CUTANEOUS MANIFESTATIONS OF INTERNAL MALIGNANCY & PARANEOPLASTIC DERMATOSES

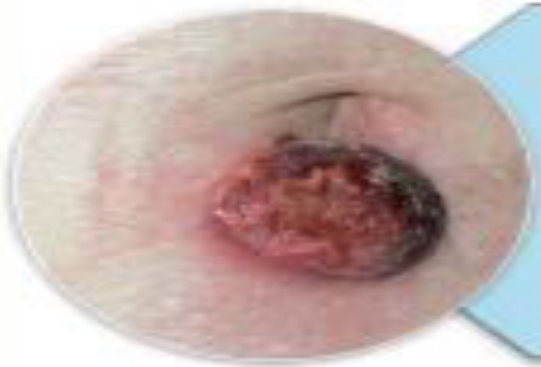
Dr. Sk. Shabana MD (DVL), FAM

Senior Resident,

Dept. of DVL, NMCH

- *Skin manifestations are a reflection of many of the internal diseases.*
- *skin disease may be the only presenting complaint of many of the internal disorders.*
- *Internal malignancy, whether organ-specific or hematological can present with a plethora of cutaneous manifestations.*
- *The skin lesions can occur as secondaries or as paraneoplastic syndromes or as a part of certain genetic syndromes.*
- *Internal malignancies may give rise to a number of cutaneous manifestations through their immunological, metabolic, and metastatic consequences.*

- Skin changes were seen in 27% of patients with internal malignancy.
- Cutaneous metastasis in 6%
- Others in 25%



CUTANEOUS METASTASIS OF MALIGNANCIES

CUTANEOUS SIGN & SYMPTOMS OF MALIGNANCY

CUTANEOUS PARANEOPLASTIC SYNDROMES

DIRECT SPREAD

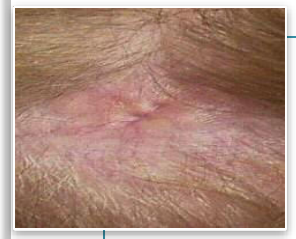
- Most of the timesTUMOR SPILLAGE is iatrogenic
- Incidence decreased in the recent times
- FNAC/ASPIRATION OF MALIGNANT ASCITIS
- LAPROSCOPIC SURGERIES &DRAINS NEAR SOLID ORGAN TUMORS
- SCAR METASTASIS

Cutaneous metastasis

- May be the first sign in -ca of lung, kidney, ovaries.
- COMMON SITE : anterior chest or abdominal wall
- Men: lung malignancy
- Women : breast
- Children : neuroblatoma

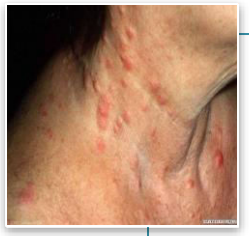
- PRECOCIOUS METASTASIS:kidney, lung, thyroid,ovary
- METACHRONOUS METASTASIS:breast, kidney, melanoma
- SYNCHRONOUS METASTASIS:breast & oral cavity

Common cutaneous sites for metastases andtheir probable primary sites



Scalp

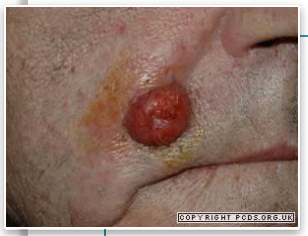
breast, lung,kidney



Neck

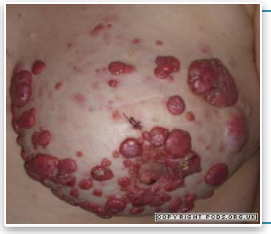
oral

SCC



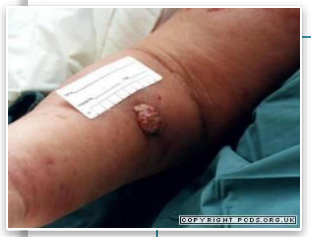
Face

oral SCC, lung, kidney



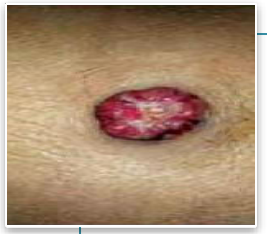
Chest

breast, lung, mela-noma



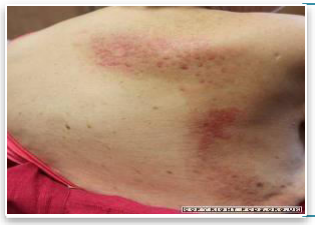
Extremities

melanoma, breast, lung, renal, GIT



Umbilicus (Sister Mary Joseph's nodule)

stomach, colon, ovary, kidney, breast



Back

lung

Metastatic pattern

- Carcinoma en cuirasse
- Carcinoma erysipelatoides
- Carcinoma telangiectatica
- Carcinoma eburnee
- Superior vene cava syndrome
- Sister Mary Joseph nodule
- Cicatricial metastasis to scalp / Alopecia neoplastica

