Cutaneous Manifestations of Leukemia

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Leukemia is a malignant neoplasm of leukocytes, characterized by immature white blood cells in peripheral blood and a diffuse infiltration of the bone marrow, liver, spleen, lymph nodes and other organs, including skin. Based on the dominating cell types and their characteristics, leukemia can be classified into four major types: Acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia and chronic lymphocytic leukemia.

The first report of acute leukemia was by Friedreich in 1857. In 1876, Biesiadecki was the first author to report a patient with leukemia cutis, and an excellent description of the mucocutaneous manifestation of acute leukemia was made by Ebstein in 1889 (Friedreich 1857; Biesiadecki 1876; Ebstein 1889).

The cutaneous manifestations of leukemia are classified into nonspecific and specific eruption (leukemia cutis). Skin lesions such as macules, papules, nodules, plaques and tumors, including chloroma, are considered to be specific when the histopathologic examination of the skin biopsy specimen confirms the presence of leukemic infiltration from superficial cortex to subcutaneous fat tissue. Non-specific eruptions include pruritus, pallor, purpura, herpes zoster, disseminated herpes simplex, erythema multiforme, urticaria, erythroderma, hyperpigmentation, pyoderma, fungal infection, leukocytoclastic vasculitis, Sweet’s syndrome, pyoderma gangrenosum and ecchyma gangrenosum. In these non-specific eruptions, there is no microscopic evidence of leukemic cellular infiltration in the tissue specimen. The two manifestations sometimes may merge imperceptibly into one, and that is called “id” reaction or leukemic. The leukemic reaction is clinically similar to non-specific eruptions, and histopathologically resembles specific eruptions of leukemia (Bluefarb 1960). Although these skin eruptions are usually seen after a diagnosis of leukemia is established, there are a few reported cases in the literature in which the diagnosis of leukemia has first been made by the cutaneous manifestation of leukemia.

Leukemia cutis is found in 10 to 50 percent of patients with monocytic leukemia, and 6 to 20 percent of lymphocytic and myelogenous leukemias (Braverman 1981). However, since chronic lymphocytic leukemia is the most common type of leukemias in Western countries, leukemia cutis is more often due to chronic lymphocytic leukemia. On the other hand, nonspecific manifestations of leukemia can be expected to be seen from most of the patients of any type.

Leukemia cutis often has its own distinctive sites of predilection in various types of leukemia: myelogenous leukemia affects primarily trunk, monocytic leukemia involves the entire skin surface and oral mucosa, and lymphocytic leukemia affects face and extremities. The colors of macules, papules, nodules, plaques and tumors of leukemia cutis vary from pink and red brown to purple. The nodules and tumors are usually firm and not stony hard as is seen in metastatic carcinoma (Bluefarb 1960; Braverman 1981). (Incidentally, these cutaneous manifestations of leukemia are similar to those of lymphomas).

Pathogenesis

The factors responsible for these cutaneous eruptions of leukemia are unknown, as are those that cause leukemic infiltrations to localize at specific cutaneous sites. It has been postulated that leukemic cells may have migrated to a certain spot as a secondary response to some unknown pathogenic stimulus common to patients with leukemia. Bluefarb, in his monograph of leukemia cutis, described numerous examples in which leukemic infiltrates were observed in areas of previous tissue injury or inflammation. He stated that this “Koebnerlike” phenomenon is seen in 8% of cases in chronic lymphocytic leukemia with cutaneous tumors. Most notable, were cases in which biopsy-proven, specific leukemic infiltrates developed in scars of previous herpes zoster. Similarly, leukemic
infiltrates have been found in scars from recent surgery, trauma, burns, herpes simplex and intramuscular injection sites. Most recently a specific leukemic infiltrate in a patient with chronic lymphocytic leukemia was demonstrated at the site of involvement with cutaneous larva migrans (Leroy et al. 1983). The incidence and severity of non-specific eruptions of leukemia, particularly viral, bacterial and fungal infections are significantly higher among the patients with defective cellular immunity. Immunological mechanism, therefore, may play a major role in the pathogenesis of cutaneous manifestation, as well as the chemotherapy and irradiation therapy for leukemia (Sokal and Firat 1965).

Pathology

Leukemia cutis is characterized by diffuse dermal and subcutaneous infiltrations of leukocytes with large, immature, irregular hyperchromatic and atypical nuclei, which would be variable, depending upon predominating cell types and their characteristics. Giemsa stain, periodic acid-Schiff (PAS) stain, cytochemical studies of chloracetate esterase and antilysozyme immunoperoxidase, and immunological studies including T and B cell markers and monoclonal antibody tests are helpful for the confirmation of the diagnosis. However, the diagnosis of leukemia should be established by the bone marrow and peripheral blood studies rather than by the cutaneous biopsy (Liver 1983).

