Review Article

Dermatological manifestations in hematological diseases

Arushi Dudeja[1*], Renu Vidolkar[2]

[1,2]Third Year Resident, Department of Dermatology, Venereology and Leprology, MGM Medical College and Hospital, Aurangabad, Maharashtra, INDIA.
Email: arushi0709dudeja@gmail.com

Abstract Disorders of the blood components and the coagulation system may have striking mucosal and cutaneous signs and symptoms and sometimes are the presenting features of haematological diseases. The emphasis in this article is on these mucocutaneous manifestations that may act as window to haematological disorders.
Key Word: forensic osteology, human remains, identification, anthropology.

Address for Correspondence
Dr. Arushi Dudeja, Third Year Resident, Department of Dermatology, Venereology and Leprology, MGM Medical College and Hospital, Aurangabad, Maharashtra, INDIA.
Email: arushi0709dudeja@gmail.com
Received Date: 20/09/2015 Revised Date: 02/10/2015 Accepted Date: 24/10/2015

Access this article online

Quick Response Code:

Website: www.medpulse.in

DOI: 25 October 2015

INTRODUCTION

Mucocutaneous changes are often an indicator of underlying haematological disease. The skin and mucous membranes are highly vascular and are susceptible to abnormalities in blood. These may result from alterations in haemoglobin concentration, oxygenation and plasma volume. In some part of the world, where laboratory investigations are not available or affordable, these manifestations prove to be useful in detecting the underlying disease.[2]

Anemia

Anemia from any cause will result eventually in pallor of the skin and mucous membrane

Iron deficiency anemia

Mucocutaneous signs of iron deficiency anemia are-

- pallor,
- nails- koilonychias (fig-1) slow growth, ridging, brittleness(maybe due to decreased oxygen availability causing decrease in disulfide bond formation thus, decreasing nail pliability)
- oral – atrophic glossitis, angular cheilitis[5]
- hair – diffuse alopecia, greying of hair, splitting , dryness
- generalised pruritus
- associated with- Blue rubber bleb nevus syndrome, Hereditary hemorrhagic syndrome, Rheumatoid arthritis, SLE, Scleroderma, MCTD (mixed connective tissue disorder).

How to site this article: Arushi Dudeja, Renu Vidolkar. Dermatological manifestations in hematological diseases. *MedPulse – International Medical Journal* October 2015; 2(10): 710-715. http://www.medpulse.in (accessed 22 October 2015).

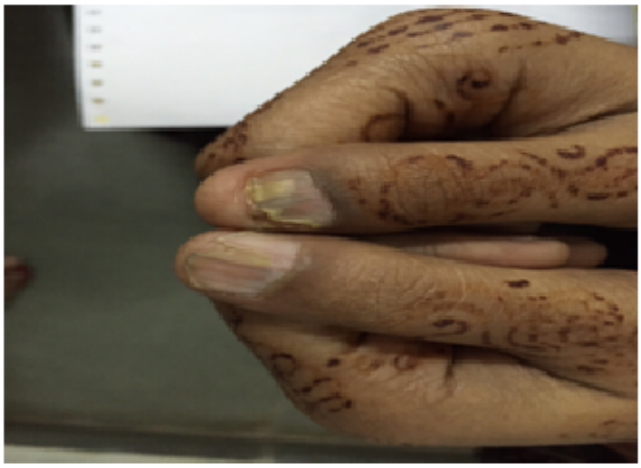

Figure1: koilonychia of both thumbs

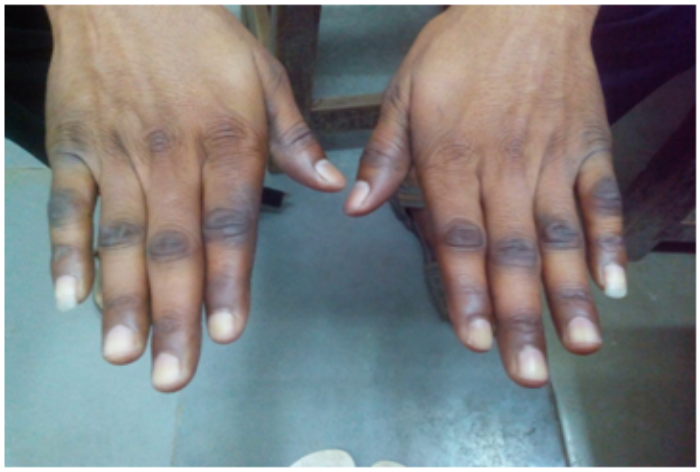

Figure 2: hyperpigmented knuckles in megaloblastic anemia

Megaloblastic anemia-(fig -2)

