2015 Annual Meeting

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Pathology Excellence Through Education
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Thank You
NEOPLASTIC DERMATOPATHOLOGY-CLUES AND
CONFOUNDERS
CUTANEOUS VASCULAR TUMOURS

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Dr Ophelia E. Dadzie declares she has no conflict(s) of interest to disclose.
Cutaneous vascular & peri-vascular lesions—all a “bloody” mess?

The Issues

• Classification (reactive hyperplasia vs. hamartoma vs. malformation vs. tumour)
• ? Lymphatic vs. ? Blood endothelium
• Distinguishing benign from malignant tumours
• Difficulties recognizing low-grade, as well as poorly differentiated vascular tumours

Importance

• Relatively commonly encountered in routine “sign-out”
• Associations with haematological abnormalities and/or systemic disorders
• Correct diagnosis is important for management of patient
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<td><strong>Cutaneous and/or mucosal capillary malformation (aka “port wine stain”)</strong></td>
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<td><strong>Telangiectasia (e.g. hereditary haemorrhagic telangiectasia)</strong></td>
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### APPROACH-CLASSIFICATION SYSTEM (3)

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<th>CM+VM</th>
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<td>Provisionally unclassified</td>
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<td>Verrucous hemangioma</td>
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<td>Atypical vascular lesion</td>
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<td>Reactive proliferations/hyperplasias</td>
<td>Cutaneous epithelioid angiomatous nodule</td>
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<td>Reactive angioendotheliomatosis</td>
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<td>*Epithelioid haemangiomá</td>
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<td>Hobnail haemangiomá</td>
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<td>Infantile haemangiomá (RICH, NICH, PICH)</td>
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<td>Tumour Type</td>
<td>Benign Tumours</td>
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<td>Microvenular haemangioma</td>
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<td>+Papillary haemangioma</td>
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<td>Sinusoidal haemangioma</td>
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<td>Symplastic haemangioma</td>
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<td>Tufted angioma</td>
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<td>Glomus tumour and its variants</td>
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<td>Intermediate grade/borderline tumours</td>
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<td>Composite haemangioendothelioma</td>
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<td>Kaposi sarcoma</td>
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<td>Kaposiform haemangioendothelioma</td>
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<td>Papillary intralymphatic angioendothelioma</td>
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<td>Retiform haemangioendothelioma</td>
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<td>Malignant tumours</td>
<td>Epithelioid haemangioendothelioma</td>
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<td>Primary cutaneous angiosarcoma</td>
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<td>Glomangiosarcoma</td>
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Approach to diagnosis: clues
Approach to diagnosis: pitfalls

Squamous cell carcinoma

High molecular weight cytokeratin
Approach to diagnosis: pitfalls

Melanocytic naevus

Giant cell fibroblastoma
Approach to diagnosis: pitfalls

Intra-cytoplasmic vacuoles

MNF-116
<table>
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<tr>
<th>Immunoperoxidase studies</th>
<th>Overview</th>
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| **CD31**                 | Excellent marker of endothelial differentiation  
Limitations: Expressed by macrophages; negative in a subset of angiosarcomas |
| **CD34**                 | Less sensitive & specific than CD31  
Limitations: Non/weakly reactive with immature or poorly formed vessels; expressed by non-vascular tumours e.g. DFSP, superficial acral fibromyxoma etc. |
| **FLI-1**                | Highly sensitive, nuclear staining pattern  
Limitations: Poor specificity (e.g. expressed in Ewing’s sarcoma/PNET, Merkel cell carcinoma, malignant melanoma and lymphoproliferative disorders (e.g. ALL) |
| **ERG**                  | Excellent marker of endothelial differentiation, nuclear staining pattern  
Limitations: Expressed in epithelioid sarcoma, Ewing sarcoma, extramedullary myeloid sarcoma and prostate adenocarcinoma |
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| **Podoplanin** | Expressed by a subset of vascular tumors with lymphatic differentiation e.g. Kaposi sarcoma, some subsets of angiosarcomas  
Limitations: Expressed by non-vascular tumours e.g. cutaneous adnexal tumours |
<p>| <strong>LYVE-1</strong> | Expressed by a subset of vascular tumors with lymphatic differentiation e.g. Kaposi sarcoma, some subsets of angiosarcomas |
| <strong>VEGFR-3</strong> | Expressed by a subset of vascular tumours with lymphatic differentiation e.g. Kaposi sarcomas, Kaposiform haemangioendothelioma, PILA, a subset of angiosarcomas, targetoid haemosiderotic haemangioma |
| <strong>PROX-1</strong> | Expressed by a subset of vascular tumours with lymphatic differentiation e.g. Kaposiform haemangioendothelioma, tufted angioma |</p>
<table>
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<th>Other Markers</th>
<th>Overview</th>
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<tr>
<td><strong>GLUT1</strong></td>
<td>Expressed by infantile haemangiomas (persists through all phases of proliferation and involution), enables distinction from vascular malformations, reactive proliferations and tumours, such as Kaposiform haemangioendothelioma</td>
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<td><strong>WT1</strong></td>
<td>Distinguishes haemangiomas (+ve) from vascular malformations (-ve)</td>
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<td><strong>MYC</strong></td>
<td>c-MYC is expressed in secondary angiosarcomas (related to chronic lymphoedema and irradiation) but not radiation-associated atypical vascular lesion</td>
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Electron microscopy

