Residents' Corner

# Viva questions from the IJDVL

## FOCUS TOPIC - KELOID

### What are the differences between a keloid and hypertrophic scar?

The differences between keloid and hypertrophic scar have been outlined in Table 1.

### What are the syndromes associated with the tendency to develop keloids?

- Rubinstein–Taybi syndrome
- Goeminne syndrome
- Ehler–Danlos syndrome
- Dubois syndrome
- Pachydermoperiostosis
- Progeria
- Osteopoikilosis.

### What are the risk factors for keloid formation?

The risk factors for keloid formation include the following:

- African, American, Asian or Hispanic ethnicity
- Family history of keloidal tendency
- In darkly pigmented skin, risk increases by 15–20 fold
- Wound healing by secondary intention
- Prolonged healing time >3 weeks
- Wounds subjected to prolonged inflammation whether foreign body related/infection/burn/inadequate wound closure
- Chronic inflammation: earring site, sites of repeated trauma
- Wounds on anterior chest, shoulders, flexor surfaces of extremities, anterior neck and wounds that cross the skin tension lines are more susceptible to abnormal scar formation
- Deep wounds like those from burns or surgical scars
- Scars from acne, vaccination or chicken pox.

### What are the preventive measures that can be taken in cases with a keloidal tendency?

The preventive measures which can be undertaken in persons who are prone to develop keloids include the following:

- Withhold non-essential cosmetic surgery/piercing
- Closing all wounds with minimal tension by making incision along Langer's lines
- Use of pressure garments up to 4–6 months post-injury
- During surgeries, aim for primary closure, adequate debridement of contaminated wounds good homeostasis and gentle handling of tissues.

### What are the treatment modalities for keloids?

The treatment modalities for keloids have been outlined in Table 2.

## DERMAL MELANOCYTOSIS

### What is dermal melanocytosis?

Dermal melanocytosis or dermal dendritic melanocytic proliferations are characterized by the presence of melanin-producing dendritic melanocytes in the dermis. Clinically, speckled or mottled, gray or blue-gray appearance is distinctive in dermal melanocytosis which is caused by Tyndall effect.

### Enumerate the various types of dermal melanocytosis

Dermal melanocytosis can be of congenital and acquired types. Most cases present at birth or may manifest clinically in early childhood. Nevus of Ota, nevus of Ito, Mongolian spot and dermal melanocytic hamartoma are congenital dermal melanocytosis. Acquired dermal melanocytoses appear in adult life which has been reported very rarely and consist of nevus of Hori (acquired bilateral nevus of Ota), nevus of Sun (acquired unilateral nevus of Ota) and a rare entity, extra-facial acquired dermal melanocytosis.

### Enumerate the salient aspects which help to differentiate the various dermal melanocytosis?

The differentiating features of dermal melanocytosis have been outlined in Table 3.



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**Table 1: Differences between keloid and hypertrophic scar**

| Salient features | Keloid | Hypertrophic scar |
|---|---|---|
| Genetic and racial predisposition | Genetic predisposition exists and it is associated with group A blood type and HLA alleles B14, 21, BW35, DR5 and DQW3<br>More commonly seen in African, American, Asian and Hispanic dark-skinned populations | No familial or racial predisposition |
| Age group | Seen between 10 and 30 years | Usually seen in children |
| Onset and duration | In general, takes a year to progressively develop. Persist for long periods and do not spontaneously regress | Generally appear within 4 weeks of trauma. After a rapid growth phase lasting for up to 6 months, they undergo partial spontaneous regression resulting in flat scars without symptoms |
| Appearance and extension | Appears initially as a firm reddish, hyperpigmented or skin-colored plaque, gradually becomes nodular Extends beyond the borders of the original wound or defect and may have irregular shapes | Remains confined to the borders of the original wound and most of the times retains the shape of the original wound or incision, it rarely rises more than 4 mm above the skin surface |
| Symptoms | Can be pruritic, painful and hyperesthetic | Can be pruritic |
| Sites | Increased sites of predisposition include shoulder, sternum, mandible and arms (at sites of tension) | No predisposition toward the sites of tension |
| Recurrence | Tends to recur after excision | Recurrences are very rare |
| Collagen | Type 1 and 3 collagens are seen as pale staining hypocellular, irregular, abnormally thick, unidirectional collagen and is arranged in a highly stressed direction with no evidence of nodule or excess myofibroblasts | Type 3 collagen is seen oriented parallel to the epidermal surface with abundant nodules containing myofibroblasts, large extracellular collagen filaments and plentiful acid mucopolysaccharides |
| Fibroblast activity | Fibroblasts have increased prolyl hydroxylase activity which is involved in collagen synthesis, seen 14 times greater than in normal skin | Prolyl hydroxylase activity of the fibroblasts is not increased |

