

Cutaneous Manifestations of Internal Malignancy

Karthik R¹, Mohan N², Ravi Kumar PT³, Saramma Mathew Fenn⁴

ABSTRACT

Malignancy inside the human body manifests as cutaneous disorders which a person was not aware of. Many of the Dermatological lesions are overseen by dermatologists and dentists in the diagnosis of various autoimmune disorders like systemic lupus erythematosus, Pemphigus and Photosensitivity and drug mediated hypersensitivity reactions. Hence the need for diagnosis of cutaneous manifestations proves a challenge to dermatologists and also dentists. This article enlightens some cutaneous manifestations that can occur in Patients with underlying internal malignancy.

Keywords: Necrolytic Migratory Erythema, Paraneoplastic Pemphigus, Sezary Syndrome

INTRODUCTION

Cutaneous manifestations still proves to be an enigma in the diagnosis of dermatological disorders and internal malignancies. Cutaneous manifestations should not be neglected and must be attended by the physician or dentist in time. Some life threatening hypersensitivity reactions like steven johnsons syndrome must be treated in intensive care unit such as treating a patient with burns where proper electrolyte loss are replaced and restore the body to equilibrium. Some of the cutaneous manifestations that occurs in internal malignancies were discussed in Table 1. The various cutaneous manifestations of internal malignancies that are inherited autosomal dominantly and autosomal recessively were discussed in Table 2 and Table 3 respectively.

CURTHS POSTULATES

The five criteria called curths postulates that establish an association between a skin disease and Internal malignancy.

1. Concurrent onset of cutaneous disease and internal malignancy- or at the time of onset of the cutaneous disease, the internal malignancy is recognizable.
2. Parallel course of the skin disease and internal Malignancy.
3. A specific type or site of malignancy associated with the skin disease.
4. Sound statistical evidence that the malignancy is more frequent in patients with the skin disease than in age and sex matched controls.
5. A genetic link between a syndrome with skin manifestations and an internal malignancy.

Sweet syndrome

Sweets syndrome occurs most commonly in women 30-60 years of age and consists of characteristic skin lesions, fever, malaise and Leukocytosis. Less commonly there is involvement of the joints, eyes, lungs, kidneys and liver. The clinical hallmark is the presence of sharply demarcated painful plaques on the face, neck, upper trunk and extremities. The surface of the plaques has a mammillated (Nipple-like) appearance and often shows papulovesicles and pustules. Some have

lesions on the lower extremities and may resemble erythema nodosum. Oral mucousmembrane and eye lesions can be seen. Skin lesions may develop at the site of minor skin trauma or needle sticks in a some patients, a phenomenon called Pathergy.¹

Peripheral Blood smear reveals 10, 000cells /mm³ in 60% of the Patients. Elevated sedimentation Rates, increased number of segmented neutrophils, Lymphopenia, anemia, thrombocytopenia and increased c reactive protein levels can be seen.²

The most common associated malignancy is acute myelogenous Leukemia. Other leukemias like chronic myelogenous leukemia, lymphocytic leukemia, T and B cell Lymphomas, Polycythemia and rarely solid tumors also have been reported.²

Acanthosis nigricans

Acanthosis nigricans is a common skin finding appears as a velvety, hyperpigmented, Papillomatous, dirty appearing skin. It is most frequently seen on the neck, axilla, groin and dorsal hand surfaces. It is often associated with numerous skin tags and rarely affects mucosal surfaces. It is frequently associated with children aged 11-16 and with obesity. It is commonly associated with diabetes and other endocrinopathies with insulin resistance.^{3,4}

Paraneoplastic acanthosis nigricans is rare and is most commonly associated with gastric carcinoma. When associated with malignancy, it is usually abrupt in onset, severe and may involve mucous membranes and palmar skin. Triple Palms resembling rugose bovine intestine and the sign of Lesar-Trelat is often seen in Patients with paraneoplastic acanthosis nigricans.⁴

Glucagonoma syndrome

Necrolytic Migratory Erythema is a characteristic skin eruption associated with an alpha cell tumor of the Pancreas. It presents as erythema with superficial pustules and erosions typically involving the face, intertrigenous skin and acral extremities. Alopecia, Weight loss, glossitis, stomatitis, nail dystrophy, anemia and Diabetes are frequent associations. The eruption tends to migrate and desquamate and most patients have elevated glucagon serum levels. Skin biopsy shows necrosis of the upper portion of the epidermis and is usually diagnostic. This unique skin disease is probably related to low serum amino acid levels.⁵