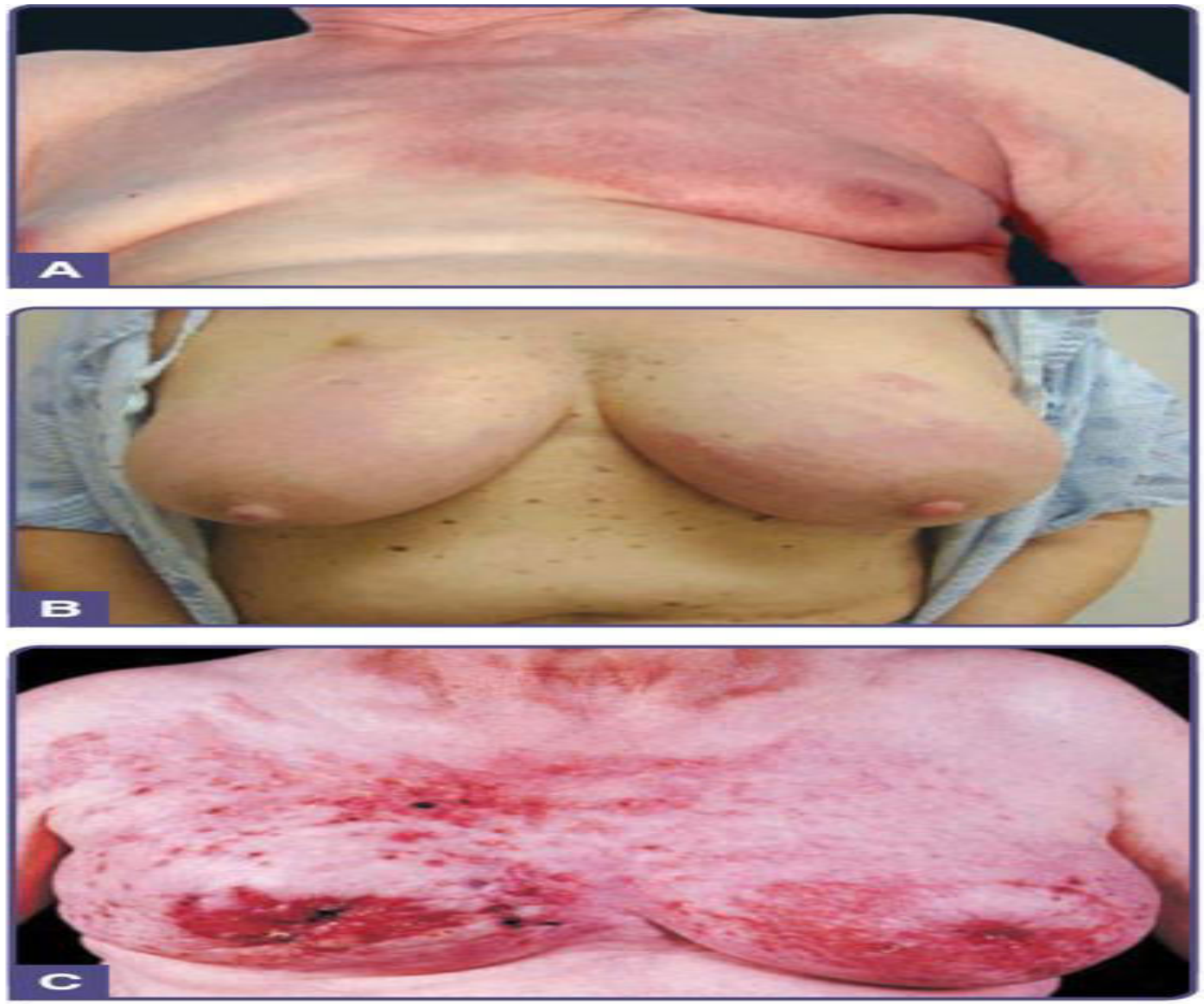


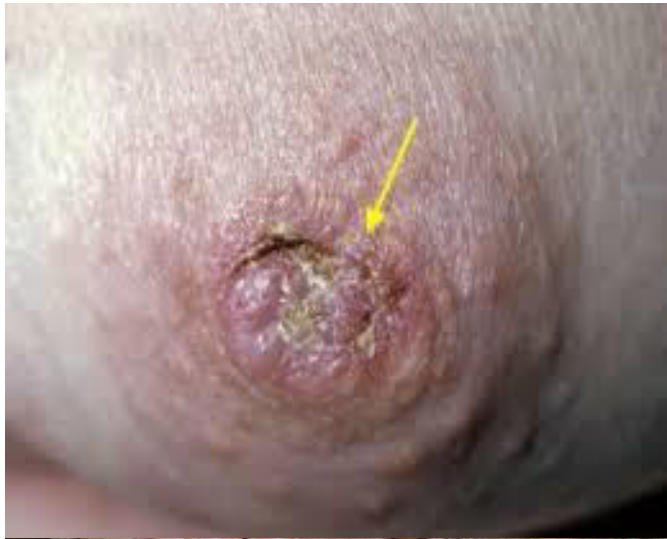
Figure 134-12 **A,** Carcinoma erysipelatoides. Intralymphatic spread of mammary carcinoma that manifests as erysipelas-like erythema. **B,** Bilateral cutaneous metastases from underlying breast carcinoma. **C,** Carcinoma en cuirasse involving both breasts and thoracic wall.

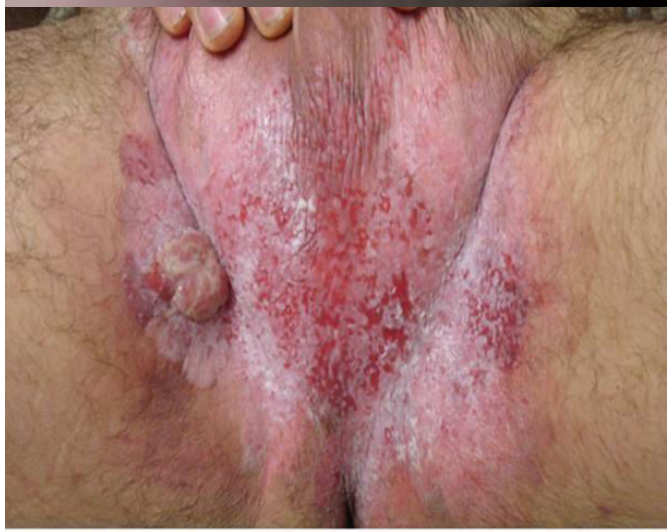
Peget`s disease of nipple :

- Eczematous, crusted skin of nipple extending to areola
- Unresponsive to topical steroids

Extra mammary Paget's disease :

- Genito urinary / gastro intestinal malignancy





EXPOSURE TO CARCINOGENS :

Arsenic: chronic exposure, diffuse or spotty rain drop pigmentation,hypopigmented macules, bowen`s disease

- Ca of lung, bladder, kidney

Vinyl chloride: Raynaud`s phenomena, scleroderma like skin changes, osteolysis of distal phalanx

Liver angiosarcoma

Ionising radiation: neck -papillary ca of thyroid

Spine : leukemias

PARANEOPLASTIC DERMATOSES

- Skin conditions that have association with internal malignancy bur not themselves malignant.
- Curth proposed criteria by which a causal relationship between a dermatosis and a malignant internal disease might be evaluated

(a) Both conditions start at the same time,

(b) both conditions follow a parallel course,

(c) the condition is not recognized as a part of a genetic syndrome,

(d) a specific tumor occurs with a certain dermatosis,

(e) the dermatosis is not common, and

(f) a high percentage of the association is noted.

CLASSIFICATION PNS

- 1.HYPERKERATOTIC DISEASES

  Acanthosis nigricans

  Tripe palms

  Acquired Icthyosis

  Pytirirasis rotunda

  Lesser Trelat sign

  Bazex syndrome

2. COLLAGEN VASCULAR DISEASES

Dermatomyositis

Progressive systemic sclerosis

3. REACTIVE ERYTHEMAS

Necrolytic Migratory erythemas

Erythema gyretum repens

4. NEUTROPHILIC DERMATOSIS

Sweets syndrome

Pyoderma gangrenosum

5. DERMAL PROLIFERATIVE DISORDERS

Multicentric reticulohystiocytosis

Necrobiotic xanthogranuloma

6. DISORDERS OF DERMAL DEPOSITION

Scleromyxedema

Systemic amyloidosis

7. BULLOUS DISORDERS

Paraneoplastic pempigus

Dermatitis herpetiformis

8. OTHER CHANGES

Hypertrichosis lanuginosa

Trousseau syndrome

Table 147.2 Strength of correlation of some potentially paraneoplastic dermatoses with internal malignancy.