## NEVOID HYPERKERATOSIS OF NIPPLE AND AREOLA

### What is nevoid hyperkeratosis of the nipple and areola?

Hyperkeratosis of the nipple and/or areola is defined as excessive keratinization of the nipple and/or areola. It includes hyperpigmentation, verrucous and filiform keratotic thickening of the nipple and areola with papillomatosis and a velvety sensation to touch.

### How is nevoid hyperkeratosis of the nipple and areola classified?

Nevoid hyperkeratosis of the nipple and areola has been classified as follows:

- Type 1: Occurs as an extension of epidermal nevus
- Type 2: Hyperkeratosis of the nipple associated with other dermatoses such as atopic disease, acanthosis nigricans, Darier's, seborrheic keratosis and Bowen's disease
- Type 3: No association with epidermal nevus or other dermatoses.

Alternately, it is classified into primary hyperkeratosis of nipple and/or areola which is idiopathic and secondary hyperkeratosis of the nipple and/or areola which is associated with the above-mentioned disorders.

### What is the management of a case of nevoid hyperkeratosis?

Unilateral primary hyperkeratosis of the nipple and/or areola must be distinguished from an underlying breast carcinoma. Pain, bleeding, ulceration, nipple discharge or loss of normal anatomy with nipple retraction or loss of nipple should prompt immediate evaluation. Lesions recalcitrant to therapy also warrant investigation. The evaluation of these lesions should include complete bilateral breast examination with evaluation of the lymph nodes, mammography and biopsy of the involved skin.

Biopsy in a classical case of primary hyperkeratosis shows orthokeratotic hyperkeratosis, acanthosis, papillomatosis with mild dermal lymphocytic perivascular inflammation and epidermal spongiosis with microabscesses containing normal lymphocytes. In secondary hyperkeratosis, the histologic findings are related to the underlying associated skin disease.

Treatments that have been previously reported include topical lactic acid (12%), topical salicylic acid 6%, tretinoin, calcipotriol, cryotherapy, low-dose isotretinoin, shave excision, $CO_2$ laser ablation, surgical excision with reconstruction and curettage.