Clinical cutaneous manifestations of leukemia

a) Specific manifestation (leukemia cutis):

Leukemia cutis is usually papular, nodular or plaque-like in configuration, small in size and red, blue or purplish in color. There are similarities of leukemia cutis between acute and chronic leukemias. Leukemia cutis is rarely seen in acute myelogenous and lymphocytic leukemia, and not infrequently in monocytic leukemia. Chronic lymphocytic leukemia is the most common cause of leukemia cutis in the Western hemisphere. When leukemic infiltration becomes severe and deeper, the large infiltrated folds and grooves may produce leonine facies. Macules and papules are seen mostly in monocytic leukemia, and are pink to reddish brown in color. These macules may resemble secondary syphilis in the beginning but later become slate blue in color (Meyer 1935). Pale shotty papules, which lie deeper in the skin, may develop into large nodules and tumors, and show a mottled appearance.

The cutaneous nodules are usually firm, globoid, edematous and rarely ulcerated unless traumatized or infected. Ulceration of leukemic nodules and tumors is very infrequently seen and is most often seen on extremities. When cutaneous ulceration is seen on the genitalia, the lesion may be misdiagnosed as syphilitic chancre or other venereal diseases. The size of nodules is variable from 0.1 cm to 10 cm. The nodular lesions may grow rapidly in a short period of time and then remain status quo for many, many years, or occasionally may disappear spontaneously, which could be due to local immunological phenomena.

The patient themselves often complain of a burning sensation, slight pain or discomfort on pressure, but do not complain of any itching.

Papules and nodules become confluent to form plaques which would be more readily palpable than visible. Plaques are seen often on the face, and are characterized by purplish and hemorrhagic discoloration, induration, scaliness and itching. Generalized plaques and infiltrations are seen very rarely. These infiltrated plaques and nodules may resemble sarcoid or mycosis fungoides.

Chloroma (granulocytic sarcoma) is the unique and pathognomonic lesion of acute myelogenous leukemia, the terminal stage of chronic myelogenous leukemia and is occasionally a precursor of the disease by as long as one year. Chloroma is seen primarily under the age of 18 years. Diffuse infiltration of immature granulocytic leukocytes into skin, periosteum of orbital and cranial bones, sinus, sternum, vertebrae, pelvis and long bones forms chloroma.

Chloroma is named for its green color, which fades within one to three hours after the tumor is exposed to air. Some of the tumors are not green and are referred to as granulocytic sarcomas. The green pigment is myeloperoxidase, which can be regenerated temporarily by exposure to hydrogen peroxide (Neiman et al. 1981). Chloroma is variable in size from 1 cm to 3 cm and may be soft and tender, or firm and non tender without any tendency to ulcerate.

Melkerson-Rosenthal syndrome is a clinically defined entity comprised of Bell's palsy, macrocheilitis and lingua plicata. Granulomatous cheilitis is often seen on histopathologic examination of the swollen lip tissue. In some cases, however, the findings may be nonspecific. We have recently reported a case of Melkerson-Rosenthal syndrome associated with hairy cell leukemia at the annual convention of the American Academy of Dermatology, Washington,
D.C., 1984, and it has been accepted for publication by the Journal of AAD (Connelly et al. 1986). The skin biopsy of the infiltrated lip of the patient with Melkerson-Rosenthal syndrome, revealed the presence of leukemic infiltrations throughout the dermis and subcutaneous fat tissue.

A patient with chronic lymphocytic leukemia presented with chronic paronychia and was found to have leukemic paronychia involving eight fingers. The diagnosis of leukemic paronychia was confirmed by skin biopsy, and the paronychia responded dramatically to irradiation therapy (High et al. 1985).
Fig. 3 Leukemia cutis, nodular and ulcerative lesions on trunk and arm of a patient with chronic myelogenous leukemia.

Fig. 4 Leukemia cutis, paronychial leukemia of 8 fingers in a patient with chronic lymphocytic leukemia.

In addition butterfly like lupus erythematosus eruptions, rosacea, lichen planus-like lesions, and hemorrhagic bullous eruptions have been reported in the literature as leukemia cutis.