Strength of correlation	Type of reaction pattern	Examples
Strong	Papulosquamous and figurate eruptions	Bazex syndrome
		Erythema gyratum repens
		Necrolytic migratory erythema
	Epidermal conditions	Acanthosis palmaris (tripe palms)
		Florid cutaneous papillomatosis
	Deposition disorders	Primary amyloidosis
		Scleromyxoedema
		Necrobiotic xanthogranuloma
		POEMS syndrome
	Others	Acquired hypertrichosis lanuginosa
		Paraneoplastic pemphigus
		Carcinoid syndrome
		Trousseau syndrome
Moderate	Papulosquamous and neutrophilic eruptions	Sweet syndrome
		Pyoderma gangrenosum
		Dermatomyositis
	Others	Multicentric reticulohistiocytosis
		Pityriasis rotunda
Weak	Epidermal conditions	Acanthosis nigricans in isolation
		Acquired ichthyosis (unless widespread, deeply fissured, truncal pattern)
		Eruptive seborrhoeic keratoses (sign of Leser–Trélat)
	Deposition disorders	Scleredema
		Calcinosis cutis
	Others	Vasculitis, Raynaud phenomenon, digital ischaemia
		Erythromelalgia
		Relapsing polychondritis
		Erythroderma/exfoliative dermatitis
		Digital clubbing (unless with hypertrophic osteoarthropathy)
		Pruritus
		Erythema annulare centrifugum
		Cushing syndrome

POEMS, *polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.*

other parts of the intestine, liver or bile duct. Other tumours include lung, breast, endometrium, kidney, bladder, prostate, testis, cervix, thyroid and adrenal. Most are solid organ tumours but lymphoma has been recorded. Sarcomas occur rarely. The prognosis with malignant acanthosis nigricans is related to the survival rate from the neoplasia concerned. However, the skin changes may improve or resolve with eradication of the cancer [7,8]. Rarely, malignancy-associated acanthosis nigricans has been associated with other paraneoplastic conditions including pachydermoperiostosis, paraneoplastic pemphigus and acquired hypertrichosis lanuginosa.

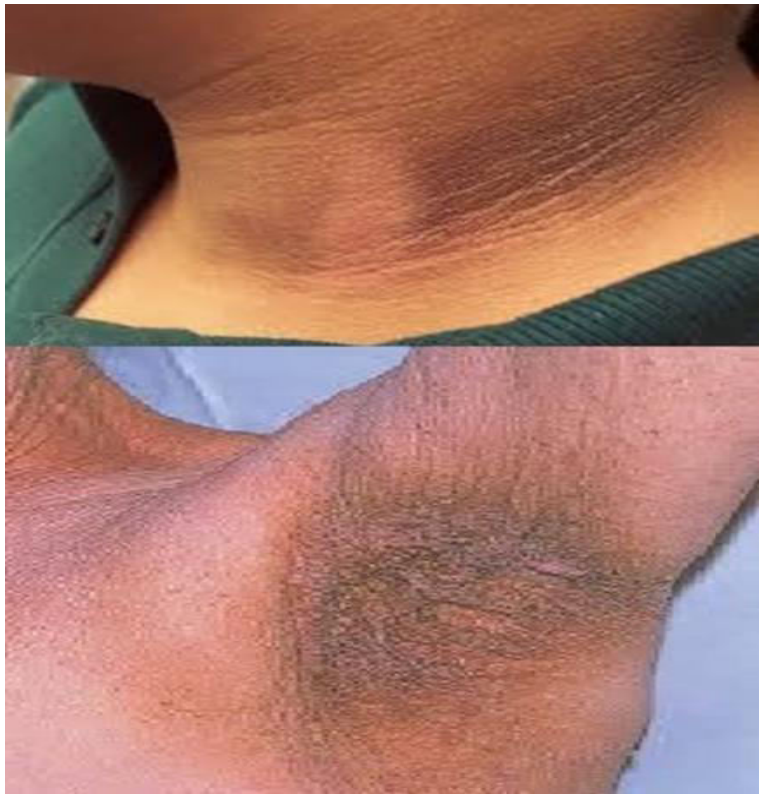
Acanthosis palmaris

causing a velvety (Figure 147.13) or less commonly a pitted, honeycombed pattern of the hand. It is associated with neoplasia in about 90% of cases; it may be the only paraneoplastic manifestation in 30–40% or it may occur with one or both of malignant acanthosis nigricans or the sign of Leser–Trélat [1–3]. It occurs particularly in men, especially when the underlying tumour is a lung cancer [2]. However, it can occur in isolation without neoplasia, or as a pattern of exfoliative psoriasis or eczema [1,2], and has been reported with bullous pemphigoid.

As the condition is usually associated with an internal neoplasm, usually of solid organ type, it requires appropriate evaluation and investigation. In the majority of cases, the onset of tripe palms precedes or occurred concurrently with the detection of a previously unsuspected malignancy [3]. Most commonly the