**Table 2: Treatment modalities for keloids**

| Modality of treatment | Mechanism of action | Dose/methodology | Adverse effects | Combination therapy |
|---|---|---|---|---|
| Intralesional corticosteroids | Suppression of inflammation, vasoconstriction leading to hypoxia and antimitotic effect, ↓ plasma proteinase inhibitors, ↓ production of β-FGF, ↓ production of TGF-β1 | 5-10 ml injected in the upper dermis (for hypertrophic scars), for tough keloids 40 mg/ml can be given. Repeated every 3–6 weeks | Pain, skin and subcutaneous fat atrophy, telangiectasia, necrosis, ulceration, hypopigmentation, Cushing's syndrome | Can be combined with surgery, pulsed dye laser, irradiation, intralesional 5 FU, cryotherapy |
| Cryotherapy | Cold-induced vascular damage leading to vascular anoxia | Intralesional with needle cryoprobe/contact/spray cryosurgery<br>Can be done at an interval of 2-3 weeks | Pain, local edema, epidermolysis, transient hypopigmentation | Can be combined with intralesional steroids |
| Compression therapy | Fibroblast degeneration due to local hypoxia with decrease in chondroitin 4 sulfate and ↓ activity of MMP-28 | Pressure of 20-40 mmHg to keloid 24 h/day for 20-25 weeks | Discomfort from heat and sweating, swelling of limb, rashes, eczema, excessive friction, blistering, break down of scar and non-compliance of patient using garment | Can be combined with surgery, intralesional therapy |
| Lasers and light | Selective photothermolysis, hypoxia, dissociation of disulphide bonds due to heating with subsequent collagen fiber realignment. Induction of apoptosis ↓ fibroblast proliferation, ↓ TGF-β1 expression, ↓ mast cells | Pulsed dye laser used with good results<br>585-595 nm, pulse duration of 0.45 s, fluence 6.5-7.25 J/cm$^2$<br>$CO_2$ laser, Er:YAG laser and intense pulse light can be tried | Purpura<br>Hyperpigmentation<br>Hypopigmentation<br>Blister formation | Can be combined with intralesional therapy |
| Silicone material as gels, gel sheets, silastic sheets and orthosis garments | Affects hydration of skin by ↓ water vapor transmission rate which causes ↓ capillary permeability, ↓ hyperremia and ↓ collagen deposition | Post surgery can be applied as soon as reepithelialization is over. To be applied daily for at least 12 h till results are achieved or at least 2 months | Itching, rash, bad smell from sheet/gel, sheet fragility, skin maceration, poor compliance | Combine after surgical excision |
| Radiotherapy | Inhibits the abnormal activated fibroblasts and promotes normal fibroblasts | 20 Gy in 4 fractions over 4 days in anterior chest wall, scapular region and suprapubic region and 10 Gy in 2 fractions over 2 days on earlobes, 10 Gy in 3 fractions over 3 days in other sites | Hyperpigmentation and hypopigmentation are seen as transient side effects | Can be combined with surgical excision |
| Intralesional 5 FU | Antimetabolite that inhibits thymidine synthase and interferes with RNA and DNA synthesis. Blocks collagen synthesis and inhibits fibroblast proliferation | 50 mg/ml IL once a week or once in 2 weeks. 5-10 injections are required for complete flattening | Pain, urticaria, skin breakdown, purpura, localized hair loss, pigment changes and systemic absorption | Can be combined with intralesional steroid |
| Bleomycin | ↓ DNA/RNA synthesis and ↓ TGF-β lysyl oxidase enzyme | Intradermal injection or multiple punctures (40 punctures/cm$^2$) with the help of 22-gauge needle or 0.1 ml (1.5 U/ml) at a dose of maximum 6 ml is used | Hyperpigmentation, pain, ulceration, Raynaud's phenomenon, gangrene, fibrosis, neutrophilic eccrine hidradenitis, alopecia, edema, nail changes | Do not combine with radiotherapy |
| Imiquimod | ↓ Collagen production by IFN release and alters expression of apoptotic gene | Apply at night for 5 days in a week with 2 days off and continue for a total of 8 weeks | Itching, burning, pain, blister, ulceration, localized hyperpigmentation, flu-like symptoms | Can be combined with surgical excision |
| Verapamil | Stimulates the synthesis of procollagenase increasing collagenase activity resulting in the reduction of fibrous tissue proliferation ↓ IL-6 and VEGF production | | | Surgical excision, pressure therapy, topical silicone |

Other drugs that have been used include - onion extract with heparin, botulinum toxin, β-FGF, TGF-β, IFNs, interleukin-10, topical tamoxifen, tranilast, prostaglandin E2, tacrolimus, rapamycin, pentoxifylline, intralesional collagenase, hyaluronic acid, catechins, extracellular matrix modulators

FGF: Fibroblast growth factor, TGF-β: Transforming growth factor-beta, IFNs: Interferons, IL: Interleukin, VEGF: Vascular endothelial growth factor, 5 FU: 5-fluorouraci, Er:YAG: Erbium-doped yttrium aluminum garnet, MMP: Matrix metalloproteinase

