Dermatological Manifestations of Haemological Malignancies

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ABSTRACT

Hematological malignancies are heterogeneous group of disorders, which are broadly divided into lymphoid, myeloid, histiocytic and mast cell neoplasms. Lymphoma, leukemia and plasmacell dyscariasia are not uncommon in our enviroment. There are no accurate global epidemiological data on the prevalence of hematological malignancies as well as the prevalence of cutaneous features found in these disorders. However, recognition of cutaneous manifestation of systemic disorders remains an important aspect in management of these patients by aiding early diagnosis of the internal disorder and limiting the number of investigations especially when resources are limited. Furthermore, it is hoped that identification of these cutaneous disorders by physicians will aid in diagnosis of the underlying disorder. The article reviews the cutaneous manifestations associated with lymphomas, leukemia's and plasma cell dyscrasias.

Keywords: lymphoma, leukemia, skin manifestation

INTRODUCTION

Hematological malignancies are heterogeneous group of disorders, which may arise from cells of the bone marrow and the lymphatic system and can be broadly divided into lymphoid, myeloid, histiocytic and mast cell neoplasms according to the World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues. The major types of hematologic malignancies include leukemia, lymphoma, and plasma cell neoplasms which will be discussed in this review.

An accurate data on prevalence of haematological malignancies may not be available globally due to different reporting system and poor availability of data in certain regions. However, an estimate of blood and bone marrow malignancies involving the skin has been put at 5.5%. In a study of mucocutaneous manifestations of lymphomas and leukemias in black Kenyan children, 17.4% had skin infiltration from malignant cells.

Dermatological manifestations of haematological malignancies can be classifies into two groups. Those resulting from infiltration of the skin by the malignant cells and non-specific cutaneous lesions which may be result from a paraneoplastic effect, or as a result of bone marrow dysfunction induced by the malignant process or chemotherapy.

The haematological diagnosis may be established before skin signs emerge, while in some cases skin lesions may be the presenting feature or may be the sole manifestation with possible subsequent systemic spread (e.g. cutaneous T-cell lymphoma).

Identification of these cutaneous signs could aid in the early diagnosis and treatment of hematologic disorders. These disorders are usually not pathgnomonic of a specific malignancy but when present they should increase the suspicion of an underlying haematologic malignancy.

The manuscript highlights the cutaneous manifestations of leukemia, lymphoma and plasma cell dyscrasias.

CUTANEOUS MANIFESTATIONS OF LEUKAEMIA

Leukaemia is malignant neoplasm of leukocytes.

The major types of leukaemia include Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia(CML) and chronic lymphoid leukemia (CLL).

The frequency of occurrence of cutaneous lesion varies in the different types of leukemia. Cutaneous lesions occur in up to 25% of patients with chronic lymphocytic leukemia (CLL).

Cutaneous features of Leukemia may result from deposition of malignant cells in the skin as in leukemia cutis (see figures 1 & 2) or they could be non-specific resulting from complications of the illness. Leukemia cutis (LC) is the non-specific term used for extra-medullary deposits of leukemic cells in the skin that could occur in any type of leukemia. It is due to localized or disseminated skin infiltration of neoplastic leukocytes or their precursors into the epidermis, the dermis, or the subcutis. This feature connotes poor prognosis. LC occurs in 3.06% of Asian patients , the frequency in African patients is not known. The frequency and age distribution depend on the leukemia subtype and it is commonly associated with acute monocytic, myelomonocytic, and the T-cell leukemias.. In chronic myelomonocytic leukemia (CMML), 10.2% are likely to present with LC. It has been described in patients with AML, chronic myelogenous leukemia, myelodysplastic syndromes, and myelodysplastic/lymphoproliferative diseases. LC is more frequent in patients with AML, and in particular it can be found in myelomonocytic (FAB-M4) and monocytic (FAB-M5) subtypes. Skin involvement is uncommon in ALL but could be an early manifestation of standard risk as well as in high-risk ALL. It is mainly associated with a B-cell precursor immunophenotype of the lymphomatous cells. It may precede the involvement of the bone marrow or peripheral blood in which case it is termed aleukemic leukemia cutis (ALC). It is also the commonest type of cutaneous manifestation..