¹Reader, ²Professor and Head of Department, ³Professor, ⁴Senior Lecturer, Department of Oral Medicine and Radiology, Vinayaka Missions Sankarachariyar Dental College, Tamil Nadu, India

Corresponding author: Karthik R., Door No:65/10, Third Cross Street, Mayor Nagar, Peramanur, Salem-636007, India

How to cite this article: Karthik R, Mohan N, Ravi Kumar PT, Saramma Mathew Fenn. Cutaneous manifestations of internal malignancy. International Journal of Contemporary Medical Research 2017;4(4):935-939.

| Disease | Internal malignancy |
|-------------------------------------|------------------------------------------------------|
| Sweets syndrome | Acute Myelogenous Leukemia |
| Paraneoplastic Acanthosis Nigricans | Gastric carcinoma |
| Hypertrichosis Lanuginosa | Lung, Breast, Gastrointestinal, carcinoid tumors |
| Dermatomyositis | Ovarian carcinoma |
| Cutaneous erythema | Lymphoma |
| Paraneoplastic Pemphigus | Lymphoma |
| Erythema gyratum repens | Breast cancer |
| Basex syndrome | Squamous cell carcinoma of upper aerodigestive tract |
| Necrolytic Migratory erythema | Alpha cell tumor of Pancreas (Glucagonoma) |
| Sezary syndrome | Lymphoma |
| Pagets Disease of the Breast | Ductal carcinoma |
| Cowdens syndrome | Breast cancer |
| Multiple mucosal neuroma syndrome | Medullary carcinoma of thyroid |
| Acquired ichthyosis | Hodgkins Disease |
| Pruritis | Hodgkins Lymphoma |
| Pyoderma Gangrenosum | Myelocytic and Myelomonocytic Leukemias |

Table-1: Diseases associated with Internal Malignancies.

| Disorder | Affected Gene | Cancer association | Clinical Features | Skin findings |
|------------------------------------|-----------------------------------------------------------------------------|----------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------|
| Neurofibromatosis | Neurofibromin | Neurofibrosarcoma (Rare) | Lisch Nodules Seizures Deafness | Neurofibromas Café-au-lait macules |
| Multiple Mucosal Neuro-ma syndrome | RET Proto oncogene | Medullary Thyroidcarcinoma | Neuromas of Lip, tongue and oral mucosa | Neuromas of lip, tongue and oral mucosa |
| Peutz Jeghers syndrome | STK11 (Serine Threonine Kinase) | Instestine | Intestinal Polyps | Pigmented macules on Vermilion border of lip, mucosa, face, acral extremities |
| Gardners syndrome | APC Adenomatosis Polyposis coli Gene | Colon | Osteomas Colon Polyps Desmoids Abnormal dentition | Epidermoid cysts |
| Cowdens syndrome | PTEN (Phosphate and tension homologue deleted on chromosome 10) | Breast Thyroid | Mucosal papules Fibrocystic disease of the Breast | Keratotic facial Papules Acral Keratosis |
| Torres syndrome | MSH2 (Melanocyte stimulating Hormone) MLH1 (Micronuclear Linker Histone) | Colon | Colon Polps | Sebaceous tumors Keratoacanthomas |

Table-2: Autosomal dominant diseases associated with skin changes and malignancy

Hypertrichosis Lanuginosa

Hypertrichosis Lanuginosa (malignant down) is an acquired excessive growth of Lanugo Hair. It usually begins on the face, neck and ears and eventually can involve most hair bearing skin. Glossitis is frequently an associated finding. The most common associated cancers are lung, Breast, Gastrointestinal and carcinoid. This rare cutaneous finding has also been reported in Patients with anorexia nervosa.⁶

Trousseau sign

Trousseau sign consists of recurrent and migratory superficial thrombophlebitis, affecting both large and small cutaneous veins which is associated with an internal cancer, crops of oval to linear, erythematous, tender skin lesions are seen mostly on the arms, legs, flanks and abdomen. Thrombosis of internal veins can also occur and lead to a variety of symptoms. Men are more commonly affected. The most common associated carcinomas are lung and Pancreatic carcinoma.⁷

