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Girdled and Hemmed In -Perivascular Epithelioid Cell Tumour

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PREFACE

Exceptional neoplasia with perivascular clear cell and epithelioid cell differentiation are diverse and constituted by angiomyolipoma, clear cell "sugar tumour" of pulmonary and extra pulmonary sites, clear cell myomelanocytic tumour offalciform ligament or ligamentum teres and lymphangioleiomyomatosis on account of distinctive histological manifestations. Variable genetic and malignant biological behaviour is exemplified within perivascular epithelioid cell tumours. Perivascular epithelioid cell tumour (PEComa) is a contemporary neoplasm of mesenchymal origin emerging within diverse sites while representing a classified group with distinctive histology and immune histochemical staining. The tumefaction is composed of epithelioid cells which demonstrate dual properties of smooth muscle and melanocytes with pertinent immune reactivity. Cellular component tends to aggregate around and circumscribe blood vessels, thus engendering the acronym "PEComa". Perivascular epithelioid cell tumour was initially described by Bonetti et al in 1992 [1]. Zamboni et al in 1996 documented perivascular epithelioid cell tumour of the pancreas and denominated the neoplasm as "sugar tumour" on account of clear, glycogen rich, cytoplasm imbued within perivascular epithelioid cells. A normal counterpart of perivascular epithelioid cell tumour is absent [2].

DISEASE CHARACTERISTICS

Perivascular epithelioid cell tumour occur within head and neck, nasal sites, gynaecological soft tissue as uterus, diverse cutaneous locations, soft tissue, bone, abdominopelvic sites, retroperitoneal sites as the kidney, orbit or skull base, although no site of tumour emergence is exempt. Perivascular epithelioid cell tumour occurs in the absence of tuberous sclerosis [3]. Perivascular epithelioid cell tumour of cervical region is an extremely exceptional mesenchymal neoplasm of unknown biological behaviour. Mean age of tumour emergence is 41 years although the neoplasm can appear within 24 years to 67 years. Uterine perivascular epithelioid cell tumour demonstrates a mean age of emergence at 51 years. The neoplasm depicts a female predilection where in an estimated 80% to 90% of incriminated individuals are females and commonly appears in middle aged women [3]. The neoplasm can be benign or of uncertain malignant potential or malignant. Malignant neoplasms depict cogent features such as tumour magnitude exceeding >5 centimetres, infiltrative pattern of tumour evolution, enhanced nuclear grade, enhanced cellularity, mitotic activity exceeding >1 per 50 high power fields, necrosis and vascular invasion. An estimated 9% of gynaecological perivascular epithelioid cell tumours are associated with tuberous sclerosis complex along with a history of childhood seizures, are aptly treated with lobectomy and demonstrate radiographic features of angiomyolipoma or sclerotic bone lesions [3]. Distinctive classification systems describe the neoplasm as "benign", "malignant" or of "uncertain malignant potential" in order to appropriately prognosticate the tumours. Classification system developed by Folpe, et al, proposes diagnostic criterion of malignant neoplasms as tumour magnitude exceeding >5 centimetres, mitotic activity ≥1 per 50 high power fields, necrosis, elevated nuclear grade and an infiltrative tumour architecture [4]. Classification system suggested by School meester, et al demonstrates diagnostic criterion as tumour magnitude ≥5 centimetres, mitotic index ≥1 per 50 high power fields, significant nuclear atypia, necrosis and lympho-vascular invasion [5].

- Absence of aforesaid criterion -benigncervical neoplasm
- One to three criterion – tumour of uncertain malignant potential
- Four or more criterion – malignant neoplasm [4,5] Malignant perivascular epithelioid cell neoplasm can demonstrate localized tumour invasion within petrous or occipital bone, clivus, foramen magnum, spinal canal and pulmonary parenchyma [3]

CLINICAL CHARACTERISTICS

The neoplasm demonstrates a varied clinical representation and can be discovered incidentally or display chronic pain or vaginal bleeding.

