Residents' Corner

Viva questions from the IJDVL

CUTANEOUS DRUG REACTIONS TO ANTI-CANCER DRUGS

Table 1: Summary of the important cutaneous drug reactions to anti-cancer drugs

Drug reaction	Drug	Mechanism of drug reaction	Clinical features
PRIDE complex (papulopustules and/or paronychia, regulatory abnormalities of hair, itching, dryness due to EGFR inhibitors)	EGFR inhibitors Cetuximab Geftinib	Action of drug alters the signaling pathways resulting in keratinocyte growth arrest, apoptosis, decreased cell migration and elicits inflammatory response	Itchy papulopustular eruptions or acneiform eruptions that commonly occur on the seborrheic areas of the body Telangiectasia Paronychia Xerosis, asteatotic eczema
Hand-foot syndrome	Sorafenib Cytarabine Doxorubicin 5-FU	Dual inhibition of VEGF and PDGF disrupts the normal repair process involving capillaries and fibroblasts. This blockade combined with repeated sub-clinical trauma and friction to areas such as palms/soles leads to inflammation	Starts as painful symmetric erythema on pads of distal phalanges and less often soles, severe blistering can occur
Hyperpigmentation	Hydroxyurea Doxorubicin Cisplatin 5-FU Etoposide Busulfan Bleomycin	Accumulation of drug in the skin or direct toxic effects on melanocytes stimulating increased melanin production or elevated adrenocorticotropic hormone	Hydroxyurea can produce diffuse pigmentation on the face, neck, palms with accentuation in areas of pressure with longitudinal and transverse bands or diffuse nail pigmentation and patchy pigmentation of the tongue and buccal mucosa
Serpentine supravenous hyperpigmentation or persistent serpentine supravenous erythema	5-FU Doxorubicin Actinomycin D Vinca alkaloids Bortezomib	Cytotoxic drugs cause loss of integrity of the vascular endothelium and leakage of the drug to overlying dermis leading to hyperpigmentation	Red streaks over the commonly injected veins followed by hyperpigmentation
Melanonychia	Vincristine Doxorubicin Hydroxyurea Bleomycin Cyclophosphamide Daunorubicin Dacarbazine 5-FU	Matrix melanin distribution in the growing nail plate	
Muehrcke's lines	5-FU Oxyplatinin Cyclophosphamide Epirubicin	Edema of the nail bed which occurs due to hypoalbuminemia and an alteration of the nail plate attachment to nail bed which occurs due to vascular compromise following chemotherapy	Muehrcke's lines are white lines (leukonychia) that extend all the way across the nail and lie parallel to the lunula. In contrast to Beau's lines, they are not grooved. The lines are actually in the vascular nail bed and as such, they do not move with nail growth. Meuhrcke's lines disappear when pressure is placed over the nail, blanching the underlying nail bed
Mees lines	Vincristine Cyclophosphamide Doxorubicin	Sudden direct toxicity to the nail matrix	They are typically white bands traversing the width of the nail. As the nail grows they move towards the end, and finally disappear when trimmed. They are also called leuconychia striata
Anagen effluvium	Doxorubicin Daunorubicin Docetaxel Cyclophosphamide	Any event or insult that causes abrupt cessation of mitotic activity of the matrix cells of the bulb leads to weakening of the partially keratinized, proximal portion of the hair shaft resulting in narrowing and subsequent breakage within the hair canal and even complete failure of hair formation. The hair bulb itself may be damaged and the hairs may separate at the bulb and fall out	Usually begins 1-2 weeks after starting the drug and becomes more apparent in the subsequent 4-8 weeks
Flagellate pigmentation	Bleomycin Docetaxel Peplomycin Bendamustine	Exact cause unknown. One theory is that trauma (scratching) causes vasodilatation with local drug accumulation in the skin causing a subsequent post-inflammatory hyperpigmentation	Flagellate erythema presents as itch, coinciding with the onset of red linear steaks which are found most commonly on the back and flanks

EGFR: Epidermal growth factor receptor, 5FU: 5-fluorouracil, VEGF: Vascular endothelial growth factor, PDGF: Platelet-derived growth factor

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Give a brief outline of the cutaneous drug reactions to anti-cancer drugs

The important cutaneous drug reactions to anti-cancer drugs have been summarized in Table 1.