Weibel-Palade Bodies  Zebra Bodies

Molecular diagnostics

- Epithelioid haemangioendothelioma
  - Balanced translocation t(1;3) (p36.3;q25), with fusion CAMTA1 and WWTR1 genes
  - Alternate balanced translocation, fusion of YAP- and TFE3 genes
- Epithelioid sarcoma-like haemangioendothelioma
  - balanced translocation t(7;19)(q22;q13)
  - rarely unbalanced der(7) t(7;19)
Intravascular papillary endothelial hyperplasia

• Synonyms:
  – hémangioendothéliome végétant intravasculaire, Masson’s pseudoangiosarcoma, Masson’s haemangioma

• Reactive
  – Develops in response to an organizing thrombus

• Three main settings:
  – Primary/Pure form (56%): occurs within a dilated vein
  – Secondary/Mixed form (40%): occurs as a focal change in vascular anomalies prone to thrombosis
  – Third/Rare form (4%): extravascular in nature (likely arising within haematomas)
Intravascular papillary endothelial hyperplasia

- Slight female preponderance
- Mostly in adults
- Extremities (especially fingers) and head and neck region
- May be preceding trauma
- Reddish-bluish papules
- Clinical appearance of secondary form is in keeping with underlying vascular anomaly
- Benign clinical course
Pitfalls

• Extra-vascular cases may occur in absence of an associated organizing thrombus, and this may simulate a well-differentiated angiosarcoma to the unwary
Pyogenic granuloma

• Propensity for children and young adults
• Gingiva (pregnant women, granuloma gravidarum), lips, mucosa of nose, face and fingers are sites of predilection
• May be preceding injury
• Evolves rapidly over weeks and then regresses over months
• Exophytic erythematous papule/nodule, bleeds easily
• May be associated with pre-existing lesions (naevus flammeus) or may occur secondary to drugs such as isotretinoin
• Eruptive widespread lesions of pyogenic granuloma described as a paraneoplastic phenomenon in Hodgkin’s disease
Pyogenic granuloma
Pitfalls

- Histologic variants
  - Intravascular
  - Subcutaneous
  - Drug induced-isotretinoin

- Morphologic simulators:
  - Kaposi sarcoma
  - Bacillary angiomatosis
  - Verruca peruana
Angiokeratoma

- Five main clinical subtypes
  - Angiokeratoma circumscriptum naeviformis
  - Angiokeratoma corporis diffusum
  - Fordyce type
  - Mibelli type
  - Solitary and multiple types

- Anderson Fabry disease
  - Associated with angiokeratoma corporis diffusum, and other rare inherited lysosomal storage disorders (e.g. fucosidosis, galactosidosis)
  - *Bear in mind that not all cases of angiokeratoma corporis diffusum are associated with metabolic disorders, some may occur in isolation without any associated metabolic disorders*
Uncommon histopathologic features

- Thrombosis
- Intravascular papillary endothelial hyperplasia
- Cytoplasmic lipid vacuoles in endothelial cells, pericytes and fibroblasts, in the setting of Anderson Fabry disease (highlighted by Sudan black B and PAS)
Pitfalls