The neoplasm can masquerade as a postpartum retained placenta or induce spontaneous haemo-peritoneum. Individuals may be asymptomatic or manifest symptoms such as functional abdominal pain, abdominal mass, occasional diarrhoea. Perivascular epithelioid cell tumour can infiltrate the uterine myometrium. Perivascular epithelioid cell tumour can expand rapidly during gestation, thereby ensuring a subacute elevation of intrauterine pressure which may induce a rupture of the uterine wall [6]. Pelvic masses with aberrant vaginal bleeding can be concurrent to the genetic condition of tuberous sclerosis complex which is characterized by mental retardation, seizures and benign neoplasia such as cutaneous angiofibromas [6]. Perivascular epithelioid cell tumour typically enunciates benign biological behaviour although tumour relapse and malignant metamorphosis is documented at several primary sites wherein metastasis can commonly ensue to cutaneous locales or orbit [6]. As the clinical representation of perivascular epithelioid cell tumour is non-specific and imaging evaluation such as ultrasound, magnetic resonance imaging (MRI) and positron emission computerized tomography (PET CT) scan may be inconclusive, assessment of cogent tissue specimen with pertinent immune histochemical assay is mandated and diagnostic [6,7].

HISTOLOGICAL ELUCIDATION

Grossly, the neoplasm is well circumscribed, encapsulated and spherical. Cut surface is homogenous and light brown, circumscribed by an uninvolved, lobular parenchyma. Characteristically, the tumour demonstrates spindle-shaped or epithelioid cells disseminated around vascular articulations. Perivascular epithelioid cell tumour is typically comprised of epithelioid cells with clear or eosinophilic, granular cytoplasm demonstrating melanocytic and smooth muscle differentiation, possibly derived from perivascular epithelioid cells [7]. Perivascular epithelioid cell tumour demonstrates distinct histological features such as epithelioid to spindle-shaped cells with clear, granular and eosinophilic cytoplasm, spherical to elliptical nucleus and inconspicuous nucleoli [7]. Perivascular epithelioid cell tumour is composed of flattened sheets of epithelioid cells with minimal cellular and nuclear pleomorphism, cytoplasmic pigmentation and a minimal mitotic index below <1 per 50 high power fields [7]. Perivascular tumour cells demonstrate a radial configuration with peri-luminal arrangement, epithelioid cells which abut blood vessels and spindle-shaped cells which are distant from blood vessel. Cells with clear to granular, eosinophilic cytoplasm, miniature, centric, spherical or elliptical nuclei with miniature nucleoli are discerned. Multinucleated giant cells are frequent and may exhibit features of malignant metamorphoses such as predominant cellular and nuclear atypia, mitotic activity and tumour necrosis [7,8]. "Pecosis" may accompany the neoplasm denominated by a continuous layer of clear, perivascular cells which appears away from sites of tumour transitioning into invasive cell nests. Cells of perivascular epithelioid cell tumour appose and appear in direct contact with abluminal surface of capillary basal lamina [7]. "Pecomatosis" can be discerned which is designated as a perivascular aggregation of clear to eosinophilic cells, a phenomenon which may simulate a mesothelioma. The neoplasm can appear as an organizing haematoma enveloped by sheets of spindle- shaped cells with eosinophilic cytoplasm, elliptical nuclei, miniature nucleoli and minimal mitotic activity [7,8]. The tumefaction consists of sheets of uniform, epithelioid, spindle- shaped cells imbued with abundant, granular, eosinophilic cytoplasm and distinctive, prominent nucleoli [8]. On cytogenetic analysis, significant genomic aberrations are discerned in a majority of instances wherein frequent imbalances appear within chromosomes 19-, 16p-, 17p-, 1p-, 18p-, X+, 12q+, 3q+, 5+, 2q+. Deletion within chromosome 16p- is indicative of loss of TSC2 gene. On ultrastructural examination, the cells are incorporated with abundant cytoplasmic glycogen, pre-melanosomes, thin, attenuated filaments with occasional occurrence of dense bodies, hemi-desmosomes and inadequately configured cellular junctions [7,8].