Reported incidence of LC in patients with acute myeloid leukemia (AML) is 2% to 20%. There are different frequencies of skin involvement in various subtypes of AML. Half of patients with acute monocytic leukemia (AML-M5) may finally develop LC. Leukemia cutis may indicate a poorer prognosis. Prognosis in CLL patients with LC is rather good and many authors claim that it does not significantly affect patients' survival unlike other leukaemia. However, prognosis is poor in patients in whom LC shows blastic transformation (Richter's syndrome) and when leukemic infiltrations in the skin appear after the diagnosis of CLL . The clinical features of leukemic cutis are diverse and include macules, papules, plaques, nodules, blister ecchymoses, palpable purpura, and ulcerative lesions. . Lesions may be solitary granulocytic sarcoma (see figure 1), multiple or generalized erythematous maculopapular eruption sometimes in a polymorphic pattern. Erythematous macules, tumor, blisters and ulcerative lesions are rarer. . Leukemia cutis may exceptionally occupy the eyelids in AML presenting with bilateral erythematous eyelid lesions (Figure 3) while gingival hypertrophy tends to occur in monocytic leukaemia. AML blasts can occur as isolated lesion in the skin and are known as chloromas. (See Figure 3)The ability of cutaneous presentation in AML is associated with monosomy 7, trisomy 8, *MLL* rearrangement, inv(16), trisomy 4 and t(8;21).. Histology shows nodular/diffuse infiltrates, often with perivascular and periadnexal accentuation, sparing the upper papillary dermis, with prominent single arraying of neoplastic cells between collagen bundles. Extension to the subcutis may be noted in all deep biopsy specimens. Immunohistochemical stains are used to determine the expression of selective cell surface markers helpful in diagnosis myeloid leukemia cutis..

Leukemic skin infilteration should be differentiated from numerous nonspecific lesions, which may be present in up to 80% of all patients with leukemia.. The non–specific cutaneous features in patients with Leukemia include features of bone marrow dysfunctions such as thrombocytopenia and coagulation abnormalities leading to bleeding in the skin. This will manifest as petechia, purpura or echymoses.(Figure 4) Immune suppression leading to infection is also seen. Para-neoplastic phenomena, induction of autoimmune disorder and chemotherapy induced vasculitis may accompany neoplasias . Drugs responsible for the vasculitis included hydroxyurea, vincristine, cytosine-arabinoside, methotrexate, all-trans retinoic acid, granulocyte-colony stimulating factor, interferon and antibiotics. Thus skin biopsy should be performed in all cutaneous lesions in patients with hemopoietic neoplasias. The chemotherapy induced neutropenia predispose to various infectious cutaneous lesions.

Skin infections are not uncommon in patients with leukemia. In a study from India, cutaneous viral infections were significantly associated with acute lymphoblastic leukemia. Viral infections include

multiple warts, herpetic infections and molluscum contagiosum.(See Figure 5) The incidence of varicella-zoster infection was significantly reduced with the use of antiviral prophylaxis. Opportunistic cutaneous fungal infections seen in these group of patients include, pityriasis versiclor, aspergillus, mucormycosis, fusariosis and disseminated candidiasis,. These are particularly frequent in patients with acute leukaemia. it is important to consider mycological examination for opportunistic fungal infections, such as aspergillosis or fusariosis, which are easily overlooked by routine culture methods using conventional media with cycloheximide. Antifungal prophylaxis is recommended during curative-intent therapy for acute myeloid leukemia

Bacterial skin infections includes cellulitis, multiple abscesses, paronychia, folliculitis, ecthyma gangrenosum (associated with *pseudomonas aerogenosa*)- necrotic centre and halo of erythema and granulomatous skin lesions from mycobacterium and nocardia.

Autoimmune cutaneous manifestation in leukaemia include subcorneal pustular dermatosis of Sneddon-Wilkinson, pyoderma gangrenosum ,erythema elevatum diutinum (found on the backs of the hands, other extensor surfaces overlying joints, and on the buttocks) neutrophilic eccrine hidradenitis. Others include Pyoderma gangrenosum(PG) and Sweet's disease(acute febrile neutrophilic dermatosis). Atypical or bullous pyoderma gangrenosum which are superficial form of pyoderma gangrenosum and presents with superficial, purulent, ulcerated plaque are commonly associated with acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, and myelofibrosis or agnogenic myeloid metaplasia.

Other secondary lesions are vasculitis, generalized pruritus, exfoliative erythroderma, and paraneoplastic pemphigus. An exaggerated reaction to an insect bite and insect bite-like reactions have been also observed.