Dermatomyositis

The classic eruption of Dermatomyositis is a reddish purple erythema involving the face, typically the eyelids (Heliotrope sign). The rash may be faint or quite inflamed and edematous. In addition to the facial rash, lesions on the scalp, neck, upper trunk and extensor extremities are common. As the lesions mature, scaling and atrophy may develop. The erythema on the hands occurs over the knuckles rather than over the phalanges. Cuticular telangiectasis seen in Dermatomyositis. Flat topped red to violaceous Papules develop over the knuckles of Patients with Dermatomyositis. The skin lesions may precede clinical or laboratory evidence by weeks, months or years. A few patients may never develop muscle dysfunction. The skin lesions are notoriously resistant to topical steroid therapy. The cancer may occur before, during or after the development of dermatomyositis. A slight increase in the incidence of ovarian carcinoma is noted in patients newly diagnosed as Dermatomyositis and female

| Disorder | Affected Gene | Inheritance | Clinical Findings | Cancer |
|--------------------------------------------|---------------|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Ataxia telangiectasia (Louis Bar syndrome) | ATM | Autosomal recessive | Progressive cerebellar ataxia Telangiectasia Recurrent sinus and Pulmonary infections Decreased or absent serum IgA | Lymphomas |
| Blooms syndrome | RecQ3 | Autosomal recessive | Photosensitivity Telangiectasia of sun exposed skin Short stature Decreased serum Igs Recurrent infections | Lymphomas Leukemias |
| Dyskeratosis congenita | DKC1 TERC | X-Linked recessive Autosomal Dominant | Skin atrophy and Hyperpigmentation Nail dystrophy Oral Precancerous Leuko-keratosis | Oral cancers Other malignancies |

Table-3: Recessively inherited diseases with skin findings and malignancy

patients must be screened for ovarian carcinoma.⁸

Sezary syndrome

Sezary syndrome represents a triad of findings cutaneous erythema, lymphadenopathy and 10-15% atypical mononuclear cells in peripheral blood. This syndrome is a subset of cutaneous T Cell Lymphoma. Patients with sezary syndrome frequently have intolerable itching often to the point that they are suicidal. Lymphadenopathy, nail dystrophy and Hair loss are common associated features. The diagnosis is established by skin biopsy showing cutaneous T Cell Lymphoma, the presence of atleast 15% atypical mononuclear cells in Peripheral blood and the typical clinical picture. Approximately 10-15% of patients with erythroderma will have an associated lymphoma or more rarely leukemia.⁹

Paraneoplastic Pemphigus

Paraneoplastic Pemphigus is a blistering skin disease with a reported association with Lymphoma, although a few cases reported with solid tumors. The clinical picture resembles pemphigus vulgaris, bullous pemphigoid or Erythema multiforme Major (Stevens-Johnsons syndrome) with significant oral mucous membrane involvement. The disease poorly responds to immunosuppressive therapy and is frequently fatal.¹⁰

Skin and oral mucous membrane biopsy reveals epidermal acantholysis, epidermal spongiosis, suprabasilar clefts, basal cell vacuolar changes and dyskeratotic keratinocytes. Direct immunofluorescent examination reveals IgG and less commonly IgA with or without complement in the intracellular spaces and C3, IgG or IgM at the Basement membrane zone.¹¹ Antibodies have been demonstrated against desmoplakins, proteins in keratinocyte attachment plaques(desmosomes) and a 230kd protein in the Basement membrane zone. Rat bladder is a useful substrate for indirect immunofluorescent examination and shows positive staining with serum from patients with Paraneoplastic Pemphigus.¹¹

Erythema Gyratum repens

It is a rare skin eruption that is characterised by widespread, ever changing pattern of skinlesions resembling wood grain. The

erythematous circinate lesions may have a fine scale and move upto 1cm a day. Almost all patients with this unique dermatosis have an associated malignancy. The most commonly associated malignancy with this unique dermatological finding is Breast carcinoma. This can also be seen in lung, Bladder, cervical and Prostate cancers. The skin lesions clear within a few weeks after the removal of the malignancy and usually recur if the cancer returns.¹²