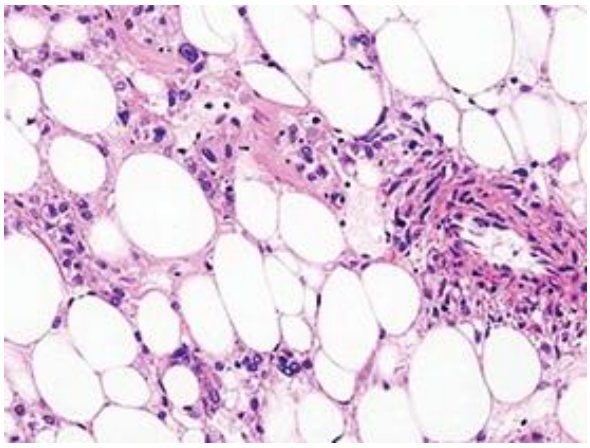

Figure 1: Peripheral epithelioid cell tumour depicting accumulation of plump spherical cells with abundant eosinophilic cytoplasm and circumscribing mature adipose tissue cells [11]

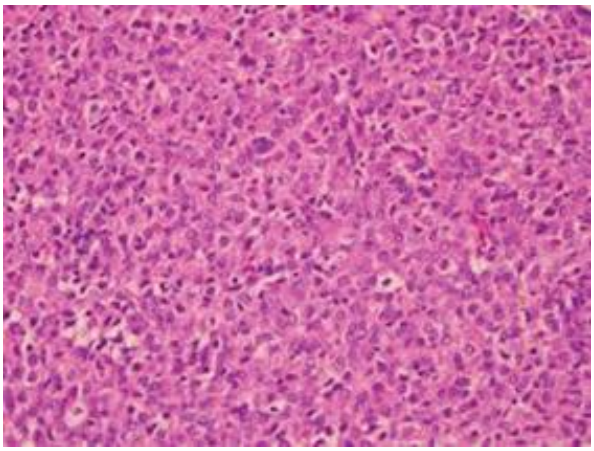

Figure 2: Peripheral epithelioid cell tumour exhibiting fascicles of spindly cells with ample, eosinophilic cytoplasm and uniform nuclei [12]

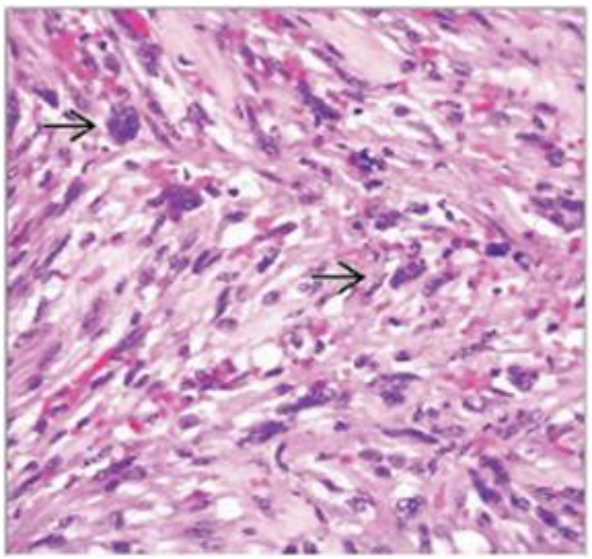

Figure 3: Peripheral epithelioid cell tumour with fascicles of spindle-shaped cells with abundant clear to eosinophilic cytoplasm and regular nuclei [13].

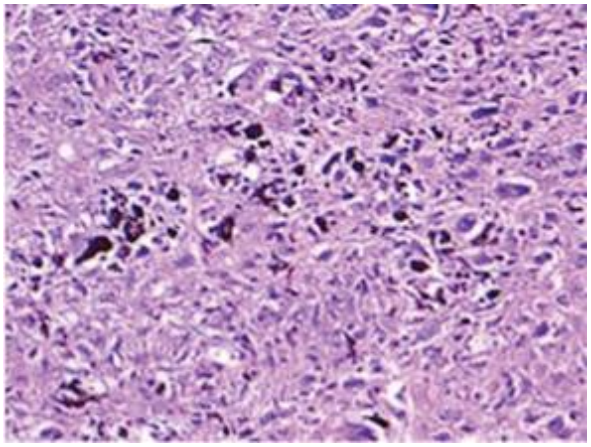

Figure 4: Peripheral epithelioidcell tumour with accumulation of plump, spindle-shaped cells with eosinophilic cytoplasm, uniform nuclei and indistinct nucleoli [14]