Cutaneous drug reactions are also seen in this group of patients especially those on imatinib .Features include dry skin, alopecia, facial edema, and photosensitivity. Complications from treatment also include exfoliative dermatitis, Stevens-Johnson syndrome, erythema nail disorders (discoloration), psoriasiform dermatititis, hypotrichosis, including alopecia, urticaria, and leukocytoclastic vasculitis.

CUTANEOUS MANIFESTATIONS OF LYMPHOMA

Primary cutaneous lymphoma originates in the skin. (See Figure 6) There may be no evidence of extra cutaneous disease at the time of diagnosis and it usually follows an indolent course in the skin for a long duration.(36) Lymphoma cells may also be deposited in the skin known as lymphocytoma cutis. Majority of the lymphoproliferative diseases involving the skin are cutaneous T- cell lymphomas (CTCL). They include mycosis fungoides (MF), and Sezary syndrome(SS). The other group of lymphoma are the B cell lymphomas of the skin .

CUTANEOUS T CELL LYMPHOMA

Mycosis fungoides (MF) is the most frequently encountered manifestation of primary cutaneous NK and T-cell lymphoma (pCNKTCL). MF is a rare indolent malignancy while SS is the erythrodermic version of MF. The skin lesions in MF/SS are due to epidermotrophic skin infiltration with formation of Pautrier's micro-abscesses. which is a pathognomonic feature of epidermotropic early CTCL.

Mycosis fungoides (MF) is initially confined to the skin but may spread to other parts of the body especially lymph nodes and visceral organs. The early MF lesions are usually eczematous after which plaques and tumours which may ulcerate may develop. The hypopigmented variant has been reported in blacks. Pruritus occur less frequently when compared to SS . Scaly erythrodermic plaque pattern is the predominant form seen in MF while in SS pruritic exfoliation or infiltrated erythroderma is common.

Sezary syndrome is the leukemic variant of mycosis fungoides. Clinical features seen in SS fea include palmar and/or plantar hyperkeratosis, alopecia, erythoderma, edema, nail dystrophy, ectropion, cutaneous talengectasia and non-migratory papulo-squamous eruption. SS/MF patients may also present with pruritus associated with nodules or plaque. (figure 6)

The nail changes usually occur in advanced MF and SS and involve multiple digits. Nail changes include discoloration, thickening, crumbling, onycholysis, onychomadesis, subungual hyperkeratosis, splinter hemorrhages and anonychia.

Pachydermatosis is an atypical manifestation of MF and LC. It presents as severely thickened skin with deep folds (leonine facies) as observed in pachyderm animals such as elephants, rhinoceros, and

hippopotami. It may occur on the face (FMF) or the extremities (MF). It is occasionally observed with primary cutaneous NK and T-cell lymphoma (pCNKTCL), primary cutaneous B-cell lymphoma (pCBCL), and leukemia cutis (LC). Histology shows dense dermal neoplastic infiltrates. The rapidly appearing pachyderma may be transitory and responds readily to oral steroids. Other cutaneous T-cell lymphomas have been reported to present as ulcer and can be misdiagnosed.

There are other cutaneous T- cell lymphomas other than mycosis fungoides (MF) and SS with wide variations in clinical presentation, biological behaviour and prognosis. The common subtypes are lymphomatoid papulosis, CD30+ large cell cutaneous T-cell lymphoma, Primary cutaneous anaplastic large cell lymphoma (ALCL) and subcutaneous panniculitis-like T-cell lymphoma. Others include peripheral T-cell lymphomas and adult T-cell leukemia/lymphomas.Primary cutaneous anaplastic large cell lymphoma (ALCL) usually starts as one or a few tumors on the skin of varying size and tend to ulcerate in the middle.

Lymphomatoid papulosis is a benign, slow-growing disease that often comes and goes on its own, even without treatment and can occur in as much as 10-20% of lymphoma. It often begins as several large pimple-like lesions that may break open in the middle. Histologically, lymphomatoid papulosis has features that look like primary cutaneous anaplastic large cell lymphoma (ALCL).

Subcutaneous panniculitis-like T-cell lymphoma is a rare lymphoma that invades the subcutaneous adipose tissue layers of the skin, where it causes nodules (lumps) formation. It usually grows slowly and tends to have a good prognosis.