These are due to impaired DNA synthesis and most common causes are either vitamin B12 deficiency or folic acid deficiency. pernicious anemia is the most common cause of vitamin B12 deficiency. It is an autoimmune disorder that attacks intrinsic factor in ileum. Second cause is anti parietal cell antibody that destroys gastric parietal cells that produce intrinsic factor. It is commonly associated with- Vitiligo, Hashimoto's thyroiditis, Addison's disease. **Cinically produces**

Hyperpigmentation on knuckles of hands, feet especially in darkly pigmented individuals.

Partially reversible poikiloderma

Premature greying of hair

Cobblestone or red beefy tongue, cheilitis

Folate deficiency is usually due to decreased intake. Dermatological causes include- erythroderma, drugs like- methotrexate, phenytoin, trimethoprim.

Aplastic anemia

Caused by lack of bone marrow activity causing pancytopenia. Manifestations include-

- Pallor
- Reticulate hyperpigmentation
- Angular stomatitis, gum bleeding
- May be associated with- Dyskeratosis congenita

Hemoglobinopathies and Hemolytic anemias

Sickle cell disease, thalassemia, hereditary spherocytosis may all be complicated by

- lower leg ulceration which may start in childhood and be both recalcitrant and recurrent. Ulcers are usually in the ankle area over medial/lateral malleoli. Stasis may play a role, other factor may be vessel occlusion by sickling and impaired local oxygenation.[4]
- Atrophie blanche like lesions may occur due to microvasculature occlusion. Hyperpigmentation of legs maybe seen in such patients owing to Cutaneous deposition of hemosiderin and melanin.
- Others- pruritus, alopecia, hand foot syndrome (unequal growth) because of childhood dactylitis.

Polycythaemia

Absolute increase of circulating red blood cells that causes an increase in hematocrit values higher than 55% characterises polycythemia vera. Skin changes are characteristic in this and are as follows-[1]

- Ruddy cyanosis (face, neck, distal extremities)
- Aquagenic pruritus (intense disabling itch after water exposure) lasts upto 1 hour, may antedate the onset of polycythaemia by several years.
- Vascular involvement with features of peripheral vascular disease, raynaud's phenomenon, leg ulcers, peripheral gangrene or deep vein thrombosis, may also occur owing to sluggish flow.
- Erythromelalgia may occur with intense burning sensation, pain and local warmth occurring in paroxysms of minute to days.
- Oral – congested, gingival bleeding, petechiae and ecchymosis in mucosa and cyanosis.

LYMPHOCYTE DISORDERS

Neutrophilia

It is associated with skin conditions like-

- Infections
- Erythrodrma
- Pustular psoriasis
- Erythema multiforme
- Systemic corticosteroid administration
- Neutrophilic dermatosis (sweet syndrome, pyoderma gangrenosum)

- Polycythaemia
- Leukemia, lymphoma

Neutropenia

Associated with-[6]

- SLE (systemic lupus erythematosus- prevalence ranging from 20-47%) (fig-3)
- Systemic sclerosis (approximately in 7% cases)