- May simulate:
  - Verrucous haemangioma, especially in the setting of a superficial biopsy
  - Superficial lymphatic malformation (lymphangioma circumscriptum)
Pitfalls

• May simulate:
  • Superficial lymphatic malformation (lymphangioma circumscriptum)
Acquired elastotic haemangioma

- Occurs in sun-damaged skin of extremities and neck of middle-aged and elderly
- Original case series reported a female preponderance, however subsequent case series reported male preponderance
- Solitary slow-growing violaceous plaque
- Benign clinical course
Uncommon histopathologic features

• Associated scant inflammatory infiltrate
  • mostly lymphocytes
• Variable hyperkeratosis/acanthosis of overlying epidermis
• Hobnail morphology of endothelial cells lining vascular lumen
  • reported in case series by Martorell-Calatayud et al
Pitfalls

- May simulate patch-stage Kaposi sarcoma
  - Look for slit-like vascular spaces, lympho-plasmacytic infiltrate, growth of vessels around pre-existing blood vessels and adnexal structures, HHV8+ve
Arteriovenous haemangioma

- Predominantly occurs in middle-aged and elderly
- Predilection for head and neck region (lip and oral mucosa), as well as extremities
- Solitary small red to blue papule
- Benign
Uncommon histopathologic features

- Dystrophic calcification
- Focal thrombosis
- Associated minimal chronic inflammation
- Stroma-interstitial oedema and/or variable fibrosis
Pitfalls

• Symplastic haemangioma:
  • Underlying haemangioma is an AV haemangioma
  • Degenerative atypia of vascular smooth muscle and interstitial cells

• Arteriovenous haemangioma in soft tissue
  • more common in younger individuals
  • associated with arteriovenous shunts and haemodynamic complications
Epithelioid haemangioma

- Synonyms: angiolymphoid hyperplasia with eosinophilia, pseudo-or atypical pyogenic granuloma, inflammatory angiomatous nodule, papular angioplasia, inflammatory arteriovenous haemangioma, histiocytoid haemangioma, subcutaneous angioblastic lymphoid hyperplasia with eosinophilia and lymphofolliculosis, and intravenous atypical vascular proliferation.
- First reported in 1969 by Wells and Whimster
  - Initially considered to be a variant of Kimura’s disease
  - Now accepted to be distinct and separate from Kimura’s disease, however some authors do consider it to be closely related to the newly described entity CEAN due to shared morphological features
Epithelioid haemangioma

- Young to middle-aged adults
- Female preponderance
- Head and neck region (especially around the ears, forehead and scalp)
- Solitary or multiple angiomatous papules or nodules
- Some cases associated with trauma, oral contraceptives, pregnancy and HIV infection
- Associated peripheral eosinophilia (albeit lower frequency compared to Kimura’s disease)
- Benign clinical course, but may recur after excision
Uncommon histopathologic features

• Presence of multinucleated cells
  – either endothelial or fibrohistiocytic / myofibroblastic origin
  – in a perivascular or interstitial regions

• Thrombi in vessels

• Associated arteriovenous malformation
Pitfalls

- May rarely be intra-arterial in nature
- Should be distinguished from conditions such as arteriovenous haemangioma, CEAN and Kimura’s disease
Cutaneous epithelioid angiomatous nodule (CEAN)

- First described in scientific literature by Brenn and Fletcher in 2004
- Unknown aetio-pathogenesis, but some shared morphological similarities with epithelioid haemangioma
- No sex predilection reported initially, although subsequent case series suggest male preponderance
- Wide age distribution (15-79 years in original case series by Brenn et al)
- Solitary lesion (less commonly multiple)
- Predilection for trunk and extremities
- Erythematous to bluish papule or nodule, develops over weeks to months
- Benign clinical course
Uncommon histopathologic features

- Involvement of deep dermis
- Arising within a pre-existing vascular malformation
Pitfalls

• Low grade mitosis should not be misinterpreted as indicating malignant biological behaviour

• Expression of oestrogen receptor especially in lesions situated on chest wall may lead to erroneous diagnosis of an adenocarcinoma
Glomus tumour