ID ERUPTION

What is an id reaction?

It is a secondary immunologic reaction to circulating antibodies or activated T lymphocytes that are directed against microbial antigens derived from nonliving organisms.

Enumerate the different types of id reactions?

Different types of id reactions based on their causative factor have been outlined in Table 2.

What are the characteristics of a dermatophytid?

- The host harbors the proven focus of infection elsewhere
- Positive skin test response to trichophyton/candida/or epidermophyton
- Fungal forms are neither recoverable from the site of cutaneous eruption nor microscopically visible in direct smears or histopathology preparations
- Lesions resolve spontaneously after an acute course, provided that the infection is identified and eliminated.

What are the clinical presentations of dermatophytids?

- The most common "id" eruption resembles widespread lichen scrofulosorum consisting of bilaterally symmetrical, small, grouped or diffusely scattered, follicular papules usually on the trunk, but may extend on to the extremities in severe cases
- Acutely inflamed tinea pedis may be associated with pompholyx-like vesicles in the web spaces and the sides of the fingers
- Erythema nodosum
- Erythema multiforme
- Erythema annulare centrifugum
- Erysipelas-like id eruption.

Table 2: Types of id reactions

Causative organism/factor	Types of id reactions
Fungal	Dermatophytid/trichophytid Candidid Sporotrichoid
Bacterial/mycobacterial	Leprid Tuberculid Micropapular - Lichen scrofulosorum Papular - Papulonecrotic tuberculid Nodular - Erythema induratum Syphillid Pintid
Viral	Herpes simplex virus and poxviruses can cause ids
Parasitic	Leishmanid Pediculid Scabid
Stasis dermatitis, contact dermatitis and other eczematous disorders	Eczematid

SYNDROMES DISCUSSED IN THIS ISSUE

Various syndromes have been described in this journal issue. Table 3 discusses the salient features of these syndromes.

MACROCHEILIA

Enumerate the differential diagnoses of macrocheilia?

Acute or chronic macrocheilia (enlargement of one or more lips) can be due to various causes as enumerated in Box 1.

Box 1: Differential diagnosis of macrocheilia

Acute	Chronic
Traumatic	Developmental
Infective	Familial/idiopathic
• Herpes simplex	Double lip
• Pyococcal	Ascher's syndrome
• Anthrax	Lymphangioma
• Diphtheria	Hemangioma
• Primary syphilis	Neurofibroma
• Trichophytosis	Mucopolysaccharidosis
• Leishmaniasis	Fucosidosis
• Trichiniasis	Acquired
Angioedema	Post- traumatic
Erythema multiforme	Post- infective on a developmental lymphatic defect
Actinic cheilitis	Infective: tuberculosis, leprosy, rhinoscleroma, leishmaniasis
Other forms of cheilitis	Granulomatous cheilitis
	Melkersson-Rosenthal syndrome
	Cheilitis glandularis
	Sarcoidosis
	Crohn's disease
	Orofacial granulomatosis
	Neoplastic

What is Miescher's cheilitis?

Miescher's cheilitis is another name for granulomatous cheilitis. In this condition, the granulomatous changes are confined to the lip and it is generally regarded as a monosymptomatic form of Melkersson–Rosenthal syndrome (labial edema + scrotal tongue + lower