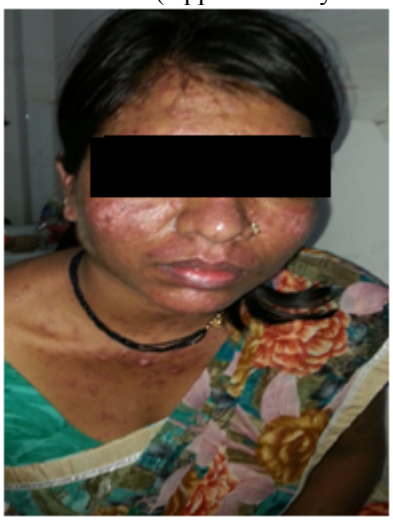

Figure 3: malar rashes over face

Eosinophilia

Associated conditions are –

- Infections- scabies Parasitic infections

Insect bites

- Allergic- atopic dermatitis Urticaria, angioedema Allergic reactions
- Immunobullous- bullous pemphigoid Pyoderma gangrenosum
- Inflammatory - eosinophilic fasciitis conditions Eosinophilic paaniculitis

Chronic GVHD

Eosinophilic pustular folliculitis

Incontinentia pigmentii

- Vasculitis- churg-strauss syndrome Eosinophilic vasculitis Drug induced vasculitis
- Neoplastic / - hypereosinophilic syndrome proliferative Cutaneous T cell lymphoma

Hodgkin's disease

Myeloproliferative disorders

Systemic mastocytosis

Leukemias and Lymphomas

Skin lesions because of infiltration by leukemias and systemic lymphomas present as flesh colored or erythematous papules or nodules sized from few millimetres to several centimetres in diameter and often have a rubbery consistency. These lesions tend to localize at sites of skin injury, including injection sites, herpes simplex or zoster lesions, burns or physical trauma. There may be diffuse involvement of the skin. Amongst the systemic lymphomas, patients with NK/T cell derived neoplasms are more likely to develop specific Cutaneous lesions. Cutaneous infiltration occurs rarely in hodgkin's disease,there may be pruritus, while non hodgkin's lymphoma involve the skin more commonly. Cutaneous disease is particularly common with diffuse large cell and high grade lymphomas but uncommon with follicular lymphomas. cutaneous infiltrates also occur in about 10% of leukemia patients (leukemia cutis).[7] Lesions include hyperplastic, friable gingival. Myelogenous leukemia often affects the trunk, monocytuc leukemia involves the entire skin as well as oral mucosa, while lymphocytic leukemia commonly affects skin of the face and extremities. In acute myeloid leukemia, periorbital region is commonly prone to leukemic infiltration. In general, all three blood cell lines are affected so, there is pallor, petechiae, ecchymosis and bleeding. Gingival haemorrhage, oral ulcers and opportunistic skin infections may occur. An unusual presentation in chronic myelogenous leukemia is a tender, edematous, purpuric area of induration on the lower leg resembling stasis dermatitis. Infiltration of the lips in Hairy cell leukemia may produce macrocheilia. Chloromas (granulocytic sarcomas) are popular or nodular infiltrations of malignant myeloid cells in the skin. These are more common in M1 and M2 subtypes of acute myelogenous leukemia. In B cell chronic lymphocytic leukemia, primary skin infiltration is rare, but malignant cells frequently infiltrate infectious or inflammatory skin lesions. In contrast, T cell CLL involves the skin in as many as one third of patients with localised or extensive erythema, or erythematous papules and plaques. This infiltration may be so extensive as to cause a leonine facies. Myeloproliferative disorders have been associated with a resistant dermatosis termed the eosinophilic dermatosis of myeloproliferative disease, consisting of a pruritic eruption of papules and nodules. A variety of other dermatosis including sweet's syndrome, pyoderma gangrenosum, insect bite like reactions and various blistering disorders have been associated with leukemias and lymphomas.

PLATELET AND CLOTTING DISORDERS

Thrombocytopenia

Idiopathic thrombocytopenic purpura

Occurs because of premature destruction of platelets. There maybe diffuse localized petechiae seen on the lower extremities in association with epistaxis, gingival bleeding, skin and mucous membrane.

Thrombotic thrombocytopenic purpura

It is a fulminant disorder. On examination, multiple ecchymosis, jaundice and pallor may be found.

Post transfusion purpura

A sudden onset of mucosal bleeding and thrombocytopenia approximately 1 week after the transfusion of RBC's characterises post transfusion purpura.

Purpura fulminans

It mainly affects children and infants. There maybe extensive blue black colored haemorrhagic necrosis and biopsy typically reveals small vessel microthrombi and vasculitis.