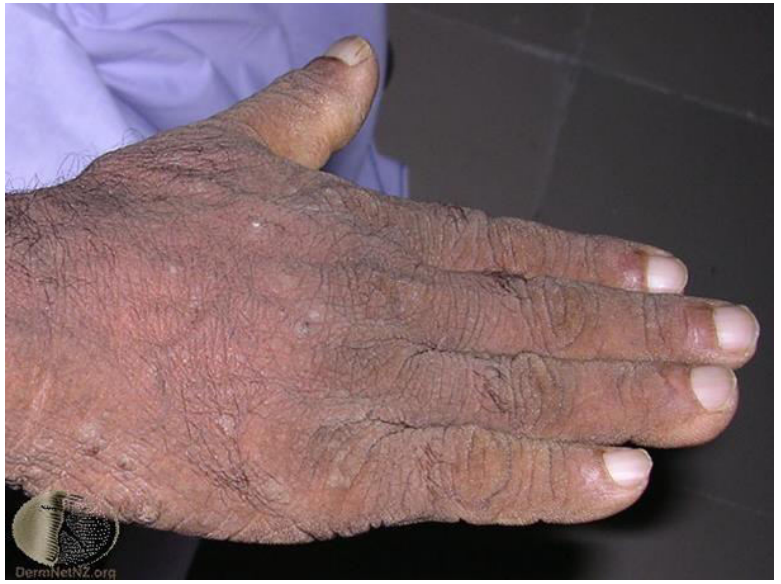
MALIGNANT ACANTHOSIS NIGRICANS

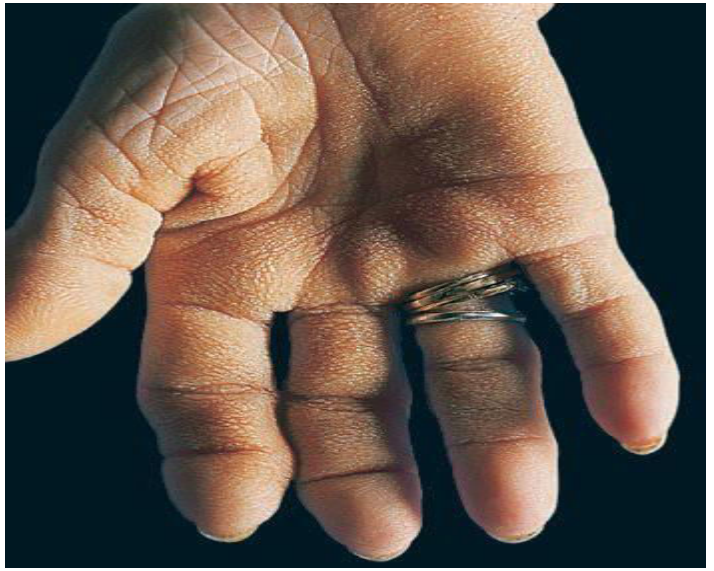
- Gray-brown, velvety plaques appearance.
- The hyperpigmentation is later accompanied by hypertrophy, increased skin markings
- Pruritus/ alopecia/mucosal involvement/rapid progression/weight loss/0ld age
- The most commonly involved locations are the axillae, neck, external genitalia, groin, face, inner thighs, umbilicus and perianal area.
- 80-90% intra abdominal malignancy [gastric in 45 -55%]



TRIPE PALMS

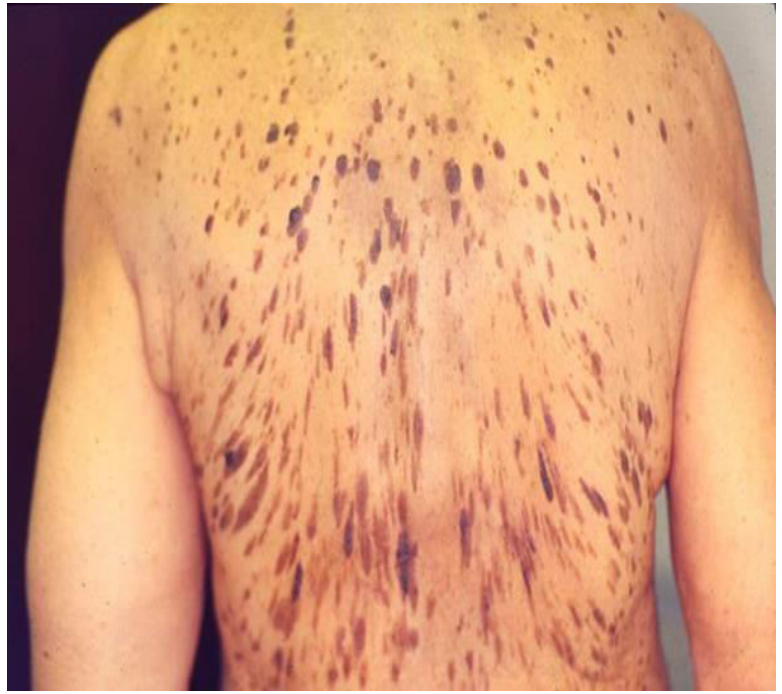
- acanthosis palmaris/ pachydermatoglyphy: hypertrophic velvety papillation of the palms and soles, along with exaggerated dermatoglyphics and hyperkeratosis.
- Gastric/ lung malignancy





LESER TRELAT SIGN

- Defined as the rapid increase in the number and size of seborrheic keratoses in patients with an internal malignancy.
- Associated with pruritus/Acanthosis
- Adenocarcinoma of stomach



ACROKERATOSIS PARANEOPLASTICA (BAZEX SYNDROME)

- symmetrical,scaly,psoriasiform violaceous plaques on the acral surfaces with severe forms progressing to bullae.

- The lesions predominantly occur on the hands, feet, ear helices, nose tip, and scalp
- More than90% males
- Scc of oropharynx/larynx

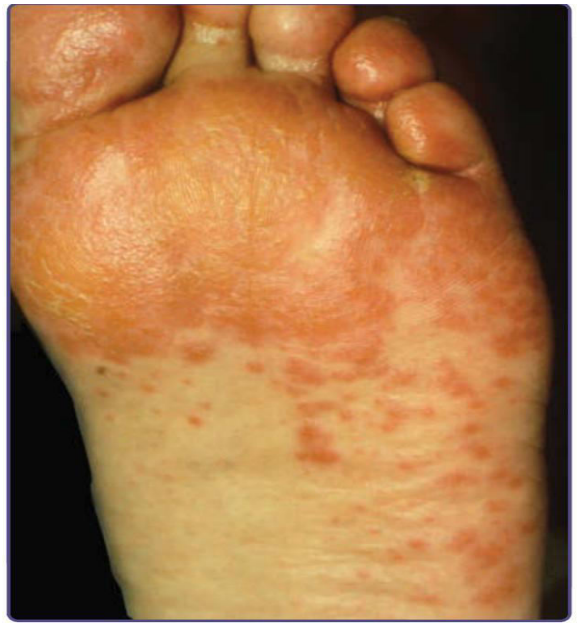
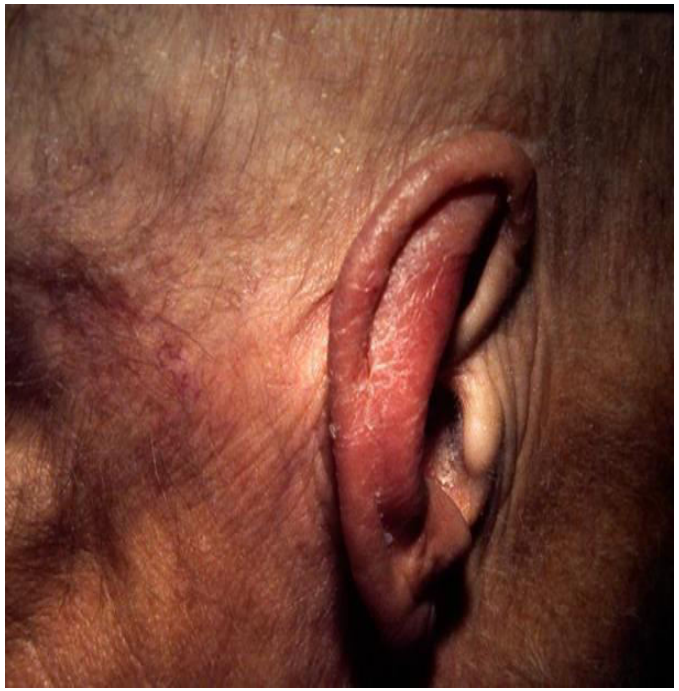
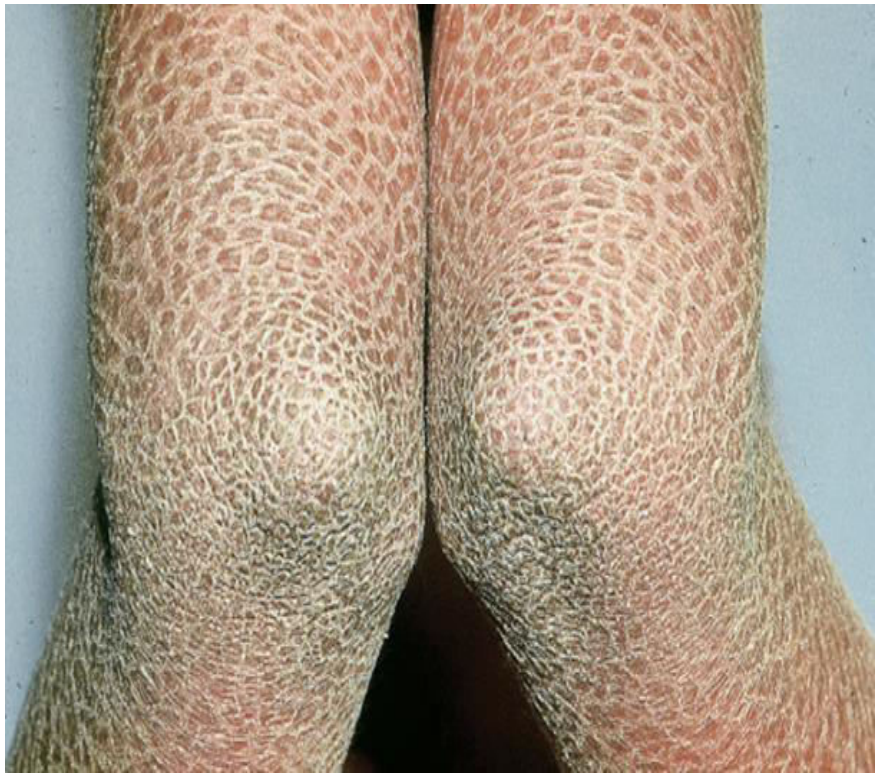