B-CELL DERIVED CUTANEOUS LYMPHOMA

Approximately one-fourth of cutaneous lymphomas are B-cell derived and are generally classified into three distinct subgroups: primary cutaneous follicle center lymphoma (PCFCL) , primary cutaneous marginal zone lymphoma (PCMZL) (mucosa-associated lymphoid tissue [MALT] type), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT) and intravascular large B-cell lymphoma. The lesion can manifest as lymphocytoma cutis which are rare benign proliferation of lymphocytes in skin. It occurs in any part of the body compare to lymphocytoma which usually occur in malar ridge, tip of nose and ear lobes. There is similarity in appearance of lymphoma cutis and Leukemic cutis. Pathologic review and an appropriate staging evaluation are necessary to distinguish primary cutaneous B-cell lymphomas from systemic B-cell lymphomas with secondary skin involvement.

Primary cutaneous marginal-zone B-cell lymphoma (PCMZL) is a curable lymphoma without extracutaneous manifestation. it is considered the cutaneous variant of extranodal marginal zone B-cell lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT)and it is sometimes linked to an infection with Borrelia, the germ that causes Lyme disease. Primary cutaneous follicle-centre lymphoma (PCFCL) is the most common B-cell lymphoma of the skin. It tends to grow slowly and have a good prognosis. Both PCFCL and PCMZL appear as pimples, plaques (raised or lowered, flat lesions), or nodules as a single or few lesions. They are indolent slow growing lymphomas that infrequently disseminate to extra-cutaneous sites and are associated with 5-year survival rates that is approximately 100%. In contrast, PCDLBCL, LT is an aggressive lymphoma with an inferior prognosis.

Leukemic phase of non-Hodgkin lymphoma can also present with leukemic cutis. Non- Hodgkin lymphoma can lead to life-threatening autoimmune skin disease characterized by severe mucosal erosions and cutaneous blisters and erosions. Classical pyoderma gangrenosum are associated with non-Hodgkin lymphoma. Para neoplastic pemphigus (PNP) is a life-threatening autoimmune skin disease characterized by severe mucosal erosions and cutaneous blisters and erosions and associated with non-Hodgkin lymphoma and chronic lymphocytic leukemia.

There are Hodgkin and non-Hodgkin lymphomas that are not strictly cutaneous lymphoma. Cutaneous manifestations are commoner in Non-Hodgkin Lymphoma than Hodgkin Lymphoma (HL). Cutaneous Hodgkin's disease is a rare condition accounting for 3.4% of HL that usually occurs late in the course of Hodgkin's lymphoma and carries an adverse prognosis . The most common clinical presentation is single or multiple dermal or subcutaneous nodules. The suggested mechanisms of cutaneous involvement are retrograde lymphatic spread distal to involved lymph nodes, direct

extension from an underlying nodal focus and hematogenous dissemination of malignant lymphocyte cells.

Indolent or 'low-grade' nodal B-cell NHLs which include follicular and small lymphocytic lymphomas usually have no cutaneous features. similarly, involvement of the skin is relatively uncommon in Lymphoblastic leukemia/lymphoma (LBL) a malignant neoplasm of precursor lymphocytes of B- or T-cell phenotype.

A large number of patients developed nonspecific skin manifestations, most of which are the result of myelosuppression, immunosuppression, or direct cytotoxic effects on tissues. It can reflect the immune status and stage of disease, and cutaneous reactions may occur from conventional and targeted agents used to treat. Skin infections usually due to viral aetiology are common in lymphoma patients in addition to generalised pruritis.

PLASMA CELL DISORDERS

Skin mainifestations in plasma cell dyscrasias are rare but may be the first clinical manifestation of the underlying disorder. They occur as a result of the production of abnormal proteins from B cells. They include cold agglutinins, cryoglobulins, light chain deposits which may cause an increase in plasma viscosity.. Skin disorders that have been associated with plasma cell dyscrasias include cutaneous amyloidosis, cryoglobulinemia, POEMS syndrome, normolipemic plane xanthoma, and plasmacytoma.

Cutaneous Amyloidosis is a rare skin disorder caused by the extracellular deposition of insoluble polymeric protein fibrils in the skin. it may be primary or secondary Cutaneous involvement in systemic amyloidosis occurs in 30 to 40% of patients . Common lesions seen include petechiae, purpura, and ecchymosis, resulting from intra-cutaneous hemorrhage as a result of infiltration of blood vessel wall by amyloid.