Disseminated intravascular coagulation

Intravascular deposition of fibrin in the vasculature and simultaneous consumption of coagulation factors and platelets. All forms of purpura can be observed including haemorrhagic bulla and purpura fulminans which can progress to peripheral gangrene,

Thrombophilia

Associated with – livedo reticularis

Acrocyanosis

Splinter haemorrhage

Thrombophlebitis

Deep vein thrombosis

Leg ulcers

Purpura fulminans

Anetoderma

Antiphospholipid syndrome-[1] (fig-4)

It is an acquired, multisystem disorder characterised by recurrent thrombosis in the arterial system, venous system or both. Secondary antiphospholipid syndrome is often associated with SLE and infrequently with other diseases like- lymphoproliferative disorders, autoimmune diseases, infections (syphilis, HIV, hepatitis C) and drugs (procainamide, quinine, hydralazine, hydroxyzine, phenytoin). Non inflammatory vascular thrombosis is the most frequent finding in skin lesions of patients with antiphospholipid syndrome. Cutaneous manifestations include livedo reticularis (violaceous, red or blue, reticular or mottled pattern of the skin of arms, legs and trunk), necrotizing vasculitis, thrombophlebitis, Cutaneous ulceration and necrosis, erythematous papules, purpura, ecchymosis, painful skin nodules and sublingual splinter haemorrhages.

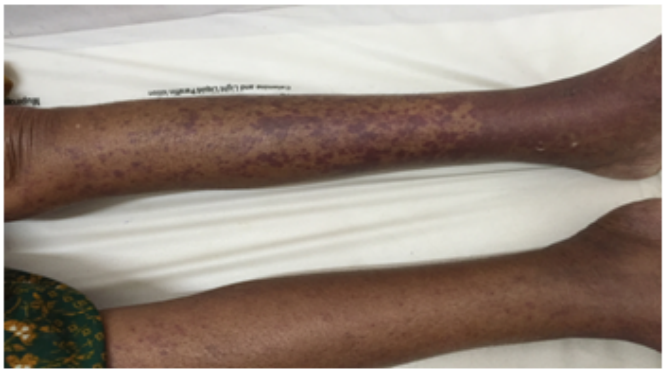

Figure 4(a): Purpura over both legs

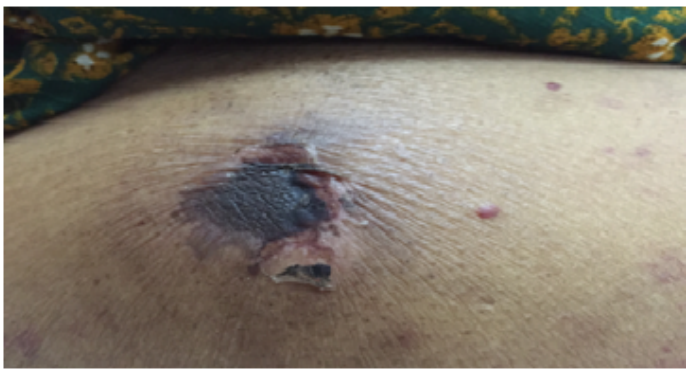

Figure 4(b): vasculitic ulcer

PARAPROTEINS AND DYSPROTEINEMIA

Diseases associated with monoclonal Ig or light chain production can cause skin findings. Associated skin lesions are-

- Amyloidosis
- Cryoglobulinemia mainly type 1
- POEMS syndrome
- Livedo reticularis
- AESOP syndrome
- Plasmacytoma
- Neutrophilic dermatosis
- Immunobullous disorders- IgA pemphigus, linear IgA disease, Epidermolysis bullosa acquisita
- Aquired cutis laxa
- Acquired icthyosis, acanthosis nigricans
- Calcinosis cutis
- SLE
- Dermatomyositis

Amyloidosis

Group of disorders in which amyloid fibrils are extracellularly deposited in internal organs including the skin.

AA type (secondary systemic amyloidosis)

Usually associated with a chronic inflammatory process such as rheumatoid arthritis, chronic osteomyelitis, TB or leprosy. Although deposition in skin is common but rarely leads to clinically apparent skin lesions.