Table 3: Syndromes and their salient features

Syndrome	Salient features
Fuch's syndrome (Incomplete Steven-Johnson syndrome or atypical Steven-Johnson syndrome)	Steven-Johnson syndrome with mucosal involvement in absence of skin lesions has been described as Fuch's syndrome and it is believed to a variant of erythema multiforme major It is more frequently seen in children and adolescents, although adult cases have been reported Mycoplasma is the most common infectious cause in children Oral mucosa is always affected. Ocular and genital lesions occur in 2/3rd-3/4th of the cases, respectively Diagnosis in cases of mycoplasma is done by serological studies, if radiological changes are absent Treatment in cases of mycoplasma infection includes macrolides, quinolones, or tetracyclines
NBCCS (Gorlin-Goltz syndrome)	This is an autosomal dominant condition, caused due to mutation in the patched gene *(PTCH1)* located on 9q22.3-q31 chromosome List of major and minor criteria in diagnosis of nevoid basal cell carcinoma syndrome **Major criteria** Two or more basal cell carcinomas in persons <20 years of age Odontogenic keratocysts of the jaw Three or more plantar or palmar pits Bilamellar calcification of the falx cerebri Bifid fused or markedly splayed ribs First degree relative with Goltz-Gorlin syndrome **Minor criteria** Macrocephaly Congenital malformations (cleft lip or palate, frontal bossing, hypertelorism) Other skeletal abnormalities (Sprengel deformity, marked pectus deformity, syndactyly of digits) Radiological abnormalities: bridging of sella turcica, vertebral abnormality such as hemivertebrae, flame shaped lucencies of hands and feet Ovarian fibroma Medulloblastoma
Pachyonychia congenita	Autosomal dominant genetic disease that affect nails, palmoplantar skin and oral mucosa It is divided into 5 subtypes depending upon the keratin mutation involvement PC-K6a, PC-K6b, PC-K6c, PC-K16, PC-K17 Thick toe nails and painful plantar keratoderma are common. Other features that can be seen are thickened fingernails, palmar keratoderma, follicular hyperkeratosis, cysts including epidermal inclusion cysts, pilosebaceous cysts, hoarseness, natal teeth
Maffucci syndrome	It is a rare, non-hereditary disorder characterized by multiple enchondromas and vascular malformations. Symptoms present before puberty in 78% of cases. It is characterized by - Enchondromas that are benign cartilaginous tumors usually found in the phalanges and long bones. They can also affect the tibia, fibula, humerus, ribs or cranium. They are usually asymptomatic but there are chances of pathological fractures and malignant sarcomatous transformation - Vascular lesions such as venous malformations, spindle cell hemangiomas, lymphangiomas are seen which are present adjacent to the areas of enchondromatosis and present as bluish nodules **Treatment** Regular monitoring to detect malignancies Osteotomy should be done for bony lesions. Sclerotherapy, radiotherapy and laser therapy have also been tried Rapamycin has been used for refractory hemangioendotheliomatosis
Schopf-Schulz-Passarge syndrome (odonto-onycho-dermal dysplasia)	This syndrome is characterised by - Multiple eyelid apocrine hidrocystomas - Hypodontia - Hypotrichosis - Nail dystrophy - Palmoplantar keratoderma
Baboon syndrome (SDRIFE)	This is characterized by skin eruption in the intertriginous areas caused by systemic absorption of agents after cutaneous sensitization Diagnosis is based upon exposure to a systemically administered drug followed by sharply demarcated erythema of the gluteal area and/or 'V' shaped erythema of the inguinal area and involvement of at least one other intertriginous site/flexural fold, symmetry of affected areas and absence of systemic symptoms and signs

SDRIFE: Symmetrical drug related inter flexural exanthema, NBCCS: Nevoid basal cell carcinoma syndrome, BCC: Basal cell carcinoma

motor neuron type facial palsy), although the possibility remains that these may be two separate diseases. There may be a genetic predisposition and some cases may represent a localized form of sarcoidosis or ectopic Crohn's disease or orofacial granulomatosis.

The earliest cutaneous manifestations are sudden diffuse or nodular swellings involving the upper lip, lower lip and one or both cheeks, infrequently associated with constitutional symptoms. After the first attack, symptoms usually subside but in subsequent attacks the swelling may persist and slowly increase. It is

accompanied by fissured or scrotal tongue in 20–40% of cases and facial palsy in 30% of cases. Facial palsy may be intermittent at first but later becomes permanent. It can be unilateral or bilateral, and partial or complete. Occasionally, other nerves such as auditory, olfactory, glossopharyngeal and hypoglossal are involved.

Treatment options include intralesional steroids, cheiloplasty, clofazimine, metronidazole, erythromycin, sulfasalazine, ketotifen and rarely systemic corticosteroids.