Cryoglobulinaemia remains asymptomatic in most cases but can lead to immune complex tissue deposition, causing cryoglobulinaemic vasculitis. Between 2% and 15% of cryoglobulin positive patients develop cryoglobulinaemic vasculitis These cutaneous vasculitis presents as palpable purpura usually seen in the lower extremities. Other cutaneous manifestations of cryoglobulinaemia include cyanosis, Raynaud phenomenon, acral haemorrhagic necrosis haemorrhagic crust and skin ulceration. The recognition offers an opportunity for causal rather than symptomatic therapy of the vasculitides. A number of dermatological features has been associated with cryoglobulinaemia, they include Necrobiotic xanthogranuloma (NXG). Previous report showed that 23% of patients with NXG had a monoclonal gammopathy. NXG is usually associated with IgG k and λ type monoclonal gammopathy. It is a chronic, progressive granulomatous disorder which manifests as yellowish plaques and nodules, most commonly seen in the periorbital region its occurrence may predate the gammopathy . Wood *et al.* reported a mean time of 2.4 years from the first appearance of NXG lesions to the development of haematologic disorders. They recommended continued surveillance for malignancies particularly multiple myeloma throughout life.

Generally plasma cell disorders may present with cold uticaria, follicular hyperkeratosis, scleromyxedema, alopecia and pigmentation.

Scleromyxedema is a rare progressive fibro-mucinous disorder. It is seen in patients with Monoclonal immunoglobulin (Ig) G paraprotein with lambda light chains. It presents with generalized sclerodermoid eruption of 1-mm to 3-mm waxy lichenoid (flat-topped) papules eruption involving the face, trunk, and limbs. The lesions have a central depression surrounded by an elevated rim “dough nut sign” which has been reported in proximal inter-phalangeal joint. Involvement of the face produces leonine facies, (sclerodermoid face). Deep furrowing usually linear commonly seen on the back gives the "Shar-Pei sign" . The histology of the skin shows numerous mucin deposits in papules and sclerotic malformations, which consist of thickened collagen fibres.

POEM syndrome consists of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes). This is are rare syndrome associated with M protein production. Cutaneous disorders are present in 68% of patients. They include dusky discoloration of the skin, hypertrichosis, skin thickening with sclerodermoid changes The latter is caused by greater collagen deposition by the dermal fibroblasts caused by increased Vascular Endothelial Growth Factor (VEGF) levels./ Other findings include acrocyanosis, hemangiomas, telengiectasis and Raynaud's phenomenon. White

fingernails hyperhidrosis, leukonychia, necrotizing vasculitis, and calciphylaxis. Hyperpigmentation can be diffuse or localized, occurring mainly on the extensor surfaces, dorsum, neck and armpits. It predominantly regresses in response to treatment. The onset of multiple cutaneous angiomas in this syndrome has been observed in the patients. They appear during the course of the disease with firm papular lesions, erythematous or violet in colour usually on the trunk or the proximal region of the limbs. They present with variable histological characteristics, the most common being cherry hemangioma, lobular capillary hemangioma and less frequently, glomerular hemangioma. Cutaneous plasmacytoma may also be observed in POEMS syndrome. Multiple myeloma rarely has cutaneous involvement which usually occurs in the late stages and is a reflection of increased tumor cell burden. Patients with multiple myeloma have a very short survival period once specific skin lesions appear, regardless of the therapy administered.

CONCLUSION

There are diverse dermatological manifestations of haematological malignancies which can be the first presentation, main manifestation of the disorders of haematological malignancies or occur in haematological remission. Skin biopsy and immunohistochemical examination, combined with routine blood analysis and bone marrow examination, are required to ensure early diagnosis and proper treatment.