AL type

Is primary form and includes forms associated with multiple myeloma and Waldenstorm macroglobulinemia. It commonly affects skin with reported incidence of 21-40%. Most common skin lesions are-

- Non pruritic, non tender, shiny, waxy, papules which commonly develops on the eyelids also known as racoon eyes. lesions can be present in skin folds, retroauricular folds, anogenital region or oral mucosa. Subcutaneous nodules/plaques are also described.
- Purpura is the type of lesion most encountered because of frequent deposition of amyloid in blood vessel walls which results in extreme fragility of skin vessels. Pinch purpura occurs when found on eyelids of patients.
- Scalp involvement may be evident with hair loss.
- Orally, rubbery papules, petechiae and ecchymosis maybe found.
- Approximately 10% patients develop macroglossis resulting in dysphagia and dysphonia.
- There maybe xerostomia due to salivary gland infiltration by amyloid.

Primary Cutaneous amyloidosis in popular form (lichen amyloidosis) manifests with extremely pruritic, hyperkeratotic, brown papules, pinhead sized upto 6-6mm in diameter usually occurs over shin. Macular amyloidosis presents as pruritic, oval, greyish brown macules on lowe limb or back.

Cryoglobulinemia[3]

Cryoglobulins are serum Ig complexed with other Ig's or proteins that reversibly precipitates in cold temperature. Dermatological manifestations are common in type-1 cryoglobulinemia. It predominantly affects skin, kidneys and bome marrow. There maybe erythematous macules to purpuric papules on lower limb. Other manifestations include- haemorrhagic crusts, ulceration, raynaud's phenomenon, livedo reticularis, acrocyanosis. Cutaneous lesions commonly occur on head, neck and mucosal surfaces.

POEMS syndrome

Rare multisystem disorder comprising of- P- polyneuropathy (usually sensorimotor) , O- organomegaly as hepatomegaly, lymphadenopathy and splenomegaly, E- endocrinopathy including impotence, gynaecomastia, amenorrhea, glucose intolerance, hyperthyroidism, hyperprolactenemia, adrenal insufficiency

Skin changes include diffuse hyperpigmentation, skin thickening with sclerodermoid changes, hypertrichosis, acrocyanosis, hemangiomas, telengiectasis and raynaud's phenomenon.

Plasmacytoma

Neoplasms originating fron mature B cells (plasma cells) can occur as a spectrum of disease ranging from multiple plasmacytomas to multiple myeloma. Multiple myeloma is associated with amyloidosis, cold urticaria, pigmentation, raynaud's phenomenon. Paraneoplastic myeloma is associated with follicular hyperkeratosis most prominent on the nose. Cutaneous plasmacytoma of skin manifests as- non tender, smooth, Cutaneous or subcutaneous nodules. Lesions are flesh/plum colored an can become crusted or ulcerated and are mostly distributed on extremities, trunk and face.

AESOP Syndrome

Adenopathy, extensive patch overlying a plasmacytoma. Mucinosis and angiomatosis occurs over a plasmacytoma with or without regional lymphadenopathy.

MISCELLANEOUS

Dyskeratosis congenita

A genetic disorder thought to be due to telomerase dysfunction. The skin changes are a mottled or reticular macular hyperpigmentation, hypopigmentation or mixture of both in light exposed distribution. Alopecia, premature hair greying, hyperhidrosis and adermatoglyphia are less common. A progressive nail dystrophy starts with ridging and splitting and ends with rudimentary nails. There is leukoplakia of tongue and buccal mucosa.

Fanconi's Anemia

This rare disorder presents in childhood with generalised hyperpigmentation particularly on the lower trunk, flexures and neck andcafé au lait macules.

Chediak Higashi syndrome

This syndrome includes vitiligo like depigmentation, blonde or silvery grey hair and blue eyes, due to melanosome autophagocytosis. Polymorphonuclear cell dysfunction leads to oral and Cutaneous infections, abscesses and pyodermas usually due to staphylococcal infection.