Prurigo-like papules, vesiculobullous lesions, purpura and erythematomacular eruptions have been described as leukemid eruptions in the Bluefarb's monograph of leukemia cutis.
b) Non-specific manifestation:

Pallor and purpura:

Pallor and purpura are common clinical presentation in all types of leukemia. Pallor is most likely due to severe anemia. The anemia is normocytic and normochromic due to the decreased erythropoiesis, unless there is a significant bleeding to develop iron deficiency anemia. Purpura may develop spon-
taneously or due to trauma and sometimes due to thrombocytopenia or fragility of blood vessels. The exact mechanism of hemorrhagic phenomenon is unclear. Severe thrombocytopenia in lymphocytic leukemia is often associated with severe and extensive purpura. On the other hand in other types of leukemia severe purpura may be associated with thrombocytosis with abnormal platelets.

The purpura may be generalized or localized, and the sacral area is the most frequent site of predilection. Minot and Isaacs (1924) reported at least 10 percent incidence of purpura one year before death from 80 patients with lymphocytic leukemia, and purpura did not occur in many patients with thrombo-
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Fig. 8 Non-specific eruption in a patient with acute myelogenous leukemia; Acute febrile neutrophilic dermatosis.

Fig. 9 Non-specific eruption in a patient with chronic lymphocytic leukemia; Pyoderma gangrenosum.

topenia, less than 60,000.

In acute leukemia purpura can be very well explained on the basis of thrombocytopenia alone (Forkner 1938). In the chronic leukemia, however, hemorrhages may occur without any abnormality in coagulation mechanism and can be an early symptom of the disease. Such purpura might be due to either leukemic infiltrations or trauma of blood vessels. In lymphocytic leukemia 30 to 40 percent of patients were found to have prolonged epistaxis after tonsillectomy, tooth extraction or other minor surgery (Warren 1929). The tendency of bleeding in chronic myelogenous
leukemia is less frequent than in chronic lymphocytic leukemia. In most patients persistent gingival bleeding can be an important factor for anemia in leukemia, according to Ramsay (1927).

**Oral Mucosal lesions:**

The patients with monocytic leukemia were found to have gingival swelling in 80 percent of cases by Osgood (1937), and the gingival swelling was mostly due to leukemic infiltration and trauma. Marked swelling of the gums and oral mucous membrane associated with ulceration and necrosis is the characteristic findings of acute monocytic leukemia, and is absent in acute myelogenous and lymphocytic leukemia. In some patients the gingival looks pale and of normal contour, while in others the gums are hypertrophic and edematous resembling sccury and acute stomatitis. As the leukemia gets progressively worse, gums become exudative necrotic and ulcerative with a foul smell (Smith 1947).

**Erythema multiforme:**

Erythema multiforme is a hypersensitivity reaction and is characterized by target or iris-like lesions and polymorphic eruptions which may be urticarial, scarlatiniform, morbilliform exzematous or blistering. Erythema multiforme can be an early manifestation of leukemia, but, most commonly, is seen during the chemotherapy or irradiation therapy for leukemia.

**Prurigo-like papules:**

Pruritic papular lesions are usually found on the pretilial area in the beginning and gradually become generalized. The papules become vesicular, hemorrhagic and crusted. The generalized form of prurigo-like papules resemble the eruptions of dermatitis herpetiformis (Stokes and Weidman 1926) because of extreme itching, chronicity of eruptions and grouping of papules. As a result of constant scratching, the skin becomes lichenified, hyperpigmented, edematous, and easily impetiginized. Jordan and Schamschin (1933) reported prurigo-like papules as the common manifestation of aleukemic leukemia of chronic lymphocytic leukemia.

**Herpes Zoster:**

The occurrence of herpes zoster in a patient with leukemia may represent a definite relationship rather than a simple coincidence, and it is significantly more correlated when herpes zoster becomes disseminated. The high incidence of herpes zoster in leukemia and lymphoma groups is most likely due to impaired immunological mechanism, particularly T cell immuinity. In addition, immuno suppressive agents and irradiation therapy for the patients with leukemia might very well be predisposing factors for the development of herpes zoster. Sokal and Firat (1965) observed the incidence of localized herpes zoster in either previously irradiated dermatomes or sites involved by Hodgkin's disease in about 40 percent of their patients, and speculated that the neoplastic involvement of the dermatomes was conducive to viral infection or reactivation. This leukemic infiltration of the nerve ganglion may activate the endogenous varicella-zoster virus as a trigger mechanism to be manifested as herpes zoster (Dolin et al. 1971).

Among 105 patients of herpes zoster associated with leukemia the leukemia preceded the development of herpes zoster in the majority of cases, and herpes zoster usually developed during the second and third year of leukemia. However, Freund and others reported herpes zoster as an initial manifestation of leukemia (Bluefarb 1963; Freund 1928).

Dissemination of herpes zoster develops usually 4 to 10 days after the initial dermatomal presentation of herpes zoster. The patient may become febrile and toxic, along with widespread vesiculo-pustular and crusted lesions; occasionally one may develop pneumonitis and encephalitis with high mortality.