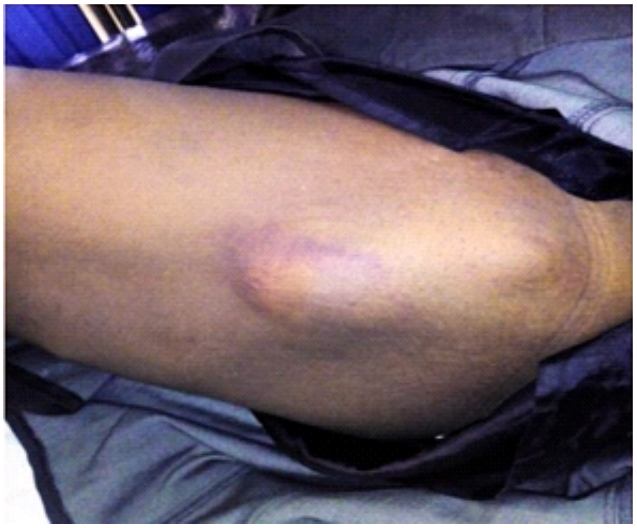

Figure 1: Subcutaneous granulocyte sarcoma in CML

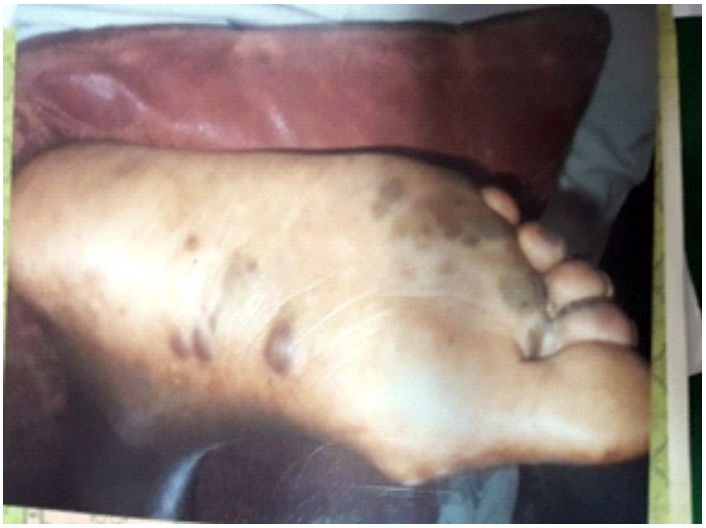

Figure 2 : Leukamia cutis

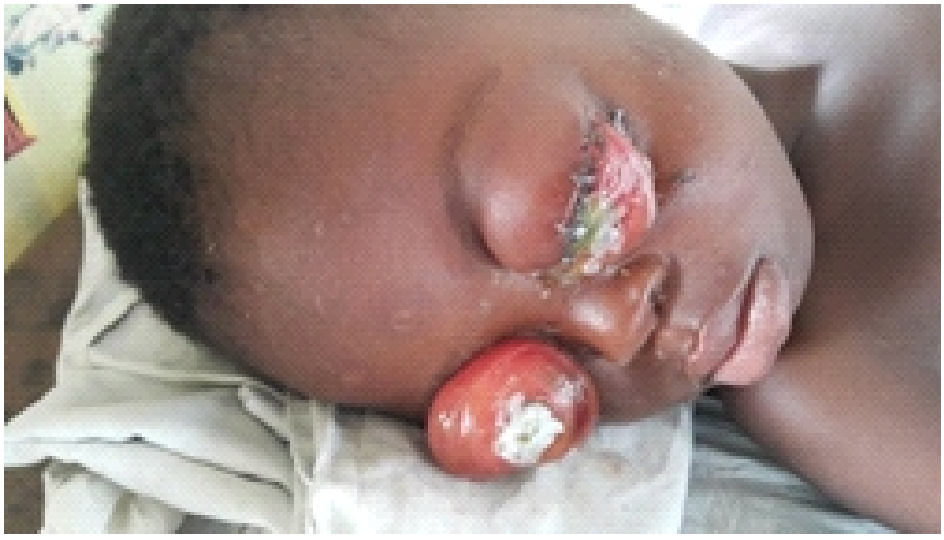

Figure 3: Leukemic infiltration of the eyelid with proptosis in a patient with AML (Chloroma)

