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Editorial

Bounteous and Roseate-Alveolar Soft Part Sarcoma

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Alveolar soft part sarcoma is an exceptionally discerned, malignant mesenchymal neoplasm of uncertain histogenesis. Initially scripted by Christopherson., *et al*. in 1952, alveolar soft part sarcoma characteristically depicts a specific genetic translocation der(17)t(X;17)(p11.2;q25) with consequent occurrence of ASPSCR1-TFE3 genetic fusion [1].

Tumour is constituted of enlarged, polygonal cells permeated with abundant, eosinophilic cytoplasm with intracytoplasmic rhomboid or rod shaped crystals which can stained with periodic acid Schiff's (PAS) stain with diastase resistance. Neoplasm configures a nested or pseudo-alveolar tumour pattern.

Alveolar soft part sarcoma is a high grade neoplasm although devoid of applicable formal grading system. Initial biological course may appear as indolent although overall prognostic outcomes are inferior.

Alveolar soft part sarcoma manifests an estimated < 1% of soft tissue sarcomas. Median age of disease emergence is 25 years although no age of disease occurrence is exempt. Majority (~70%) of incriminated subjects appear < 30 years with neoplastic occurrence commonly discerned within 15 years to 35 years.

A female predominance is encountered with female to male proportion of 1.4:1. Implicated older subjects > 30 years or paediatric subjects may denominate minimal female predominance [2,3].

Alveolar soft part sarcoma commonly emerges within deep seated soft tissues of extremities, predominantly lower extremity (51%), trunk (20%), internal organs (8%) or head and neck (9%). Implicated adults frequently depict tumours confined to deep seated soft tissues of thigh or gluteal region. Paediatric subjects delineate a predilection for head and neck region and neoplasm may especially be confined to tongue or orbit.

Uncommonly, tumour is exemplified upon sites such as female genital tract, bone, breast, cardiac muscle, larynx, urinary bladder, mediastinum or vertebral column [2,3].

Alveolar soft part sarcoma delineates ASPSCR1-TFE3 genetic fusion protein confined within the nucleus. The protein functions as an aberrant transcription factor. Consequently, overexpression of c MET with activation of c MET signalling ensues, thereby ensuring a population of tumour cells sensitive to c MET inhibition.

On account of lactate concentration necessitated for cellular growth, alveolar soft part sarcoma commonly occurs within skeletal muscle while demonstrating the presence of lactate transporter, monocarboxylate transporter (MCT1) protein and CD147 [2,3].

A specific genetic alteration der(17)t(X;17)(p11;q25), which engenders fusion of TFE3 transcription factor gene derived from chromosome Xp11 with ASPSCR1 gene situated at chromosome 17q25.3 may be encountered. Thus, ASPSCR1-TFE3 translocation configures as an inciting genetic event for generation of the neoplasm.

Alveolar soft part sarcoma remains devoid of concurrence with exposure to radiation or a cancer predisposition syndrome.

Alveolar soft part sarcoma represents as a painless, gradually progressive tumefaction. Orbital tumours manifest with proptosis. Vaginal bleeding ensues with neoplasms confined to female genital tract.

Upon initial representation, tumefaction may be localized (38%), confined to regional sites (11%) or associated with distant metastasis (43%) [2,3].

Upon gross examination, a solid, partially circumscribed, yellow, grey, whitish or tan tumour mass with embedded fleshy nodules and bands of fibrous tissue is encountered. Tumour magnitude varies from 1.2 centimetres to 24 centimetres with median magnitude of 6.5 centimetres. Enlarged peripheral vascular articulations frequently circumscribe the neoplasm [3,4].

Upon frozen section, enlarged polygonal cells permeated with abundant, eosinophilic cytoplasm, eccentric nuclei and prominent nucleoli are encountered. Nests of tumour cells appear circumscribed with innumerable vascular channels.

Upon cytological examination, enlarged tumour cells appear permeated with abundant granular and vacuolated cytoplasm. Cellular scrapings may depict aforesaid morphology and cytological features [3,4].