Figure 134-6 Keratoderma characteristically spares central aspects of plantar (and palmar) surfaces in acrokeratosis paraneoplastica.



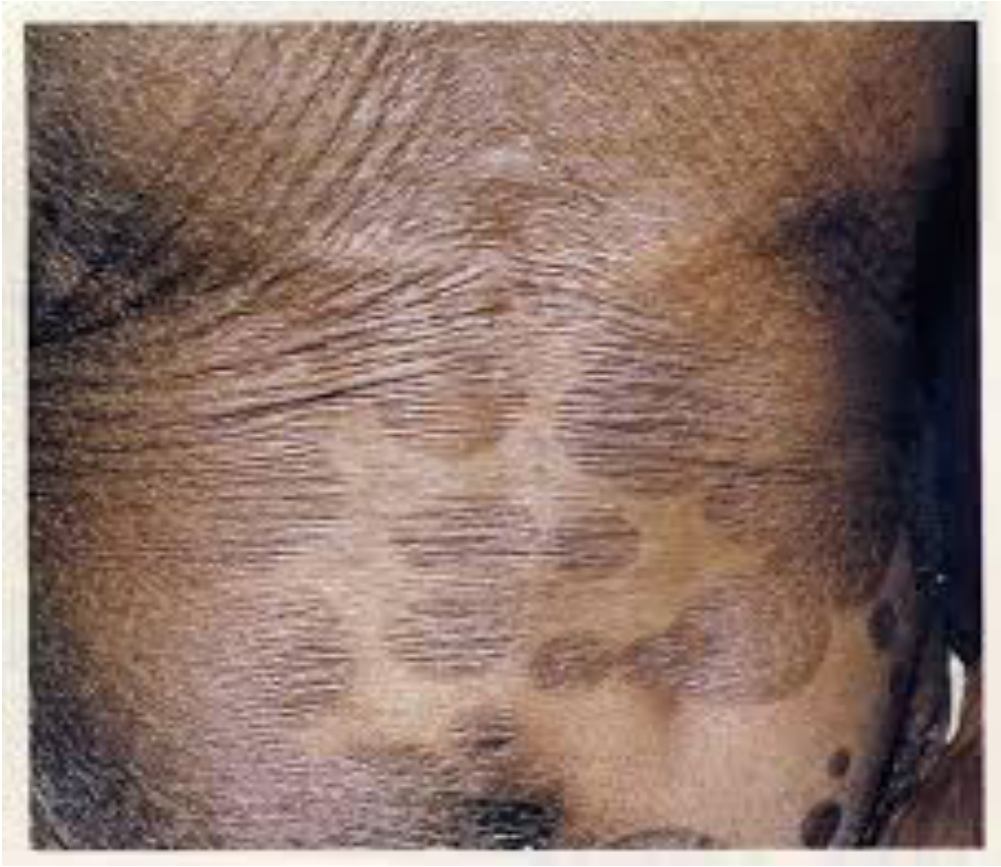
ACQUIRED ICHTHYOSIS

- Condition's manifest with small, whitish to brownish, polygonal scales that lift up at the free edge and are widely distributed on the trunk and extensor surfaces of the extremities.
- The palms and soles are usually spared.
- Hodgkin's lymphomas -80%
- CTCL
- Production of TGF ALFA
- Emolients & keratolytics



PITYRIASIS ROTUNDA

- Fixed, annular, non inflamed, hyperpigmented scaly plaques
- Hepatocellular carcinoma



ERYTHRODERMA

- Lymphomas & leukemias
- Most often presents before the diagnosis of malignancy.

COLLAGEN VASCULAR DISORDERS

- Dermatomyositis : Adult onset, males
- Ovarian, lung, stomach, colorectal
- Asians : Nasopharyngeal ca
- Risk factors:old age/male sex/cutaneous necrosis/dysphagia/1st yr of diagnosis
- SLE : myeloma, paraproteinemia's
- Systemic sclerosis -ca of lung/ esophagus

BULLOUS DISEASES

- **PARANEOPLASTIC PEMPHIGUS:**

- It is characterized by painful, intractable, erosive ulcerative stomatitis and polymorphic cutaneous eruption.