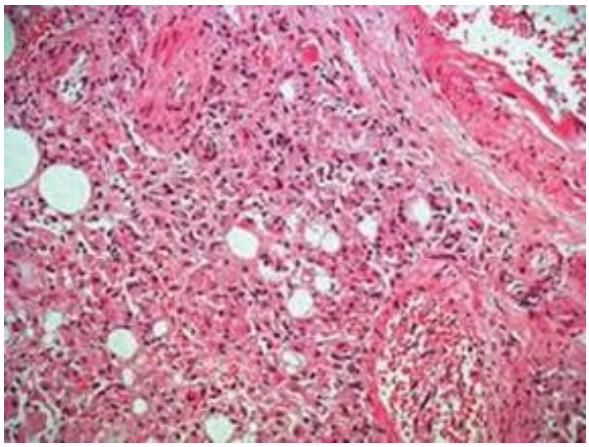

Figure 5: Perivascular epithelioid cell tumour demonstrating accumulation of epithelioid and spindle-shaped cells surrounding foci of haemorrhage and red cell extravasation [15]

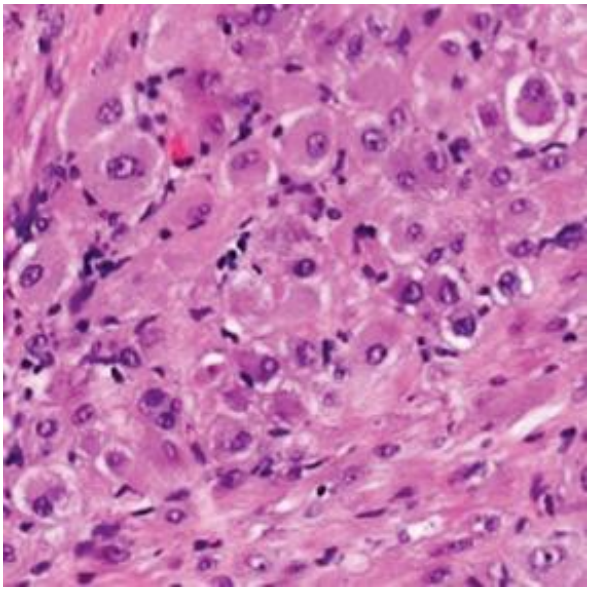

Figure 6: Perivascular epithelioid cell tumour delineating nests of spherical cells with abundant eosinophilic cytoplasm, uniform nuclei and indistinct nucleoli [16]

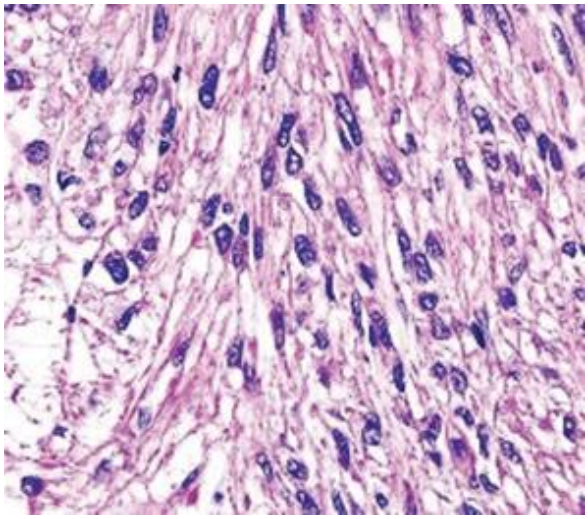

Figure 7: Perivascular epithelioid cell tumour displaying fascicles of spindle-shaped cells with eosinophilic cytoplasm and regular nuclei [17]