**Table 3: Differentiating features of dermal melanocytosis**

| Salient aspects | Nevus of Ota/ nevus fuscoceruleus ophthalmomaxillaris | Nevus of Ito/nevus fuscoceruleus acromiodeltoideus | Mongolian spot | Nevus of Hori/nevus fusco-caerulus zygomaticus/acquired circumscribed facial melanocytoses | Dermal melanocytic hamartoma |
|---|---|---|---|---|---|
| Epidemiology | Appears at birth or at puberty<br>Asian and female preponderance (80%) | Appears in early infancy or at puberty<br>Asian and female preponderance | Appears at birth or within the first few weeks of life<br>Asian, African, Hispanic population with a slight male preponderance | Seen more in women of Asian descent after the third decade of life | Congenital |
| Clinical presentation | Blue to slate gray mottled pigmentation<br>5% bilaterally | Blue to slate gray mottled macular hyperpigmentation | Uniform blue to slate gray macular hyperpigmentation | Speckled blue - brown and/or slate gray macules | Mottled hyperpigmentation with small blue gray macules in a diffuse pigmented patch |
| Distribution | Occurs in the distribution of ophthalmic and maxillary branches of trigeminal nerve<br>Conjunctiva, sclera, palate and nasal mucosa can be involved | Occurs in the distribution of acromioclavicular nerve | Lower back and sacrum<br>Aberrant Mongolian spots are located in areas distal to the lumbosacral region, these tend to persist beyond 1 year | Common sites are bilateral malar areas and less commonly on forehead, upper eyelids, cheeks and nose without ocular or mucosal pigmentation | Dermatomal distribution |
| Histology | Presence of melanocytes in the epidermis and mainly in the upper, middle and deep dermis | Presence of melanocytes in the epidermis and mainly in the upper, middle and deep dermis | Spindle-shaped dendritic melanocytes variably pigmented melanosomes typically located in the deep reticular dermis | Presence of melanocytes in the epidermis and mainly in the upper and middle dermis with sparing of deeper dermal region | Dermal melanocytes in the upper two-third of the dermis (including the sub-papillary layer) |
| Therapy | Persists throughout life<br>Q-switched Nd:YAG laser<br>Cryotherapy<br>Surgery | Persists throughout life<br>Q-switched Nd:YAG laser<br>Cryotherapy<br>Surgery | Usually spontaneous resolution by 4 years of age | Usually difficult to treat. Q-switched Nd:YAG laser in combination with hydroquinone-based cream and chemical peels | None |
| Associated features | Glaucoma, ipsilateral sensorineural hypoacusia<br>Melanoma | No associated features of medical concern | Large size, extra-sacral location, dark colored lesions, multiple patches tend to persist beyond 1 year<br>Persistent Mongolian spots have an increased risk of inborn errors of metabolism: Hurler syndrome, GM1 gangliosidosis Type 1, Niemann–Pick disease, mannosidosis<br>Other associations: cleft lip, spinal meningeal tumor, melanoma, phakomatosis pigmentovascularis 2 and 5, Sjogren–Larsson syndrome | No associated features | None |

Nd:YAG: Neodymium-doped yttrium aluminum garnet

## ANTICOAGULANTS IN DERMATOLOGY

### Classify anticoagulants and enumerate the therapeutic applications in dermatology

Anticoagulants have been broadly categorized into heparins, vitamin K antagonists and direct inhibitors of thrombin and factor Xa. These can be administered orally or parenterally.

The therapeutic applications of anticoagulants in dermatology have been outlined in Box 1.

**Box 1: Therapeutic applications of anticoagulants in dermatology**

| |
|---|
| **Thrombotic cutaneous vasculopathies** |
| Livedoid vasculopathy |
| Purpura fulminans |
| Hypersensitivity reactions |
| Superficial and deep vein thrombosis |
| Antiphospholipid syndrome |
| Raynaud's phenomenon/disease |
| Digital ischemic ulcers of systemic sclerosis |
| Sneddon syndrome |
| Malignant atrophic papulosis |
| Coagulopathies associated with vascular malformation |
| **Non-thrombotic dermatoses** |
| Lichen planus |
| Chronic idiopathic urticaria |
| Recurrent aphthous stomatitis |
| Dermatitis herpetiformis |
| Lipoid proteinosis |
| Renal pruritus |

### Describe the dermatological adverse effects of anticoagulants?

The dermatological adverse effects of anticoagulants and their clinical manifestations include the following:

#### *Warfarin-induced skin necrosis*

It manifests as sudden onset pain which is followed by the development of well-demarcated erythema that evolves to hemorrhagic bullae, necrosis and eschar formation. Areas with abundant fat such as the breasts, abdomen, hips and buttocks are predominantly involved.