VITAMIN D AND SKIN

Briefly describe the role of topical vitamin D analogs in psoriasis

Various vitamin D analogs, including calcitriol, calcipotriol, tacalcitol, maxacalcitol and hexafluoro-1, 25-dihydroxyvitamin D_3 are useful as topical agents in the treatment of psoriasis. These can be used in combination with agents such as tumor necrosis factor-α inhibitors, methotrexate (MTX), low-dose oral cyclosporine (2 mg/kg/day), oral acitretin, topical dithranol, topical steroids and ultraviolet B therapy.

Thet are useful in chronic plaque psoriasis, scalp psoriasis and nail psoriasis. Vitamin D analogs do not exhibit tachyphylaxis and are effective in the treatment of psoriatic skin lesions in children and in human immunodeficiency virus patients. The use of calcipotriol ointment on face and flexures should be avoided due to its irritancy.

Mechanism

The therapeutic effects of topical vitamin D occur due to the following:

- Vitamin D receptor-mediated genomic mechanism results in inhibition of keratinocyte proliferation
- Non-genomic mechanism induces keratinocyte differentiation by increasing intracellular calcium levels
- Modulation of various markers of epidermal proliferation (proliferating cell nuclear antigen and Ki-67 antigen) and differentiation (involucrin, transglutaminase K, filaggrin, cytokeratins 10, 16) has been shown *in situ* in lesional psoriatic skin following topical application of vitamin D analogs
- Anti-inflammatory effects of topical vitamin D is due to inhibition of T cell differentiation and proliferation in response to interleukin 1 (IL-1). The anti-inflammatory effects are also due to inhibition of production of IL-2, IL-6 and interferon-gamma. Topical calcipotriol also inhibits human beta defensin 2 (HBD2), HBD3, IL-17A, IL-17F and IL-8 which are found in increased levels in psoriatic lesions, thus it blocks the cathelicidin pathway and reduces inflammation.

Enumerate the role of vitamin D in various dermatological disorders

The role of vitamin D in various dermatological disorders can be grouped into the following categories.

Well established role

Role in etiopathogenesis: psoriasis.

Therapeutic role: psoriasis, lichen sclerosus et atrophicus, morphea.

Inconclusive role

Role in etiopathogenesis: atopic dermatitis, vitiligo, ichthyosis, keloids, autoimmune diseases.

Therapeutic role: skin cancer (prevention), tuberculosis.

Less characterized roles

These include various diseases such as acne vulgaris, rosacea, ageing, seborrheic keratosis, telogen effluvium and female pattern hair loss, leg ulcers, xerosis, Behcet's disease, autoimmune bullous disorders and polycystic ovarian syndrome with acne and hirsutism.

PITYRIASIS RUBRA PILARIS

Classify pityriasis rubra pilaris

Pityriasis rubra pilaris comprises a group of rare disorders characterized by a cephalo-caudal cutaneous eruption of follicular hyperkeratotic papules with characteristic islands of spared skin along with palmo-plantar keratoderma as a frequent feature.

Griffith's classification is commonly used and includes:

- Type 1: Classic adult
- Type 2: Atypical adult
- Type 3: Classic juvenile
- Type 4: Circumscribed juvenile
- Type 5: Atypical juvenile.

Pityriasis rubra pilaris associated with immunodeficiency such as human immunodeficiency virus has been added and described as type 6 or human immunodeficiency virus-associated follicular syndrome.

What are the characteristic histological findings in pityriasis rubra pilaris?

The characteristic histological findings are alternating orthokeratosis and parakeratosis (checkerboard pattern), follicular plugging along with dilatation of dermal capillaries and a lympho-histiocytic infiltrate. The foci of parakeratosis are typically seen as areas of perifollicular shouldering (shoulder parakeratosis).

Enumerate treatment modalities for pityriasis rubra pilaris

Supportive treatment with emollients is needed. Retinoids are considered as first line of treatment. Systemic retinoids such as acitretin and isotretinoin can be used in extensive and erythrodermic cases, topical vitamin D analogs are also useful. Other systemic therapies include methotrexate, cyclosporine, phototherapy and biologicals can be tried in resistant cases.

