Cutaneous Manifestations In Hematological Malignencies
A Yalcin, A Keskin, S Ergin, H Akdam, S Degirmenciglu

Citation

Abstract
In this retrospective study skin lesions of the patients who were hospitalized in Haematology Department between October 2001 and May 2003 were evaluated. A total of 99 patients, 21 with lymphomas (Hodgkin disease, Non-Hodgkin lymphomas, Castleman's disease), 42 with myeloproliferative disorders and multiple myelomas (MM), 36 with leukemias (AML, ALL, CLL, HCL) were included in the study. Two-thirds of the patients had skin lesions independent from malignancy types. The frequency of skin lesions did not differ according to the types of malign disorders. Malign infiltrative lesions were prominent features in leukemias whereas cutaneous infectious manifestations were more common in lymphomas.

INTRODUCTION
Various cutaneous lesions can be observed in patients with hematologic malignancies. These include specific cutaneous lesions resulting from infiltration of the skin by the malignant cells, characteristic diseases such as pyoderma gangrenosum and Sweet syndrome, cutaneous signs of infection or hemorrhage resulting from the bone marrow dysfunction induced by the malignant process or chemotherapy. Specific cutaneous involvement has been reported in 10% to 50% of patients with acute myelogenous leukemia (AML) of the French-American-British (FAB) classification subtypes M4 and M5, up to 10% of patients with AML-FAB subtypes M0, M1, M2, M3, and in about 2% of patients with chronic myelogenous leukemia (CML) \( (12,13,14) \). Clinical and histopathologic features are variable \( (15,16,17,18) \). Histopathologically, differentiation of specific cutaneous infiltrates from lymphoproliferative and inflammatory skin conditions may be challenging. Accurate identification is important in planning subsequent management of these patients, especially in cases where skin lesions precede the onset of leukemia. The introduction of FAB-classification of AML in 1976 \( (19) \) and the use of immunohistologic techniques in the last 2 decades have added new criteria for diagnosis of myeloproliferative disorders. Most of the literature on specific skin manifestations of AML and CML, however, predates FAB classification and cellular immunophenotyping techniques \( (20) \). Immunophenotyping of infiltrates with specific markers is a valuable adjunct in confirming the diagnosis of leukemia cutis and in differentiating specific from nonspecific cutaneous infiltrates. Specific markers include the following: CD3 (T cells), CD45RO (mature T cells), CD45/LCA (leukocyte common antigen) (lymphocytes, monocytes), CD43 (T cells, monocytes, and granulocytes), CD20 (B cells), CD30 (activated T cells), CD68 (monocytes), and lysozyme (granulocytes, monocytes) \( (21,22) \).

Cutaneous involvement by a hematopoietic malignancy may occur secondarily in certain forms of leukemia (leukemia cutis), in nodal or extranodal B-cell or T-cell lymphomas, or as a primary cutaneous B-cell or T-cell lymphoma. Primary cutaneous T-cell lymphoma (CTCL) encompasses a diverse group of diseases with distinct clinical presentations, pathologic features, treatment approaches, and outcomes \( (23) \).

In this study, we demonstrated the cutaneous findings of patients with various hematological malignancies.

METHODS

PATIENTS
In this retrospective study skin lesions of the patients who were hospitalized in Haematology Department between October 2001 and May 2003 were evaluated. A total of 99 patients, 21 with lymphomas (HD, NHL, Castleman’s disease), 42 with myeloproliferative disorders and multiple myelomas (MM), 36 with leukemias (AML, ALL, CLL, HCL) were included in the study.

Twenty-one patients had lymphomas (Hodgkin disease in 5 patients, Non-Hodgkin lymphomas in 16), 22 had myeloproliferative disorders (CML in 6 patients, other myeloproliferative disorders in 16) and 20 had multiple
myeloma (MM). Of 36 patients with leukemia 5 had Hairy cell leukemia (HCL), 7 had Chronic lymphocytic leukemia (CLL), 3 had Acut lymphocytic leukemia (ALL), 21 had AML. Cutaneous herpes infections and mucosal candidiasis were grouped as infectious cutaneous manifestations. Petechia and ecchymosis observed secondary to thrombocytopenia were grouped as hemorrhagic findings. Localised or generalized cutaneous reactions due to chemotherapeutic agents were grouped as cutaneous drug eruptions. Malign infiltrations were demonstrated on biopsy (Table 1).

**DISCUSSION**

Leukemic infiltrates may present as widespread macules and papules infiltrated plaques or nodules, which are distinctive, blue violet or red brown color. Some patients with leukemia develop diffuse maculopapular eruptions interpreted as allergic reactions to circulating leukemic cells but most are probably true leukemic infiltrates with very few malignant cells.

The histologic findings in leukemia cutis vary depending on the subtype of leukemia. Typically, little epidermal involvement with an underlying Grenz zone is present. A dermal infiltrate of leukemic cells, which is often perivascular and periadnexal, is present. Collagen bundles may be prominently separated by leukemic cells. The leukemic cells may also infiltrate along the fibrous septae of the subcutaneous fat. The cells may be seen in the lumina of the blood vessels as well as infiltrating the walls, producing a leukemic vasculitis. Cells in AML are large with an oval, vesicular nucleus and basophilic cytoplasm. In CML, a variety of cells at varying degrees of maturation are present. Eosinophils may be present. AML shows medium-to-large blast cells, with a high nuclear-to-cytoplasmic ratio. CLL shows small, more uniform, mature lymphocytes. These have dense nuclear chromatin. T cell CLL may show epidermotropism, as do other T-cell leukemias. Monocytic leukemia may be confused with large cell lymphoma because of the large nucleus with fine chromatin and prominent nucleoli. The nuclei are often indented or kidney shaped and slightly basophilic in appearance.