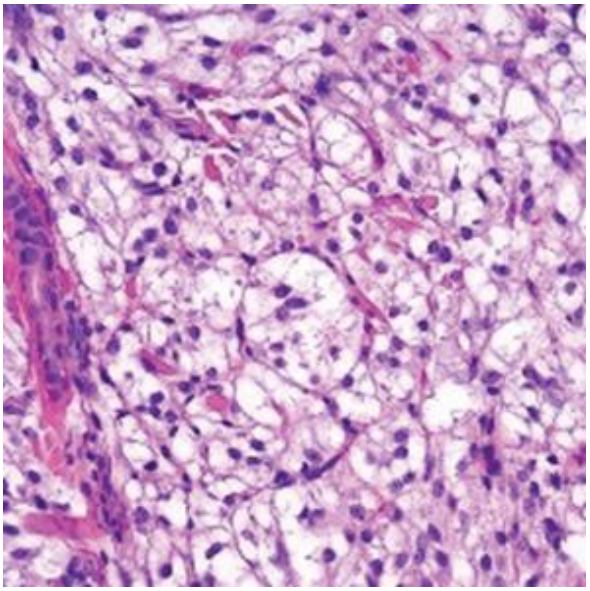

Figure 8: Perivascular epithelioid cell tumour depicting aggregates of spindle shaped epithelioid cells with clear cytoplasm and uniform nuclei [18]

IMMUNE HISTOCHEMICAL ELUCIDATION

Immune reactivity to myogenic and melanocytic markers is observed. Perivascular epithelioid cell tumour is intensely immune reactive to human melanoma black -45 (HMB-45) antigen, cathepsin-K, smooth muscle markersdesmin and actin andweakly immune reactive to melan-A [3]. The neoplasm is immune reactive to melanocytic markers human melanoma black-45 (HMB-45)(92%) antigen, melan-A(72%), microphthalmia transcription factor (50%), NKI/ C3, tyrosinase, S100 protein (33%) and smooth muscle markers such as Myo D1, smooth muscle actin (SMA) (80%), desmin (40%), calponin and vimentin (80%). The tumour is immune non reactive to cytokeratin, CD117/ c-kit and CD34. Also, reactivity to desmin and H-caldesmon is less frequent. A subset of tumours are immune reactive to TFE3 anddepict a TFE3 chromosomal rearrangement [6,7]. Tumour cells are immune non reactive to synaptophysin, chromogranin A, pan cytokeratin CK20, CK7 and S100 protein [7].

DIFFERENTIAL DIAGNOSIS

Perivascular epithelioid cell tumour requires a differentiation from neoplasms as Clear cell or oxyphilic carcinoma which is immune reactive to cytokeratin. Epithelioid or clear cell smooth muscle tumours are immune non reactive to human melanoma black -45 (HMB-45) antigen. Malignant melanoma is intensely immune reactive to S100 protein. Undifferentiated or high grade sarcoma which depicts morphological features of malignancy such as cellular and nuclear pleomorphism, atypia, nuclear hyperplasia or hyperchromasia and prominent mitotic figures [3,6]. Cervical perivascular epithelioid cell tumour necessitates a segregation from primary and secondary cervical malignant melanoma. However, minimal cellular and nuclear pleomorphism with minimal mitosis favours a perivascular epithelioid cell tumour [6,7]. Perivascular epithelioid cell tumour of pterygopalatine fossa requires a segregation from lesions such as epidermoid cyst, meningocoele, mucosal carcinoma, schwannoma, chordoma, teratomaor neurofibroma. Majority of aforesaid masses are benign although localized tumour invasion can ensue [6,7]. Histological differentiation of pancreatic perivascular epithelioid cell tumour is required from pancreatic neuro-endocrine tumour (NET), malignant metastasis and carcinoma pancreas. Segregation is also mandated from pseudo-papillary neoplasm, gastrointestinal stromal tumour (GIST), acinar cell carcinoma of pancreas, metastasis of clear cell renal cell carcinoma (CCRCC) or malignant melanoma [7,8].