- First described in 1924 by Masson and co-workers
- Group of peri-vascular tumours derived from components of the glomus apparatus
- Solid glomus tumour (or glomus tumour proper)
  - Solid tumour, with minimal vascular structures and a predominance of glomus cells,
- Glomulovenous malformation
  - Previously known as glomangioma, used for a similar peri-vascular tumour, however vessels predominated over glomus cells. Recent data indicates that glomangiomas represent vascular malformations, and for this reason the preferred term for this latter entity is glomulovenous malformation
Glomus tumour

- Early adulthood
- Equal sex incidence (exception glomus tumours of the subungual region, shows a female predominance)
- Often solitary (although multiple lesions may occur)
- Acral sites (includes subungual regions of digits, palms and wrists) and forearm, although worthwhile noting anatomic distribution is wide and may occur in any body site
- Purplish, reddish or bluish papules or nodules
- Paroxysmal pain is a characteristic feature, with pain being precipitated by pressure or changes in temperature, (especially exposure to the cold)
- Benign clinical course
Uncommon histopathologic features

- Prominent myxoid stroma
- Hyalinized, sclerotic stroma
- Intravenous glomus tumour
- Intraneural glomus tumour
- Epithelioid glomus tumour
- Oncocytic glomus tumour
Histopathologic variants

- Glomangiomyoma
- Infiltrative glomus tumour
- Glomus tumour of uncertain malignant potential
- Malignant glomus tumour
Histopathologic variants

Symplastic glomus tumour
Pitfalls

• Incidental glomus coccygeum

  • Vestigial structure located in the coccygeum
  
  • Histologically indistinguishable from a glomus tumour
  
  • Must consider this diagnosis in the setting of a glomus tumour-like lesion occurring in excision specimens around the coccyx region e.g. pilonidal sinus excisions
Tufted angioma

- Synonyms: progressive capillary haemangioma, angioblastoma of Nakagawa, juvenile tufted angioma
- Rare benign vascular tumour
- Predominantly in childhood
- Benign clinical course, spontaneous regression documented
- Close relationship with Kaposiform haemangioendothelioma
Tufted angioma

- Childhood
- May be congenital, also familial cases documented
- Predilection for the neck and trunk
- Asymptomatic ill-defined dull red macule/plaque that has been growing slowly for years
- Sometimes associated tenderness, hyperhidrosis or hypertrichosis
- May be complicated by Kasabach-Merritt syndrome or may have chronic coagulopathy (without thrombocytopenia)
Uncommon histopathologic variants

- Focal crystalline inclusions in cytoplasm of endothelial cells
- Associated proliferation of sweat glands
- Present in superficial dermis, abutting overlying epidermis
- Intravenous location
Pitfalls

- Indentation of crescent shaped lymphatic vessels by vascular tufts/lobules may lead to an erroneous diagnosis of glomeruloid haemangioma
- Association with Kasabach-Merritt syndrome (similar to Kaposiform haemangioendothelioma)
Glomeruloid haemangiomma

- Multifocal circumscribed lesion in dermis
- Composed of multiple dilated thin-walled vessels with intravascular aggregates of capillaries
- Simulates renal glomeruli
- Intravascular capillaries lined by flat endothelial cells with scant cytoplasm, and surrounding pericytes

*Ann Bras Dermatol, 2011*
Kaposiform haemangioendothelioma

- Early childhood, including neonatal period
- Predilection for extremities and head and neck region
- Enlarging erythematous violaceous plaque
- KHE may be associated with lymphangiomatosis, congenital lymphedema (Milroy disease) or a pre-existing vascular malformation.
- KHE may be associated with Kasabach–Merritt syndrome. The occurrence of Kasabach-Merritt syndrome is an important cause of mortality.
Vascular anomalies in childhood

- **Congenital haemangioma** exhibits growth in utero such that it is fully formed at birth
  - either persists (non-involuting congenital haemangioma, NICH) or involutes over a period of time (rapidly involuting congenital haemangioma, RICH)
- **Infantile capillary haemangioma** arises in infancy (usually a few weeks after birth)
  - Subsequently demonstrates rapid growth in the first year of life (proliferative phase), with subsequent involution in later years
- **Vascular malformations**, similar to congenital haemangioma are also present from birth
  - they have a tendency to grow with the child and often persist without regression
- **Distinguishing all three entities** can be challenging and is based on distinguishing:
  - Clinical features
  - Morphological features including use of appropriate immunoperoxidase studies (WT1 distinguishes haemangioma (positive) from vascular malformations (negative) and GLUT1 distinguishes infantile capillary haemangiomas (positive) from congenital hemangioma (negative)
  - Imaging e.g. Doppler ultrasound and MRI
Kaposi sarcoma