Upon microscopy, enlarged, uniform, spherical or polygonal cells with equivalent individual tumour cell magnitude appear permeated with abundant, eosinophilic, granular cytoplasm, spherical vesicular nuclei, prominent nucleoli and well defined cellular perimeter. Frequently, neoplastic cells demonstrate focal or diffusely disseminated intracytoplasmic rod-like or rhomboid crystalline structures.

Neoplasm delineates an organoid or nest-like tumour configuration with centric cellular dis-cohesion and emergence of characteristic pseudo-alveolar-like tumour articulations. Neoplastic lobules appear subdivided by thickened fibrous tissue septa [3,4].

An intense network of capillaries and vascular articulations are commingled with tumour lobules. Distended venular configurations appear congregated upon periphery of tumefaction. Vascular invasion is commonly encountered [3,4].

Additionally, features such as cytoplasmic clearing, rhabdoid cells and focal pseudo-glandular tumour pattern is observed. Besides, focal cystic or myxoid alterations may ensue.

Microscopic features as nuclear pleomorphism, hyperchromatic nuclei, giant cells, mitotic figures, tumour necrosis, calcification, lymphocytic infiltration or xanthomatous modifications are uncommonly discerned.

Tumours confined to lingual region may enunciate miniature cells, non-alveolar pattern of tumour evolution and inconspicuous vascular articulations [3,4].

Upon ultrastructural examination, tumour cells demonstrate numerous mitochondria and well developed Golgi apparatus. Characteristic rhomboid or rod shaped intracytoplasmic crystals appear to configure a uniform lattice pattern [3,4].

Staging system of soft tissue sarcoma of extremity or trunk as per American Joint Committee on Cancer (AJCC) 8th edition

Primary tumour

- T1: Tumour ≤ 5 centimetres in greatest dimension.
- T2: Tumour > 5 centimetres and ≤ 10 centimetres in greatest dimension.
- T3: Tumour > 10 centimetres and ≤ 15 centimetres in greatest dimension.
- T4: Tumour > 15 centimetres in greatest dimension.

Regional lymph nodes

- NX: Regional lymph node metastasis cannot be assessed.
- N0: Regional lymph node metastasis absent.
- N1: Regional lymph node metastasis present.

Distant metastasis

- M0: Distant metastasis absent.
- M1: Distant metastasis present.

Tumour stage is designated as

- Stage I A: T1, N0, M0, GX/ G1
- Stage I B: T2, T3 or T4, N0, M0, GX/G1
- Stage II: T1, N0, M0, G2/G3
- Stage III A: T2, N0, M0, G2/G3
- Stage III B: T3, T4, N0, M0, G2/G3
- Stage IV: Any T, N1, M0, any G OR any T, any N, M1, any G [3,4]

Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) histological grading of soft tissue sarcoma

Tumour differentiation

- Score 1: Closely recapitulating normal tissue.
- Score 2: Histological typing is certain.
- Score 3: Embryonal or undifferentiated sarcomas.

Mitotic count (per 1.7 mm^2)

- Score 1: 0 - 9 mitoses per 1.7 mm^2.
- Score 2: 10 - 19 mitosis per 1.7 mm^2.
- Score 3: > 19 mitosis per 1.7 mm^2.

Tumour necrosis

- Score 1: Absence of necrosis.
- Score 2: < 50% tumour necrosis.
- Score 3: ≥ 50% tumour necrosis.

Histological grade

- Grade X: Grade cannot be assessed.
- Grade 1: Total score 2 or 3.
- Grade 2: Total score 4 or 5.
- Grade 3: Total score 6,7 or 8 [4,5].

Alveolar soft part sarcoma is immune reactive to TFE3, cathepsin K, MCT1 or CD147. Vimentin or neuron specific enolase (NSE) may be immune reactive in ~50% instances.

Periodic acid Schiff's (PAS) stain can be employed to emphasize intracytoplasmic crystals and granules which appear resistant to digestion by diastase [5,6].

Upon immunohistochemistry, nuclear expression of TFE3 is encountered. Besides, confirmation of TFE3 genetic rearrangement or an ASPSCR1-TFE3 genetic fusion may be obtained.

Alveolar soft part sarcoma is immune non-reactive to pancytokeratin, epithelial membrane antigen (EMA), synaptophysin, chromogranin, HMB45, melan A, calretinin, smooth muscle actin (SMA), caldesmon, desmin, myogenin or MyoD1.