**Herpes simplex disseminate:**

Disseminated herpes simplex is usually seen in newborn babies delivered through the natural birth canal of a mother with herpetic vulvo-vaginitis, premature baby, malnourished children or patients with atopic dermatitis. It has also been observed from a patient with Hodgkin's disease, leukemia, other lymphomas and immuno-compromised patients (Solomon 1961).

A disseminated or generalized herpes simplex is usually characterized by localized grouped vesiculo-pustular eruptions on erythematosus bases at the mucocutaneous junction with subsequent widespread dissemination of vesicles and pustules. It can be presented with hepatitis, pneumonitis, encephalitis, gastroenteritis, adrenal insufficiency and viremia.

**Bacterial and fungal infection:**

Since patients with all types of leukemia have very low resistance to infection, there is significantly increased incidence of bacterial and fungal infections particularly in acute leukemia. The most frequent sites of bacterial infection are around the teeth, gingiva, tonsils and rectal area.
Pseudomonas septicemia, disseminated candidiasis primary cutaneous mucor-mycosis, primary aspergillosis, cryptococcosis, histoplasmosis, systemic sporotrichosis and nocardiosis have been reported from patients with immuno-compromised status including leukemia (Rippon 1974).

Erythroderma: (Generalized exfoliative dermatitis)
A generalized, extensive erythematous exfoliating eruption is most often caused by psoriasis, chronic dermatitis, drug eruptions or lymphoproliferative diseases. After reviewing most of the cases being reported as erythroderma secondary to leukemia, Braverman (1981) felt that those cases were more likely due to Sezary syndrome than leukemia.

The patient with erythroderma complains of severe itching, loss of hair and nails, and is often suffering from dehydration, hypoproteinemia, anemia and loss of temperature control.

Pruritus:
Itching is not seen as often in patients with leukemia as with Hodgkin's disease. However, if the patient has urticaria, prurigo-like papules, jaundice or eczematous dermatitis, pruritus may be a significant problem.

Urticaria:
Chronic urticarial eruptions and angioneurotic edemas have been observed in all types of leukemia.

Hyperpigmentation and jaundice:
Hyperpigmentation is observed infrequently in leukemias and is charactertized by greyish brown discoloration resembling Banti's disease (Ebstein and McEachern 1937; Jaffe 1927). The pigmentation could be due to increased tyrosinase activity in leukemia (Haden and Orr 1924).

Jaundice, which is rarely seen in leukemia, is usually due to diffuse infiltration of leukemic cells into hepatic tissue or obstruction of the common bile duct compressed by lymph nodes infiltrated by leukemia.

Priapism:
Priapism has been reported in association with all types of leukemia. Craver (1933) felt that the infiltration of male and female erectile tissue is extremely rare, even though it has been frequently described in textbooks. According to Craver, actual leukemic thrombi have been found in the corpora cavernosa in a few patients but no clot was found in other cases.

Sweet's syndrome and leukocytoclastic vasculitis:
This acute febrile neutrophilic dermatosis is characterized by the sudden onset of high fever, leukocytosis with neutrophilia and tender raised erythematous plaques on the face and extremities, most commonly in women.

The etiology is unknown, but it has been reported in acute myelogenous leukemia (Raimer and Dunkan 1978). Most of the vasculitis seen in leukemia, lymphoma or multiple myeloma is associated with monoclonal antibody or mixed cryoglobulins (Brout et al. 1974).

Ecthyma gangrenosum:
Ecthyma gangrenosum has been seen most often in severely burned patients, debilitated patient and patients with leukemia. It is caused by Pseudomonas aeruginosa and cepacia infection, and clinically is characterized by the hemorrhagic bulla formation and subsequent development of multiple punched out ulcers (Hall et al. 1968).

Pyoderma gangrenosum:
The initial eruptions of pyoderma gangrenosum are pustules or fluctuating nodules which progress to form ulcerations. As the ulcers get bigger peripherally, the margins of the ulcer becomes purplish red and underminded with remarkable tenderness. Pyoderma gangrenosum is often associated with ulcerative colitis, rheumatoid arthritis and occasionally with macroglobulinemia and leukemia. The ulcer of pyoderma gangrenosum secondary to leukemia has been reported to be more superficial with purplish marginal bulla formation (Perry and Winkelmann 1972).

Mikulicz disease:
Mikulicz disease is characterized by symmetrical enlargement of the lacrimal, orbital and salivary glands due to lymphocytic infiltration and has been reported to be associated with leukemia an lymphoma (Bluefarb 1960; Braverman 1981). Dermatomyositis, bullous pemphigoid and eczematous dermatitis have also been reported with leukemia.

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