- **Classic (endemic)**
  - Middle aged and elderly males
  - Jewish Askenazic or Mediterranean origin
  - Predilection for lower extremities (but mucosal and visceral lesions may develop)
  - May be associated with haematopoietic malignancies
  - Indolent biological behaviour

- **AIDS-related KS**
  - Occurred mainly in homosexual males and intravenous drug users (20-50 years), but now also equally affects women and children in Africa
  - Disseminated mucocutaneous and visceral lesions, including involvement of gastrointestinal tract, lymph nodes, lung and spleen.
  - Aggressive biological behaviour, with regression or flare with initiation of antiretroviral therapy
Kaposi sarcoma

- **Iatrogenic or immunosuppression-related KS**
  - Presents as localized mucocutaneous or disseminated lesions
  - Association with immunosuppression as a result of drugs, autoimmune disease or post-renal transplantation
  - Variable biological behaviour, may have a protracted and aggressive course

- **African KS**
  - Middle-aged adults and children from equatorial Africa.
  - Occurs as multiple localized skin tumours, involving lower extremities and/or lymph nodes
  - The lymphadenopathic form, typically occurring in young individuals has an aggressive biological behaviour, with often-fatal outcome
Histopathologic variants

- Anaplastic/pleomorphic KS
- Bullous KS
- Eccymotic KS
- Glomeruloid KS
- Hyperkeratotic/verrucous KS
- Intravascular KS
- Keloidal KS
- Lymphangiomatous or lymphangioma-like KS
- Lymphangiectatic KS
- Lymphoedematous KS
- KS with myoid nodules
- Micronodular KS
- Pigmented KS
- Pyogenic granuloma-like KS
- Partially regressing/regressed KS
- KS with granuloma
- Telangiectatic KS
Pitfalls

• There must be an awareness of the wide spectrum of histopathologic variants of Kaposi sarcoma
• Kaposi sarcoma may simulate a range of benign vascular lesions: careful attention must be paid to distinguishing morphological features
  • Hobnail haemangiomia
  • Microvenular haemangiomia
  • Spindle cell haemangiomia
Hobnail haemangioma

• Described by Santa Cruz and Aronberg in 1988
  • Targetoid haemosiderotic haemangioma (reflected that lesions had a distinctive targetoid appearance, as well as dermal haemosiderin deposition)
  • Subsequent reports shows much wider clinical appearance
  • Diagnostic hobnail cyto-morphology of endothelial cells
  • Guillou and co-workers proposed appropriate morphologic descriptor hobnail haemangioma.
Hobnail haemangioma
Microvenular haemangioma

- Young to middle-aged adults
- All sexes affected (slight male predominance in original case series by Hunt and co-workers)
- Extremities (especially the forearm) and trunk
- Solitary lesion (multiple lesions rarely reported)
- Purple to red nodules or plaques
- Lesion is usually asymptomatic, although mild erythema and tenderness have been reported
- Lesion usually present for a few months prior to presentation
- Specific cases reported in relation to changes in hormonal contraception or during pregnancy, as well as
  - Systemic conditions e.g. POEMS syndrome, Wiskott-Aldrich and acute myelogenous leukaemia
- Benign clinical course
Microvenular haemangioma
Spindle cell haemangioma

• First reported by Weiss and Enzinger in 1986
• “Spindle cell hemangioendothelioma”
• Initially considered to be a low-grade angiosarcoma, given that one of the reported patients developed regional lymph node metastases.
• Subsequent published data, with longer follow-up intervals, has shown that this entity is not a low-grade angiosarcoma as previously thought, but behaves in a benign fashion, leading to a change in nomenclature to spindle cell haemangioma (SCH).
• It remains unknown if this entity represents a reactive phenomenon, a benign neoplasm or a vascular proliferation.
Spindle cell haemangioma