POROKERATOSIS

Enumerate the different types of porokeratosis

Porokeratosis is a group of hereditary or acquired disorders of epidermal keratinization characterized by keratotic lesions with an atrophic center and a prominent peripheral ridge, the histological hallmark of which is the cornoid lamella.

Clinically, seven variants have been identified:

- Plaque type
- Disseminated superficial porokeratosis
- Disseminated superficial actinic porokeratosis
- Linear porokeratosis
- Giant porokeratosis
- Porokeratosis palmaris et plantaris disseminata
- Punctate porokeratosis.

Describe the histological features of porokeratosis

The characteristic histopathological feature is the cornoid lamella seen at the edge of the lesion as a column of poorly staining parakeratotic stratum corneum cells. The granular layer is absent below and the underlying keratinocytes are edematous with spongiosis and shrunken nuclei. A moderate dermal lymphocytic infiltrate may be seen under the lamella. The central area is usually atrophic but may show hyperkeratosis. Uncommonly, a lichenoid pattern and the presence of amyloid material may be detected.

Enumerate treatment modalities in porokeratosis

Topical retinoids, tacalcitol, 5-fluorouracil ointment, imiquimod and systemic retinoids have been tried. Other modalities include cryotherapy, CO_2 laser, pulsed dye laser therapy and photodynamic therapy.

ONYCHOMYCOSIS

What are the clinical patterns of onychomycosis?

Onychomycosis has been classified into five clinical presentations according to the modes of invasion:

- Distal and lateral subungual onychomycosis
- Proximal subungual onychomycosis
- Superficial white onychomycosis
- Endonyx onychomycosis (EO) and
- Mixed onychomycosis (total nail dystrophy, secondary onychomycosis and paronychia -associated onychomycosis).

What is endonyx onychomycosis?

Endonyx onychomycosis is an unusual variant of onychomycosis which involves the inner surface of nail plate without inflammation of the nail bed, onycholysis or subungual hyperkeratosis. The classic nail lesion shows milky-white discoloration in the nail plate without nail surface change. It is caused by *Trichophyton soudanense* and *Trichophyton violaceum*.

BACILLARY ANGIOMATOSIS

What is the etiologic agent in bacillary angiomatosis?

Bacillary angiomatosis is an uncommon infectious vasoproliferative disorder, caused by *Bartonella henselae* or *Bartonella quintana* and is commonly associated with immunosuppression. Skin is the most common site of infection. The disease may be preceded by a history of traumatic cat contact or exposure to cat fleas. Ticks, lice and sandflies have also been implicated in the transmission of various *Bartonella* species.

What are the clinical manifestations of bacillary angiomatosis?

Clinically bacillary angiomatosis has three distinct morphological presentations:

- Pyogenic granuloma-like
- Subcutaneous nodules
- Hyperpigmented indurated plaques

The first type is more common and is characterized by solitary or multiple, reddish, angiomatous papules and nodules affecting different areas of the skin. The face, neck, trunk, extremities and back are most commonly affected. Atypical lesions have been described including those resembling Kaposi's sarcoma, verruga peruana or leg ulcers. Regional lymphadenopathy can occur and it is often painful. Disseminated disease involves the liver, spleen, lymph nodes, gastrointestinal tract, bone, brain and other organs and can occur without cutaneous lesions.

How is bacillary angiomatosis diagnosed and treated?

Histological examination reveals lobular proliferations of small blood vessels with a diffuse and a predominantly perivascular inflammatory infiltrate involving the superficial and deep dermis. The diagnosis can be confirmed by the demonstration of bacilli in histological sections stained with silver dyes or Warthin–Starry stain. Culture from the biopsied tissues (which can be difficult due to the fastidious nature of organism), electron microscopy examination, serology (which may be unreliable in immunocompromised patients due to lack of antibody response) and polymerase chain reaction are other procedures that can be used to establish the diagnosis.

Long courses of treatment with doxycycline or erythromycin for a period of 8 weeks or longer is recommended.

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