Non Hodgkin`s lymphomas 45%

Chronic Lymphocytic leukaemia's 18%

Castleman tumour18%

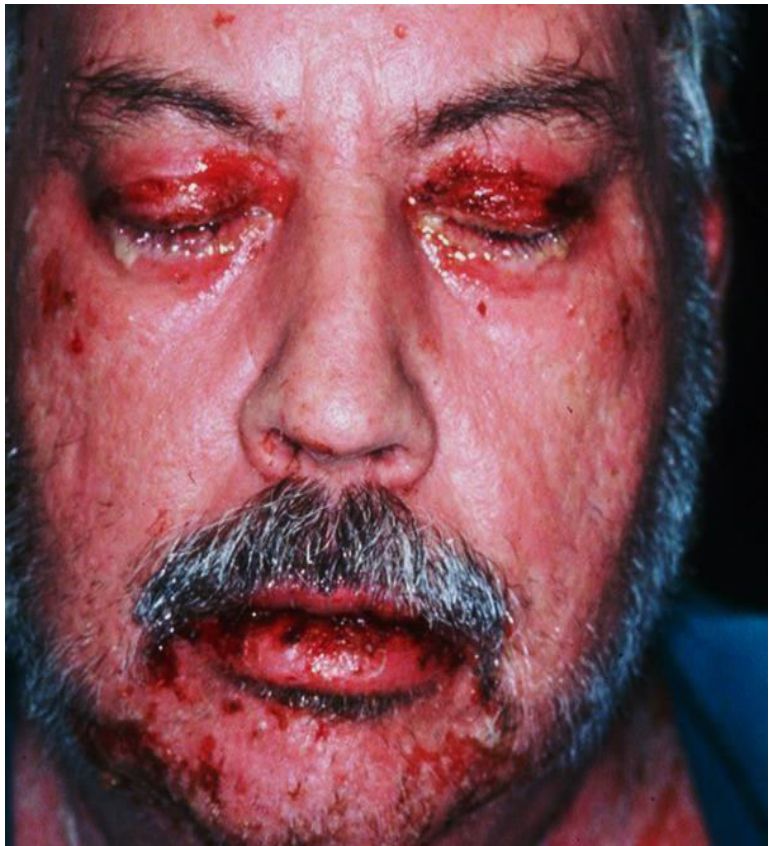
Thymomas 6%

Bronchiolitis obliterans

Histopathology:

Combination of supra basal acantholysis,lichenoid interface changes

Keratinocyte necrosis



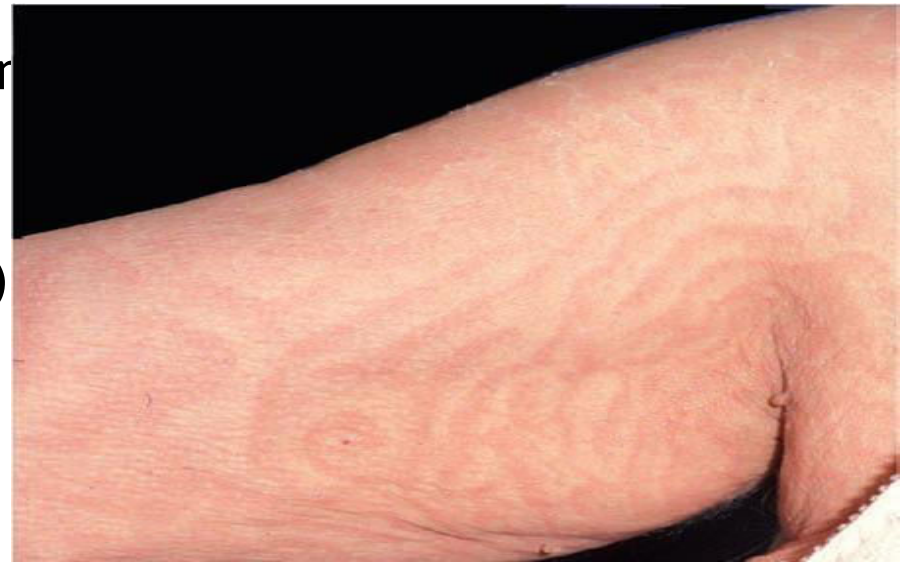
REACTIVE ERYTHEMAS

- **ERYTHEMA GYRATUM REPENS:** erythematous, flat/raised , pruritic, concentric rings with fine marginal scales, which leads to classic wood-grain appearance.
- 80% of cases associated with malignancy
- Spread rapidly at rate of 1cm/day.
- They are localized to the trunk and proximal extrer

face.

- Lung malignancy commonly(oesophageal , breast)
- Resolve completely within 6 weeks

  after tumor resection.



HUMORAL SYNDROMES

- **CUSHING`S SYNDROME** : ectopic ACTH production
- Oat cell ca of lung
- Diffuse hyperpigmentation with edema, muscle weakness, electrolyte imbalance, hypertension
- **CARCINOID SYNDROME** : Intestinal carcinoids with hepatic metastasis
- Flushing : plethoric facies
- Pellagra like rash with photosensitivity
- SEROTONIN , bradykinin , histamine, catecholamines
- Increased urinary 5-HIAA

Table 50.37: Hormone Secreting Tumors with Cutaneous Manifestations

Clinical entity	Cutaneous manifestations	Associated malignancy
Glucagonoma syndrome	Necrolytic migratory erythema	Neoplastic proliferation of the glucagon-secreting alpha cell of the pancreas
Carcinoid syndrome	Flushing Permanent facial cyanotic flush and telangiectasia, resembling rosacea Leonine facies due to persistent facial edema and erythema Pellagroid rash	Carcinoid tumors are most often found in the appendix or small intestine; extraintestinal carcinoids may arise in the bile ducts, pancreas, stomach, ovaries, or bronchi
MEN	Carcinoid-like syndrome in MEN 2A Mucocutaneous lesions occur only in MEN 2B (multiple mucosal neuromas syndrome)	Medullary thyroid cancer
Ectopic ACTH	Intense hyperpigmentation. Systemic features are common—hypokalemic metabolic alkalosis, hypertension, glucose intolerance or frank diabetes, weight loss, myasthenia gravis-like syndrome manifested as profound proximal muscle weakness	Small cell carcinoma of the lung, carcinoid tumors, pancreatic islet cell tumors, pheochromocytomas