Pyoderma Gangrenosum

Pyoderma gangrenosum is an ulcerative skin disease of unknown etiology characterised by painful, rapidly enlarging ulcers with an erythematous or violaceous undermined border with a necrotic centre associated with internal malignancy in 7.2% of the Patients. Other reported hematologic cancers are multiplemyeloma, Polycythemia vera and Lymphoma.¹³

Erythromelalgia

Erythromelalgia is a rare skin disease characterised by erythematous, painful, burning of the feet, ankles and lower extremities. This disease is aggravated by Heat exposure and relieved by cooling. Many Patients find relief only by soaking their legs in ice water. The incidence of associated malignancy is variable between 3% and 65% of the cases. The associated haematological malignancy are polycythemia or essential thrombocythemia.¹⁴

Acquired ichthyosis

Acquired ichthyosis was first reported to be associated with Hodgkins disease in 1940s. It is also reported in T- cell lymphoma, Kaposi sarcoma, Malignant Histiocytosis, Leiomyosarcoma, Multiple myeloma.¹⁵

Pruritis:

Generalised pruritis without skin lesions has been reported as a sign of internal malignancy. Pruritis is reported as an initial symptom of Hodgkins disease in 5- 10% of Patients and in 3% of those with non-hodgkins lymphoma.¹⁶

Extramammary Pagets disease

Extramammary Pagets disease occurson the axilla, breast, groin or anofenital region. It begins as a small eczematous patch on the nipple that gradually spreads to the areola and eventually to

the skin of the breast. It is often associated with an underlying adnexal carcinoma and about 20% of cases have carcinoma of the rectum or genitourinary tract.¹⁷

Primary systemic Amyloidosis

The cause of this disease is plasma cell dyscrasia. The most common associated skin lesions are pruritic or ecchymoses that are seen most frequently on the skin areas like eyelids, neck, groin, axilla, umbilicus or oral mucosa. The haemorrhagic lesions may occur on areas of clinically normal skin or in skin having waxy papules, Plaques, nodules or tumors. The intracellular bleeding is due to infiltration of blood vessel walls with amyloid protein. Other less common skin lesions include alopecia, nail dystrophies, Scleroderma like lesions, Macroglossia, cutis verticis gyrata, bullous lesions and dyspigmentation.¹⁸

Basex syndrome (Acrokeratosis Paraneoplastica):

Basex syndrome begins with acral violaceous erythema on the ears, nose, hands and feet. Early lesions may show small vesicles. As the lesions progress, they become hyperkeratotic and psoriasiform, especially on the hands and feet. Paronychia and nail dystrophy are common. Later the eruption may generalize and lesions on the face may appear dermatitis or lupus like. This syndrome is more common in men and is associated with squamous cell carcinoma of the upper aerodigestive tract.

Another variant of Basex syndrome inherited as an autosomal dominant disease is characterised by acral follicular atrophoderma, early development of Multiple facial Basal cell carcinoma and in some hypohidrosis.¹⁹

Multiple mucosa Neuroma syndrome

This syndrome is characterised by the presence of multiple flesh coloured papules on the tongue, lips and occasionally other mucosal surfaces early in life. These patients have a characteristic thick prominent lips and a marfanoid habitus. 90% of these patients develop medullary thyroid carcinoma and pheochromocytoma that is often multifocal or bilateral.²⁰

Gardners syndrome

The cutaneous Hall mark of Gardners syndrome is epidermoid cysts which often appear before puberty, frequently on the extremities. These cysts may be many or few. The syndrome is also characterised by osteomas (typically on facial bones), fibrous and desmoid tumours, abnormal dentition, lipomas, hypertrophy of renal pigmented epithelium and leiomyomas of the gastrointestinal tract. The syndrome is characterized by the early onset of colonic polyposis and has a very high incidence of colon cancer.²⁰

Peutz Jeghers syndrome

Brown to Blue –black macules (lentiginos) are present at birth or early infancy on the lips, oral mucosa, nasal mucosa, palms, soles, dorsal hand surfaces, central face and elbows. Polyps of the small intestine develops in 90% of the Patients. Polyps also occur in the stomach, colon and rectum. The average age of death is 36 years intussusception occurs in about 50% of the cases.²⁰