Monocytic leukemia often involves the entire dermis and the superficial panniculus. ATLL cells show an indented to lobulated nucleus, which has led to the term flower cells to describe the morphology. ATLL unlike many of the other leukemic infiltrates often shows epidermotropism. Pautrier microabscesses, as can be seen in mycosis fungoides, may be present. Hairy cell leukemia, like many other forms of leukemia cutis, infiltrates the dermis and the subcutaneous fat. It too shows prominent periadnexal and perivascular infiltration. The infiltrate consists of monomorphous mononuclear cells. A Grenz zone is typically present. The frequency of leukemic infiltration of the skin is variable according to the type of leukemia.

A recent retrospective study of 26 patients with either AML or CML with specific cutaneous infiltrates showed that, in 22 patients the onset of skin lesions correlated with an aggressive course and short survival, with a mean survival of 7.6 and 9.4 months for AML and CML patients, respectively.

**Table 1: Cutaneous Lesions In Hematological Malignencies**

<table>
<thead>
<tr>
<th>Cutaneous Lesions</th>
<th>No lesion</th>
<th>Infected</th>
<th>Malign infiltration</th>
<th>Hemorrhagic lesions</th>
<th>Drug reaction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas (NHL, HD)</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>MDS pro lif. Dis.</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>Leukemias</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>30</td>
<td>3</td>
<td>12</td>
<td>11</td>
<td>99</td>
</tr>
</tbody>
</table>

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**Gingival hyperplasia** is secondary to infiltration of the gingival tissue with leukemia cells and is well described in the literature. In the most extensive review of the topic, gingival hyperplasia was observed in AML with a frequency of 3% to 5% among 1,076 patients receiving anti-leukemia chemotherapy at a referral centre. Gingival hyperplasia is most commonly seen with the AML subtypes acute monocytic leukemia (M5) (66.7%), acute myelomonocytic leukemia (M4) (18.5%), and acute myelocytic leukemia (M4) (18.5%), and acute myelocytic leukemia (M1, M2) (3.7%). Gingival hyperplasia was observed in AML with a frequency of 3% to 5% among 1,076 patients receiving anti-leukemia chemotherapy at a referral centre. Gingival hyperplasia is most commonly seen with the AML subtypes acute monocytic leukemia (M5) (66.7%), acute myelomonocytic leukemia (M4) (18.5%), and acute myelocytic leukemia (M1, M2) (3.7%). Gingival hyperplasia is characterized by progressive enlargement of the interdental papillae as well as the marginal and attached gingiva. In the condition's most pronounced form, the crowns of the teeth may be covered. Gingiva appear swollen, devoid of stippling and pale red to deep purple in colour. Mucosal hemorrhages, ulcerative gingivitis, infectious gingivitis and odontalgia may be observed. Pallor, spontaneous hemorrhage, petechiae and ulceration have been described to occur more frequently.
in acute than chronic leukemia \( (26,27,22,23,26) \). In this study, 4 patients with AML M4 and M5 had gingival hyperplasia.

Cutaneous involvement in malignant lymphomas may be primary or secondary. Malignant lymphomas may occur de novo in the skin or after spread from internal organs. Non-specific skin findings such as pruritus, hyperpigmentation, nodular or papular prurigo, ichthyosis-like lesions and viral infections are present in 50% of HD patients. Specific lesions are rare and are mainly limited in the areas of nodal involvement. Of 21 patients with NHL and HD, 11 had mucocutaneous candidiasis and cutaneous herpes infections independent of malignancy types. One patient with HD had fix drug eruption triggered by vincristine. Castleman's disease is a rare disorder that results in the underregulated growth of lymphoid tissue. It may present as benign involvement of one lymph node group or as multicentric disease with systemic symptoms. We presented a patient with Castleman's disease of mixed-type and multicentric involvement \( (27,28) \).

CLL is a malignant lymphoproliferative disorder characterized by an accumulation of monoclonal lymphoid cells within the peripheral blood \( (29) \). Unusual papular and occasionally bullous skin lesions occur in some patients with CLL. Both a genetic component and an environmental component appear to be involved in many leukemias. A variety of well-characterized chromosomal translocations result in specific leukemic syndromes. CLL shows some familial tendency in approximately 20% of CLL cases \( (27,29) \). Although patients usually do not recall being bitten, these lesions have been postulated to represent an exaggerated response to arthropod bites \( (29,30) \). One group suggested that these lesions are a variant of bullous pemphigoid \( (31) \). In this study, of 7 patients with CLL, 2 had malign cutaneous infiltrations presented with papules.

CONCLUSION

Of all patients two-third had skin lesions independent from malignancy types. No statistical result was found between different type of malign disorders according to lesions. In leukemias, malign infiltrative lesions and in lymphomas, infectious findings were predominated.

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