NECROLYTIC MIGRATORY ERYTHEMA

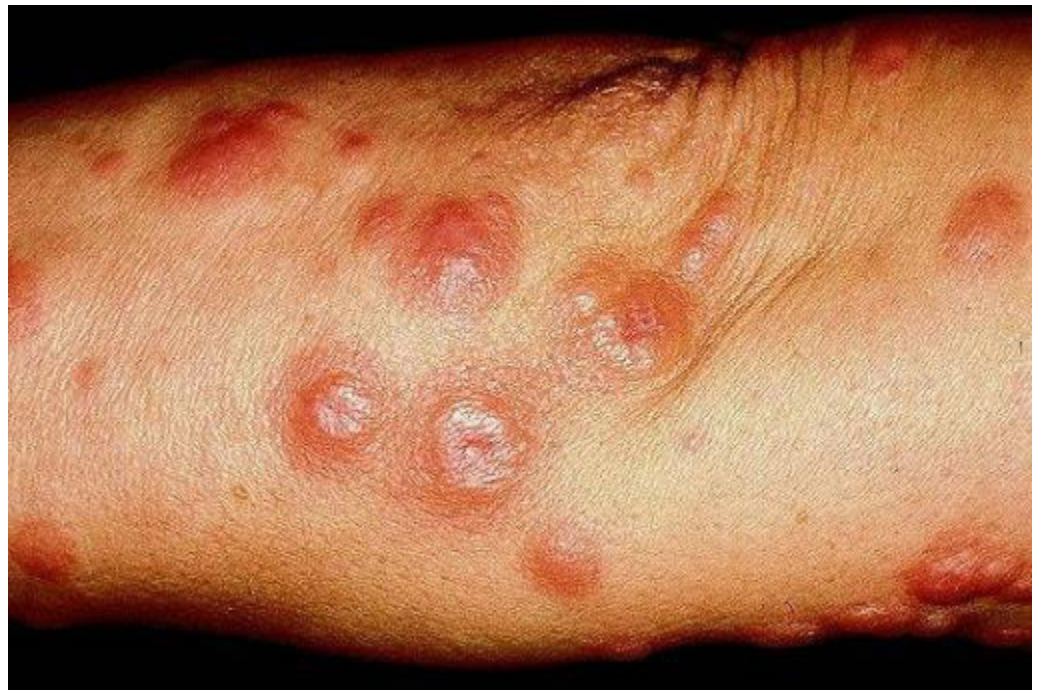
- GLUCAGONOMA: A rare Pancreatic islet alpha cell tumors
- NME is pathognomonic for pancreatic glucagonoma and is present in more than two thirds of patients at the time of tumor diagnosis.
- Waves of erythema with flaccid vescicle and bullae followed later by crusting and erosions.
- Intertrigenous area,oral mucosa
- New onset of DM, diarrhoea,weight loss
- Necrolysis and keratinocyte vacuolation in upper epidermis

- When the characteristic eruption occurs without underlying pancreatic malignancy the condition is referred as Pseudo glucagonoma Syndrome


(a)
(b)
(c)
10×

NEUTROPHILIC DERMATOSES

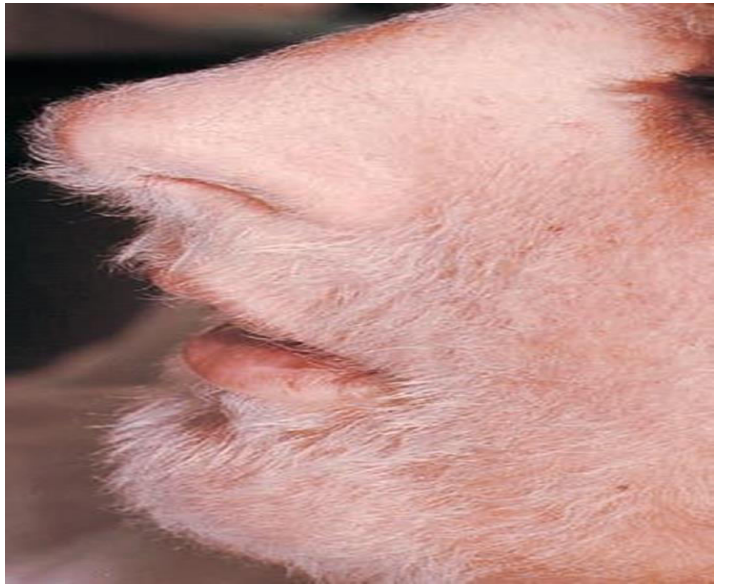
- SWEET`S syndrome:**Tender juicy plaques on face and upper body associated with fever, arthralgias**
- Dense neutrophilic infiltrate withpapillary dermal edema
- 7 – 35% associated with malignancy
- Myeloproliferative & myelodysplastic disorders
- 1% Acute myeloid leukemias
- no female predominance, no neutrophilia



- PYODERMA GANGRENOSUM: Bullous variant
  upper extremity
- Hematological malignancies like AML,CML,PRV

HYPERTRICHOSIS LANUGINOSA ACQUISITA

- A rare PNP condition characterized by the relatively sudden appearance of long,fine, nonpigmented lanugo hairs.
- The lanugo most frequently appears on the face and ears early in the course.
- The hairs may grow to an extraordinary length; eyebrows and eyelashes may grow to inches long.
- The long fine hairs may also be seen on the trunk and limbs including the axillae.
- Lung/ colorectal carcinoma
- Ominous sign indicative of advanced malignancy