#### *Heparin-induced thrombocytopenia*

It commonly begins 5–15 days after heparin administration. Cutaneous microvascular involvement manifests as a well-demarcated, tender, purpuric rash with a characteristic retiform configuration and minimal erythema/inflammation. These may occur at the site of subcutaneous injection or at distant sites when heparin is infused intravenously and may progress to cutaneous necrosis and eschar formation.

#### *Anticoagulant-associated cholesterol embolization syndrome*

It occurs 4–8 weeks after anticoagulation therapy in patients with an underlying asymptomatic or severe atheromatous disease. Cutaneous findings include livedo reticularis (most frequent), acrocyanosis (blue/purple toe syndrome) or acral gangrene with preserved peripheral pulses. Other manifestations include nodules, infiltrated plaques and purpura.

#### *Other cutaneous adverse reactions*

Various cutaneous reactions may be observed at the injection site of heparins such as purpura, ecchymoses, necrosis and infiltrated plaques. Calcinosis cutis, hypersensitivity reactions such as urticaria, angioedema and Baboon syndrome and patch test positivity can occur. Telogen effluvium and nail changes such as reduced growth, transverse bands and subungal hematomas have also been reported.

## PAGETOID BOWEN'S DISEASE VERSUS EXTRAMAMMARY PAGET'S DISEASE

### Enumerate the clinical differential diagnoses for Pagetoid Bowen's disease

Pagetoid Bowen's disease is a vulvar intraepithelial neoplasia and it is a histological variant of Bowen's disease which simulates the pattern of Paget's disease.

Pagetoid Bowen's disease is commonly confused with extramammary Paget's disease both clinically and histologically. It can also mimic other common conditions such as eczema, intertrigo, pruritus vulvae, erosive lichen planus and seborrhoeic dermatitis.

### Which are the sites of involvement for extramammary Paget's disease?

Vulva is the most common area involved in extramammary Paget's disease. This is followed by the perianal area which is more frequently affected in men than women. Other sites of involvement include the scrotum, penis, eyelids, ears and axilla.

### Describe the histological and immunohistochemistry features which differentiate pagetoid Bowen's disease from extramammary Paget's disease

Histologically, extramammary Paget's disease is characterized by a collection of large cells with abundant pale cytoplasm and atypical round-to-oval nuclei (Paget's cell) and these are sharply demarcated from the surrounding keratinocytes. These cells can be arranged in nests and are located primarily within the lower levels of the epidermis and often demonstrate extension into cutaneous adnexal structures.

Histologically, pagetoid Bowen's disease demonstrates either single or groups of atypical keratinocytes which are present at all levels of the epidermis. Additional histological features include intercellular bridges between nested pagetoid cells, atypical cells and multinucleated cells between the nests of cells.

***Immunohistochemistry markers***

- p63 is a useful immunohistochemistry marker for the differentiation of pagetoid Bowen's disease and extramammary Paget's disease; it shows a strong positivity in pagetoid Bowen's disease
- Syndecan-1 immunoreactivity is seen on the cell membrane in pagetoid Bowen's disease whereas in extramammary Paget's disease, cytoplasmic syndecan-1 immunoreactivity is seen
- CAM 5.2, carcinoembryonic antigen, gross cystic disease fluid protein 15 and c-erb B2 staining are strongly positive in extramammary Paget's disease and negative in pagetoid Bowen's disease
- Overlap between pagetoid Bowen's disease and extramammary Paget's disease is seen for the following markers: cytokeratin 5/6/7/19 and keratin 903.