- Young adults
- Predilection for distal extremities
- Solitary or multifocal
- Red-blue nodule, may be painful, develops slowly over many years
- Associations with vascular anomalies: early-onset varicose veins, congenital lymphedema, superficial cutaneous lymphatic malformations, epithelioid haemangioendotheliomas, Maffucci’s syndrome and Klippel-Trénaunay syndrome
- Excellent prognosis, no metastases reported, however local recurrences observed (likely represents contiguous spread along a vessel, or multifocal involvement of a vessel)
Epithelioid haemangioendothelioma

- Rare vascular tumour occurs in various anatomic sites, includes soft tissue, lungs, liver and skin
- Initially classified as a low-grade vascular malignancy, now recognized to be a sarcoma, akin to angiosarcoma, based on the high risk of distant metastasis and tumour-associated mortality
Epithelioid haemangioendothelioma

- Rare
- No sex predilection
- May occur in any age group, but rare in childhood
- Predilection for extremities
- Poorly defined subcutaneous mass or ulcerated nodule
- Rarely may present as multifocal lesions
Ancillary investigations

- **Immunohistochemistry**
  - CD31, CD34, FLI-1, ERG, INI-1, Podoplanin, Lyve-1, and Prox-1, positive
  - SMA and cytokeratins, focal positivity

- **Genetics**
  - Characteristic balanced translocation t (1;3)(p36.3;q25) with fusion of *WWTR1* and *CAMTA1* genes
  - Alternate balanced translocation has been reported, demonstrates fusion of *YAP1–TFE3* genes
Uncommon histopathologic features

- Hyperplasia of eccrine ducts simulating eccrine syringofibroadenoma
- Bone metaplasia of associated stroma
Pitfalls

• Distinguish from metastatic adenocarcinoma

• EHE confined solely to the skin extremely rare phenomenon, must exclude metastases from an extra-cutaneous EHE

• Tumour size >3cm and high mitotic rate (>3 mitotic figures per 50 high-power fields) indicates a high risk EHE with a propensity for distant metastases
Angiosarcoma

- Idiopathic angiosarcoma of the head and neck (37% of cases in study by Buehler et al, 2014)
- Radiation-induced cutaneous angiosarcoma (16% of cases in study by Buehler et al, 2014)
- Lymphoedema-associated angiosarcoma (Stewart-Treves syndrome; 5% of cases in study by Buehler et al, 2014)
- Primary cutaneous epithelioid angiosarcoma (based on case series (n=13) by Suchak et al, 2011)
- Paediatric cutaneous angiosarcoma (based on a case series (n=10) by Deyrup et al, 2011)
Uncommon histopathologic features

- **Unusual morphology**
- Clear cell change
- Foamy cell change (lesional cells may express CD68 and CD163)
- Granular cell change
- Plasmacytoid appearance
- Rhabdoid appearance
- Signet ring cell change (presence of optically clear intra-cytoplasmic vacuoles, which pushes nuclei to periphery. Differs from conventional signet ring cells seen in epithelial malignancies such as gastric adenocarcinoma, by the absence of mucin)
- Pseudolymphomatous angiosarcoma

- **Unusual growth pattern**
- Pseudoepidermotropism (lesional tumour cells infiltrate and obscure the dermal-epidermal junction mimicking epidermotropism)
- Macrophage rich epithelioid angiosarcoma (presence of admixed macrophages which stain with S100 may lead to the erroneous diagnosis of malignant melanoma)
Pitfalls
Pitfalls

- Pseudolymphomatous angiosarcoma may mimic inflammatory dermatoses or a lymphoproliferative disorder
- Aberrant expression of pan-cytokeratin markers, EMA, CD30, MELAN-A, and SMA may occur in primary cutaneous epithelioid angiosarcoma
- AFX/pleomorphic dermal sarcomas may exhibit pseudoangiomatous features, as well as aberrant expression of CD31 and FLI-1
- Metastatic angiosarcoma of the skin must be considered in the setting of multiple cutaneous angiosarcomas and when lymphovascular invasion is present
  - Unusual primary tumour sites to consider when faced with the possibility of cutaneous metastatic angiosarcoma includes a cardiac or aortic angiosarcoma and appropriate imaging must be undertaken to exclude these considerations
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