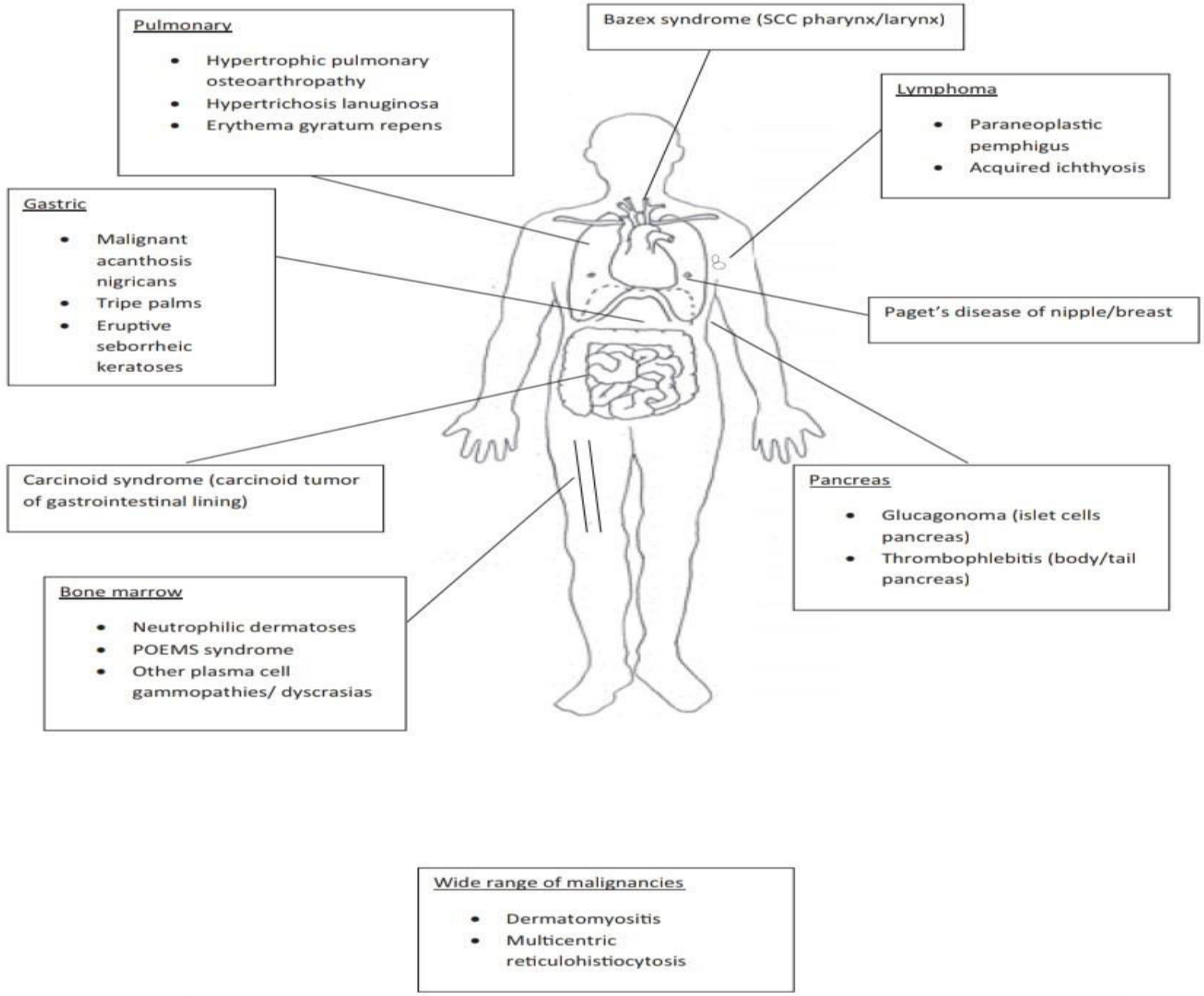


Fig. 3. Paraneoplastic syndromes presented visually in association with commonly involved internal organ malignancy.

VASCULAR RESPONSES

- FLUSHING
- PURPURA : leucocytoclastic vasculitis
  cryoglobulinemia
- MIGRATORY SUPERFICIAL THROMBOPHLEBITIS/ TROUSSEAU`S SIGN
- 30% pancreatic malignancy, pulmonary
- DIGITAL ISCHEMIA
- ERYTHROMERALGIA

CUTANEOUS DEPOSITIONS

- Icterus
- Melanosis
- Hemochromatosis
- Xanthomas
- Amyloidosis
- Scleromyxedema

Table 1
Cutaneous syndromes associated with underlying gammopathies

Name	Cutaneous Findings	Hematologic Disorder	Other Associated Conditions
Scleromyxedema	Widespread firm waxy papules, sclerodermoid induration, "doughnut sign" over proximal interphalangeal joints, Shar-Pei sign of the trunk	IgG-λ; multiple myeloma	Dermato-neuro syndrome
Necrobiotic xanthogranuloma	Necrotic ulcerated xanthomatous plaques in periorbital area and upper chest	Immunoglobulin (Ig)G-κ; multiple myeloma, lymphoma	
Primary systemic amyloidosis	Periorbital purpura, waxy translucent papules, macroglossia	Ig light chain; multiple myeloma	
Cryoglobulinemia (type I)	Acral retiform purpura, livedo reticularis, digital necrosis	Monoclonal Ig (usually IgM); Waldenstrom macroglobulinemia, lymphoma	
Normolipemic plane xanthoma	Yellow thin plaques in periorbital location, intertriginous areas, upper trunk	Multiple myeloma; IgG-κ; lymphoma	
Schnitzler syndrome	Chronic urticaria	IgM-κ; lymphoma	Associated with fevers, arthralgias, bone pain

Data from Bolognia J, Jorizzo J, Schaffer J, eds. Dermatology, 3rd ed. Philadelphia, PA: Elsevier Saunders, 2012.

PARANEOPLASTIC CUTANEOUS SIGNS & SYMPTOMS

- PRURITUS
- SWEATING
- VITILIGO
- CLUBBING
- URTICARIA
- PANNICULITIS/CALCINOSIS CUTIS

MALIGNANCY ASSOCIATED PRURITUS

- Skin cancer pruritus
- Paraneoplastic pruritus
- 13% pts with malignancy
- Severity correlate with stage of malignancy
- Hodgkins25%,Non hodgkins15%,multiple myeloma
- PRV:aquagenic pruritus
- Pruritus localized to nostrils:tumor invading 4^{th} ventricle
- Paroxetine/thalidomide/butorphanol/prednisone/gabapentine&mirtazepine

GENODERMATOSES WITH RISK OF MALIGNANCY

- A number of mechanisms underlie the association of Geno dermatoses with internal malignancy;
- these include chromosomal instability, faulty DNA repair mechanisms, abnormal lymphocyte function, and immunosurveillance, and in some cases, a combination of these.
- More precise genetic diagnosis, understanding of mechanisms, awareness of the benefits, and ability to focus screening of family members for genetic abnormalities or for cancers.
- Internal malignancies are linked to many of genomic instabilities

Table 50.35: Genodermatoses with Cutaneous and Internal Malignancies

Entities with chiefly benign tumors of the skin and visceral neoplasms	Salient cutaneous features	Associated Malignancy
Cowden's syndrome	Facial trichilemmomas, acral keratoses, lipomas, angiomas	Breast cancer, thyroid cancer, endometrial cancer, malignant transformation of gastrointestinal polyps
Birt-Hogg-Dube (BHD)	Fibrofolliculomas, trichodiscomas, acrochordons	Renal cancers
Muir Torre	Sebaceous adenomas, keratoacanthomas	Colorectal, genitourinary carcinomas

Table 50.36: Inherited Immunodeficiency Syndromes and Internal Malignancies

Clinical entity	Cutaneous features	Associated malignancy
Bloom's syndrome	Malar rash, telangiectasias	Leukemia, lymphoma, and adenocarcinoma of the gastrointestinal tract
Rothmund–Thomson syndrome (poikiloderma congenitale)	Erythema, telangiectasia, dyspigmentation, and atrophy on the face, extensor extremities, and buttocks. Alopecia and dystrophic nails	Osteosarcoma, fibrosarcoma, gastric carcinoma, and cutaneous squamous cell carcinoma
Ataxia-telangiectasia (Louis-Bar syndrome)	Telangiectasias initially on the bulbar conjunctiva; other sites include cheeks, corners of the eyes and the ears	Leukemia or lymphoma
Wiskott–Aldrich syndrome	Purpura, eczema, secondary infectious complications	Lymphoreticular malignancy, usually non-Hodgkin's lymphoma

CONCLUSIONS

- *Skins acts as a mirror for various underlying disorders including malignancies.*
- *Some times cutaneous manifestations are only symptoms of internal malignancy.*
- *A keen eye with thorough knowledge of various cutaneous manifestations and regular follow ups required promoting earlier screening and diagnosis, as well as increased intervention measures, there by significantly affecting the chances of survival and improving the quality of life of the patient.*


THANK
YOU