## TRICHOSCOPY IN ALOPECIA

### Describe the various trichoscopic patterns in different types of alopecia

The various trichoscopic patterns have been described in Table 4.

## PATCH TESTING IN HAIR DYES

### Which is the most important allergen in hair dyes?

Para-phenylenediamine is one of the most important antigens responsible for allergic contact dermatitis to hair dye. It is an effective dye ingredient that, when mixed with other ingredients, enables black or other color dyes to dye hair permanently.

### What are the ingredients in permanent hair dyes?

The common ingredients include para-phenylenediamine, aminophenols, henna, toluene-2,5-diamine sulfate, pyrogallol, resorcinol, ferrous sulfate, oxidizers such as hydrogen peroxide and sodium perborate and other ingredients such as tartaric acid, glycerin, naphthol and cresols.

### Which are the chemicals which can cross react with para-phenylenediamine?

Hair dye intermediate chemicals such as aminophenols and toluene-2,5-diamine sulfate can cross react with para-phenylenediamine.

### Why does a patient experience an allergic reaction despite using hypoallergenic hair dye products?

Although many hair dye products available in the market are advertised as hypoallergenic, para-phenylenediamine-free, non-allergenic or herbal, they may contain either small amounts of para-phenylenediamine or other substances that cross react with para-phenylenediamine. Hence, allergic reactions can occur in a significant number of patients despite claimed safety. Patients with hair dye contact dermatitis must always choose their hair dye

**Table 4: Trichoscopic patterns in different types of alopecia**

| Type of alopecia | Common trichoscopic features |
|---|---|
| Alopecia areata | Black dots, yellow dots, short vellus hair and tapering hair<br>Yellow dots and short vellus hair are sensitive diagnostic markers whereas black dots, tapering hairs and broken hair were the most specific markers |
| Androgenetic alopecia | Yellow dots, hair shaft diameter diversity, thin hair, vellus hair, honeycomb pigment network and peripilar sign |
| Telogen effluvium | Thin hair, yellow dots, yellow brown dots, short tip regrowing hair, peripilar erythema |
| Trichotillomania | Broken hair, black dots, split ends, frayed hair, cadaverized hair, follicular hemorrhage, yellow dots, coiled hair |
| Tinea capitis | Comma hair, cadaverized hair, coiled hair, hemorrhagic spots, honeycomb pigment network, yellow/black dots, white areas, loss of follicles, corkscrew hair |
| Lichen planopilaris | Loss of follicles, white dots, honeycomb pigment network, blue-gray dots in targetoid/speckled pattern, yellow dots, peripilar scaling, crusting and erythema |
| Discoid lupus erythematosus | Loss of follicles, scattered dark brown discoloration of the skin, large yellow dots, perifollicular whitish halo, follicular keratotic plugs and telangiectasias, arborizing red loops, peripilar erythema/scaling, red dots, honeycomb pigment network, interfollicular red loops |

by checking the contents and undergoing sensitivity testing.

## SCLEROMYXEDEMA

### What are the types of lichen myxedematous?

Lichen myxedematosus is a form of idiopathic cutaneous mucinosis occurring in the absence of thyroid disease and characterized by abnormal dermal mucin deposition and fibrosis. The two types are a generalized papular and sclerodermoid form (scleromyxedema of Arndt–Gottron) with a monoclonal gammopathy and systemic manifestations and a localized papular form without systemic features.

### Enumerate the salient clinical features and differential diagnosis in scleromyxedema

Scleromyxedema is characterized by widespread eruption of small, waxy papules on the upper limbs, thighs, trunk and head and neck region; the papules may be arranged in a linear pattern. There may be a diffuse sclerodermoid or hardened skin giving rise to leonine facies. The differential diagnosis includes systemic sclerosis, scleredema and nephrogenic systemic fibrosis.

### What is the characteristic histological feature in scleromyxedema?

The characteristic feature is deposition of mucinous material (Alcian blue positive) between thick collagen bundles and abundant proliferation of fibroblasts in the upper and mid-reticular dermis.

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