Hermansky Pudlak syndrome

An autosomal recessive disorder characterised by oculocutaneous albinism, bleeding due to platelet dysfunction and ceroid accumulation in lysosomes. The skin is pale and the hair blonde. Trichomegaly and acanthosis nigricans like flexural pigmentation has been described. Freckles and lentigenes are common. Lack of melanin increases the risk of non melanoma skin cancer as well as melanoma.

Griscelli syndrome

Partial albinism is associated is associated with immunodeficiency. Silver or grey hair in infancy may be there.

Wiskott Aldrich syndrome

X linked recessive disorder characterised by thrombocytopenia, an atopic eczema like dermatitis and recurrent infections due to an inherited defect of T cell function. Purpura and ecchymoses may occur in the eczematous areas.

HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENT

Bone marrow transplant recipients may have a variety of cutaneous manifestations. Graft vs host disease is an important complication in bone marrow transplant patients with major skin findings.

Acute graft vs host disease

Acute gvhd develops within 1-3 months of allgeneic transplantation and can involve the skin, the liver and/or the gastrointestinal tract. Skin involvement is characterised by the sudden development of a maculopapular eruptionof a variable extent; it may be preceded by pain or itching. Involvement may first be evident on the cheeks or the sides of the neck. Perifollicular papules, an erythematous palmoplantar rash and a violaceous discoloration of the ears may be good indicators of the diagnosis of acute GVHD. Mucosal involvement also occurs, in 6% cases, epidermal necrosis occurs, this is either localised to pressure sites or is widespread resembling toxic epidermal necrolysis. A scarlatiniform rash with confluent erythema followed by desquamation and hyperpigmentation and a varicella like picture. Clinically, it has been graded on the basis of its involvement-

Grade0- no clinical evidence of disease

Grade1- rash involving <50% surface area and no gut or liver involvement

Grade2- rash involving >50% surface area, bilirubin 2-3mg/dl, diarrhea 10- 15ml/kg/day

Grade3- generalised erythroderma with a toxic epidermal necrolysis like picture,

or 4 bilirubin>3mg/dl, or diarrhea >16ml/kg/day

Chronic Graft vs Host Disease

It develops in 30-40% of allograft recipients and usually begins at least 100 days after bone marrow transplantation. It may appear de novo or following acute GVHD in continuity. The skin is involved in almost all cases of chronic GVHD and the mouth in 90%. 2 main types of cutaneous manifestations are- lichenoid and sclerodermatous lesions. Cutaneous lichenoid lesions occur early, typically on perorbital skin, ears, palms and soles. Perifollicular, vesicular or confluent lesions are sometimes seen. Thinning of the nails, pterygium, phimosis or vaginal strictures may also develop. Oral involvement is very common, with areas of erythema and atrophy, lichenoid or hyperkeratotic plaques, ulceration and atrophic glossitis. Sclerodermoid chronic GVHD usually presents later, with ill defined, indurated, shiny, white-yellow plaques that subsequently develops patchy hyperpigmentation or a poikilodermatous appearance. Localised lesions may ulcerate or cause peripheral neuropathy owing to entrapment of nerve endings.

REFERENCES

1. Margaret, K. (2014, October 22). Dermatological manifestations of haematological disease. Retrieved from http://www.medscape.com
2. Piette WW. Hematologic diseases. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in General Medicine. 5th ed. New York:Mc GrawHill; 1999.p. 1867-81.
3. Pande SY, Kharkar V. Clinical profile of cutaneous manifestations with and without hematologic diseases: A comparative study. Indian Dermatol Online J 2014;5:138-43.
4. Jones H, Blinder M, Anadkat M. Cutaneous manifestations of Sickle Cell Disease. Open J Blood Diseases 2013;3:94-99.
5. Sambanandan T. Review on oral manifestations of blood diseases. J Indian Acad Dental Specialists 2010;4:41-43.
6. P Fietta, G Delsante, F Quaini. Hematologic manifestations of connective autoimmune diseases.
7. A Yalcin, A Keskin, S Ergin, H Akdam, S Degirmencioglu. Cutaneous manifestations in hematological malignancies. The Internet Journal of Dermatology 2005;3(2):3994

Source of Support: None Declared
Conflict of Interest: None Declared