INVESTIGATIVE ASSAY

Appropriate evaluation of tissue specimen obtained from incriminated sites as pterygopalatine fossa is indicated to eliminate a malignant metamorphoses, except in prominently vascular juvenile nasopharyngeal angiofibroma [9]. Mild anaemia or elevated levels of chromogranin A may be discerned. The exceptional perivascular epithelioid cell tumour of pancreas can be pre-operatively discerned by endoscopic, ultrasound guided fine needle aspiration cytology (FNAC) [6,7]. Endoscopic ultrasound guided fine needle aspiration (EUS FNAC) is a superior imaging modality for obtaining tissue specimens for assessment. Ultrasound of the tumefaction demonstrates a spheroidal, well defined, hypoechoic mass. Pancreatic neoplasm depicts a well defined, heterogeneous, predominantly hypoechoic mass with lateral shadow extending into homogenous, circumscribing pancreatic tissue and an absence of dilatation of pancreatic duct. Aforesaid manifestations can be confirmed upon computerized tomography (CT) and magnetic resonance imaging (MRI) [9,10]. On ultrasonography, a hypoechoic tumefaction is observed. Colour Doppler demonstrates a certain degree of internal vascular flow. Uterine neoplasms can be isointense, in contrast toencompassing myometrial tissue, upon T1 and T2 weighted imaging. Antenatal diagnosis is challenging as pregnancy associated pelvic magnetic resonance imaging is performed in the absence of gadolinium contrast. Several neoplasms depict oestrogen receptors (ER) and progesterone receptors (PR) which contribute to tumour evolution in context to hormonal alterations during pregnancy [9,10]. Diverse imaging techniques such as abdominal or endoscopic ultrasound, computerized tomography (CT) or magnetic resonance imaging (MRI) display a well circumscribed, spherical to elliptical mass with normal circumscribing soft tissue and lack of tumour infiltration. On colour Doppler or contrast- enhancement, arterial hyper-vascularity is observed. Elastography demonstrates a hard lesion with lateral shadowing, thus indicating an encapsulated tumour. Aforesaid features can simulate a neuro-endocrine tumour (NET). Contrast enhancement within an endoscopic ultrasound (EUS) may differentiate the lesion from NET. In contrast, an adenocarcinoma displays a poorly defined, infiltrative, hypodense tumefaction [9,10]. Magnetic resonance imaging (MRI) depicts a nodule of intermediate signal intensity. Positron emission computerized tomography (PET-CT) of the incriminated zone depicts a soft tissue mass with significant uptake of nuclear contrast, indicative of a malignant neoplasm. The tumour can be in proximity to abutting viscera although direct tumour invasion is absent. Tumour metastasis or abnormal, infiltrated lymph nodes are absent. In situ hybridization may or may not be able to discern EWS and TFE3 genomic rearrangements, features which support the diagnosis of conventional perivascular epithelioid cell tumour [9,10]. Nodules of pterygopalatine fossa can be detected with nasal endoscopy, computerized tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) [10].

PROGNOSTIC OUTCOMES

The neoplasm is usually benign although certain instances can demonstrate malignant metamorphoses and recapitulate a high grade sarcoma. Factors associated with inferior prognosis are tumour magnitude exceeding > 5 centimetres to 8 centimetres, infiltrative tumour articulation, enhanced nuclear grade with mitotic figures exceeding > 1 per 50 high power fields or atypical mitotic figures and coagulative cell necrosis [7,8].

THERAPEUTIC OPTIONS

Comprehensive surgical resection of the neoplasm is generally curative due to benign biological behaviour. Cervical perivascular epithelioid cell tumour is appropriately treated with total hysterectomy. Prognostic outcomes are superior than a uterine neoplasm. Localized surgical excision is accompanied by disease reoccurrence in around 8.3% of cervical lesions and nearly 21.5% of uterine neoplasms [3]. Radical surgical excision of the neoplasm is contingent to tumour histology. As pancreatic perivascular epithelioid cell tumour is imbued with a malignant potential, cogent surgical extermination as pancreatectomy with splenectomy can be adopted. Neoplastic occurrence may be absent within the tumour perimeter, abutting viscera and resected lymph nodes. Surgical extermination is recommended for solid pancreatic tumefaction exceeding >2 centimetre magnitude or neuro-endocrine tumour. Nevertheless, clinical signs and symptoms, location of tumour, evidence of malignant metamorphoses and individual comorbidities are critical factors in selecting cogent therapeutic options [9,10]. Majority of pancreatic perivascular epithelioid cell tumours are benign and associated with superior prognosis as the tumefaction is devoid of relapse or distant metastasis. Nevertheless, the neoplasm can delineate a potential for malignant metamorphoses. Hepatic metastasis can occur and malignant features such as tumour infiltration, necrosis or tumour magnitude exceeding > 5 centimetres can ensue. Adjuvant chemotherapy with epirubicin and ifosfamide can be adopted for metastatic lesions [9,10]. Radiation therapy can be therapeutically employed in instances with significant tumour progression. Nevertheless, established indications for adjuvant radiation are as yet undescribed [10].

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