Discussion**

The occurrence of vesicobullous cutaneous lesions in patients having chronic lymphocytic leukemia has been recognized for some time and in one series of 289 cases, Beck reported a 10 per cent incidence of bullous lesions. Dameshek has suggested that both the exaggerated response to mosquito bites and the severe reaction to smallpox vaccination seen in some patients with chronic lymphocytic leukemia may represent examples of abnormal immune mechanisms. Bluefarb in a recent extensive review of cutaneous involvement in leukemia, has emphasized the difficulty in distinguishing between nonspecific cutaneous lesions and true tumor, both clinically and pathologically. Bluefarb suggests that when the clinical picture is that of a toxic cutaneous lesion, but the pathologic picture consistent with true leukemic infiltration, the abnormality should be designated a leukemid. Severe lesions of the type described in this report would appear to fall into the leukemid category, since both the occurrence of eosinophilia and edema as well as the spontaneous resolution are not features of true leukemia cutis.

Cutaneous reaction to mosquito bites has been recognized for some time to represent a form of delayed hypersensitivity. Studies of the reactivity of adults previously unexposed to *Aedes aegypti* and of the natural sequence of reaction in children have called attention to the fact that primary sensitization produces both immediate and delayed hypersensitivity. Continued exposure, however, generally results in amelioration of the delayed hypersensitivity, followed after further exposure by amelioration of the immediate hypersensitivity to give the usual response of an adult to the bite of the mosquito. Thus, the exaggerated response of our patients, both to bites and mosquito antigen is like that seen in normal children who have not yet been desensitized by continued exposure.

Although the occurrence of cutaneous anergy in Hodgkin’s disease has been well documented, it is not true that all malignant disorders of the lymphatic system are associated with anergy. Lamb, Pilney, Kelly and Good have studied the reactivity to delayed antigens of patients with lymphocytic leukemia and non-Hodgkin’s lymphoma and, in contrast to Hodgkin’s disease, have found them to be normal except when the patients were extremely debilitated.

In our group of patients, not only did their cutaneous reactivity to delayed antigens appear normal but, with the mosquito antigen it was greatly exaggerated. It is not possible to establish, however, whether this phenomenon in
Fig. 3.—Strongly positive skin test to 1:100 dilution of mosquito antigen. Note necrotic center.

this group of patients is related to a greater immune responsiveness per cell, mediated through some leukemic alteration or whether the cells simply have normal immune responsiveness and the exaggerated response is based on greater local mobilization of lymphocytes in these patients.

Recent studies have indicated that delayed antigens are mitogenic in blood cultures from normal individuals because of their role as antigens. Dr. Goh in our department has demonstrated that the mosquito antigen is a modest mitogenic agent in cultures of both normal and chronic lymphocytic leukemia blood. The stimulation of mitosis by mosquito antigen is consistent with its role as a delayed allergen, but the failure of the leukemic cell cultures to respond more strikingly than normal cells would seem to suggest that the individual cells are not responding in an exaggerated fashion. Thus although Perillie and Finch and Weber have demonstrated that over a few hours, and after some initial delay in onset, the cellular cutaneous response in chronic lymphocytic leukemia appears the same as in normal individuals and in spite of a poor correlation with peripheral blood leukocyte counts, it seems that our patients have mobilized immunologically competent cells locally in greater than normal numbers to account for the exaggerated response.

In summary, this report has reviewed the clinical histories of 8 patients with chronic lymphocytic leukemia who manifested a marked delayed hypersensitivity type of local skin reaction to insect bites, and mosquito antigen and were capable of reacting normally to other delayed hypersensitivity
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antigens. We have suggested that this abnormality may represent another example of altered immunologic responsiveness in this disease, consistent with the notion that the lymphocyte is of prime importance for the development of delayed cutaneous hypersensitivity.

SUMMARIO IN INTERLINGUA

Es describite le occurrentia de inusual phenomenos de hypersensibilitate cutanee in certe patientes con chronic leucemia lymphocytic. Le reactiones observate es de natura a suggerer que il se tracta hic de un exaggerate hypersensibilitate tardive pro morsuras de insecto e certe altere antigenos. Le datos presentate e lor analyse pare justificar le conclusion que iste anormalitate representa un exemplo additional pro le alterate responsivitae immunologic in chronic leucemia lymphocytic, congruentemente con le notion que lymphocytos es de importantia eminente in le disveloppamento de tarde hypersensibilitate cutanee.

REFERENCES

Exaggerated Delayed Hypersensitivity to Mosquito Bites in Chronic Lymphocytic Leukemia

ROBERT I. WEED