Torres syndrome

This syndrome includes cutaneous sebaceous neoplasia and a high incidence of low grade colon cancer. The sebaceous tumors includes sebaceous adenomas, epitheliomas, carcinomas. About

one-third of patients develop keratoacanthomas. The sebaceous skin tumours may be few or many but even one sebaceous adenoma should alert the clinician that patient may have this syndrome.²⁰

Carcinoid syndrome

Carcinoid syndrome is a systemic manifestation of neuroendocrine carcinoid tumors that most commonly manifest by flushing that progress to persistent telangiectasia and diarrhoea. Less common findings include bronchospasm, cardiovascular dysfunction and Pellagra like skin changes (Photo disturbed Dermatitis). Development of this syndrome has prognostic significance as liver metastases underlie most cases and thus it signifies metastatic unresectable disease.²¹

CONCLUSION

Cutaneous manifestations provide a challenge to the clinicians and dentists for treatment. A proper diagnosis of such cutaneous manifestations in a body is essential to treat the diseases early and betterment of the patients.

REFERENCES

1. Cohen PR, Sweet's syndrome – a comprehensive review of an acute febrile neutrophilic dermatosis, *Orphanet J Rare Dis.* 2007;26:2:34.
2. Von den Driesch P: Sweets syndrome (Acute Febrile neutrophilic Dermatitis). *J Am Acad Dermatol.* 1994; 31:535-556.
3. Yin WB, Gao Y, Lu Y, Gastric cancer associated with malignant acanthosis nigricans, *Am J Med Sci.* 2017;353:416.
4. Schwartz RA: Acanthosis nigricans. *J Am Acad Dermatol.* 1994;31:1-19.
5. Mountjoy L, Kollmorgen D, Glucagonoma associated rash, *N Engl J Med.* 2017;376:e18.
6. Hovenden AL: Acquired lanuginose acquisita associated with malignancy. *Clin Dermatol.* 1993;11:99-106.
7. Leshner JL Jr: Thrombophlebitis and thromboembolic Problems in Malignancy. *Clin Dermatol.* 1993;11:159- 163.
8. Callen JP: Dermatomyositis. *Lancet.* 2000;355:53-57.
9. Foss F: Mycosis Fungoides and the Sezary syndrome, *Curr Opin Oncol.* 2004;5:421-428.
10. Anhalt GJ, Kim SC, Stanley JR et al. Paraneoplastic Pemphigus. *N Engl J Med.* 1990;323:1729-1735.
11. Kasperkiewicz M et al, Pemphigus, *Nat Rev Dis Primers.* 2017;11:3:17026.
12. Tchernerv G et al. Erythema Gyrateum repens: a pathogenetic mystery and therapeutic challenge, *Wien Med Wochenschr.* 2017;167:117-119.
13. Duguid CM, O Loughlin S, Otridge B, Powell FC. Paraneoplastic pyoderma gangrenosum. *Aust J Dermatol.* 1993;34:17-22.
14. Hou JL, Onajin O, Gangat N, Davis MD, Wolanskyj AP. Erythromelalgia in patients with essential thrombocythemia and polycythemia vera, *Leuk Lymphoma.* 2017;58:715-717.
15. Rizos E, Milinois HJ, Pavlidis N, Elisaf MS. Acquired ichthyosis: A Paraneoplastic skin manifestation of Hodgkins disease. *Lancet oncol.* 2002;3:727.
16. Lober CW: Pruritis and Malignancy. *Clin Dermatol.* 1993; 11:125-128.
17. Bhatia P, Ahuja A, Dey P, Suri V. Vulval intraepithelial neoplasia with extra mammary Pagets disease: a rare association. *J Clin Pathol.* 2007;60:110-2.

18. Gonzalez – Ramos J et al. Relapsing bullous amyloidosis of the oral mucosa and acquired cutis laxa in a patient with multiple myeloma: a rare triple association. *Clin Exp Dermatol.* 2017;1.
19. Bologna JL. Basex syndrome. *Clin Dermatol.* 1993; 11:37-42.
20. Koh KJ, Park HN, Kim KA. Gardner syndrome associated with multiple osteomas, intestinal polyposis, and epidermoid cysts. *Imaging Sci Dent.* 2016;46:267-272.
21. Owen CE, cutaneous manifestations of lung cancer, *Semin Oncol.* 2016;43:366-9.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 05-04-2017; **Accepted:** 11-05-2017; **Published:** 17-05-2017