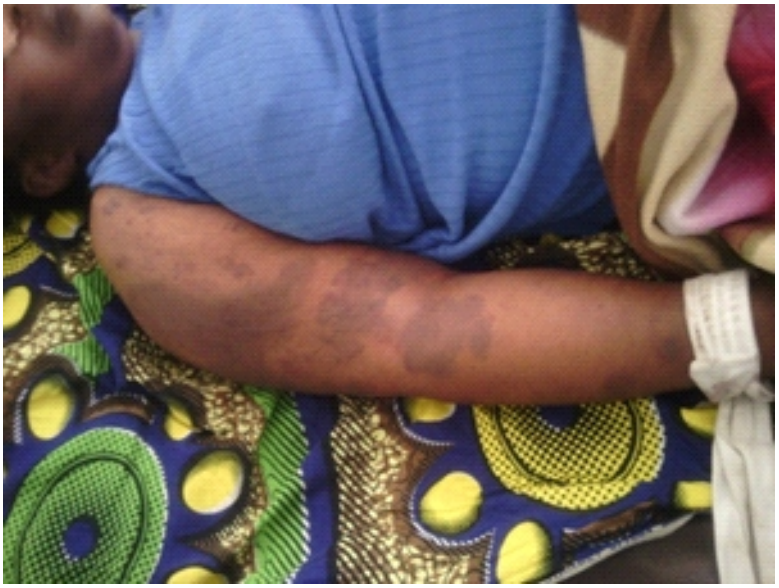

Figure 4 : bleeding diatheses (Petechiae, purpura, echymotic patches in a patient)

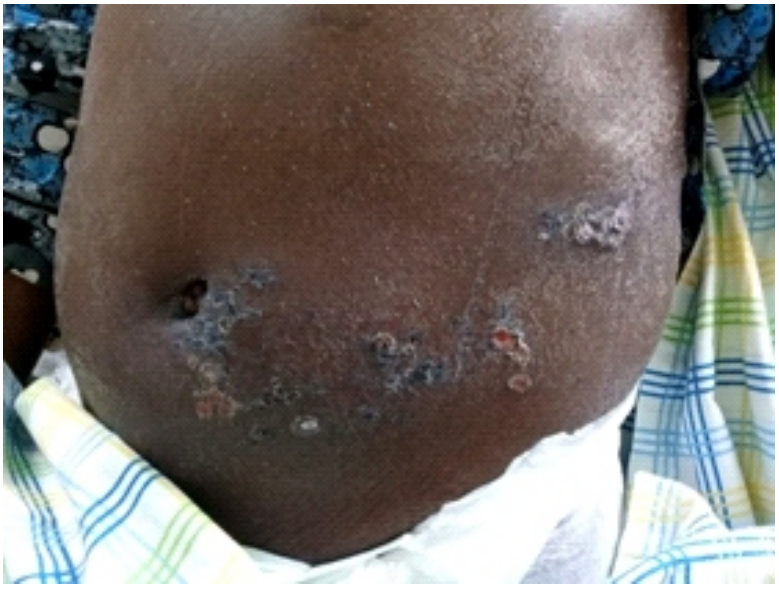

Figure 5: Herpes simplex infection in patient with chronic lymphocytic leukaemia

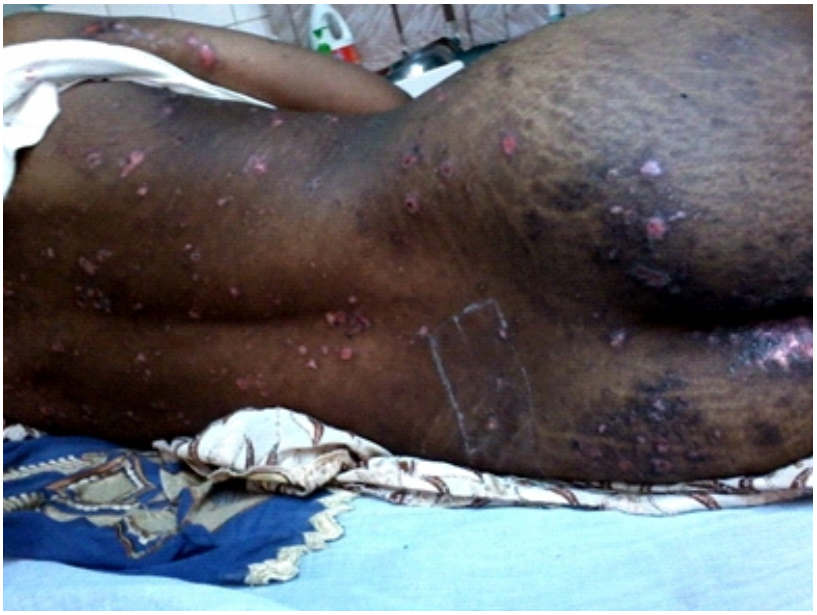

Figure 6: Cutaneous lymphoma (T-cell lymphoma)

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