Upon ultrastructural immunohistochemistry, intracytoplasmic rhomboid crystals are comprised of aggregates of MCT1 and CD147 particles [5,6].

Alveolar soft part sarcoma requires segregation from neoplasms such as metastatic renal cell carcinoma, metastatic adrenal cortical carcinoma, metastatic hepatocellular carcinoma, granular cell tumour, paraganglioma, PEComa, malignant melanoma, rhabdomyoma or alveolar rhabdomyosarcoma [5,6].

Alveolar soft part sarcoma can be appropriately discerned upon morphological assessment demonstrating nests of eosinophilic, polygonal tumour cells imbued with rod shaped intracytoplasmic crystals circumscribed by a dense capillary network.

Fluorescent *in situ* hybridization (FISH) is optimal for confirming genetic rearrangements of TFE3. Reverse transcription polymerase chain reaction (RT-PCR) can appropriately detect the significantly specific and sensitive genomic fusion transcript of ASPSCR1-TFE3 gene.

Infrequently, fusion partners of TFE3 may be discerned as HNRNPH3-TFE3, DVL2-TFE3 and PRCC-TFE3 genetic fusion [5,6].

Computerized tomography (CT) and tumour angiography can be optimally adopted to assess the hyper-vascular tumour delineating prominent draining veins and prolonged capillary staining.

Magnetic resonance imaging (MRI) exhibits a characteristic vascular pattern with moderate to intense image enhancement following administration of contrast medium. Upon angiography, alveolar soft part sarcoma may simulate an arteriovenous malformation [5,6].

Recommended mode of therapy is radical surgical extermination of the neoplasm. Additionally, surgical excision of pulmonary or brain metastasis may extend survival.

Radiation therapy may be adopted to decimate possible localized tumour reoccurrence [5,6].

Adjuvant chemotherapy appears inefficacious. Clinical trials with c MET inhibitor (crizotinib) exhibit stabilization of disease in the absence of significant tumour shrinkage. Multiple pulmonary metastases may be decimated with administration of interferon alfa 2a [5,6].

Extensive clinical monitoring is mandatory on account of distant metastasis occurring beyond > 10 years following initial tumour detection. Localized tumour reoccurrence varies from 11% to 50%.

Distant metastasis may ensue within pulmonary or hepatic parenchyma, bone, brain and exceptionally within lymph nodes. Brain metastasis is commonly encountered with alveolar soft part sarcoma. Overall survival emerges at 82% within 2 years and 56% at 5 years.

A 5 year disease free survival of ~71% is documented in subjects manifesting with localized disease, in contrast to ~20% 5 year disease free survival within individuals demonstrating distant metastasis [5,6].

Factors contributing to superior prognostic outcomes manifest as

- Tumour magnitude < 5 centimetres
- Absence of metastases upon initial disease representation
- Incrimination of younger subjects < 10 years
- Preliminary detection of tumour amenable to comprehensive surgical resection.

Factors contributing to inferior prognostic outcomes are denominated as

- Incrimination of older subjects
- Tumour magnitude > 10 centimetres
- Distant metastasis upon initial tumour discernment
- Primary tumour confined to the trunk [5,6].

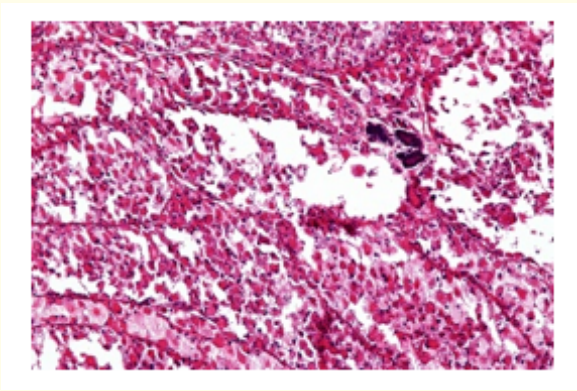

Figure 1: *Alveolar soft part sarcoma delineating uniform tumour cells pervaded with copious, eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli and intracytoplasmic rhomboid crystals. Tumour cells configure an organoid pattern [7].*

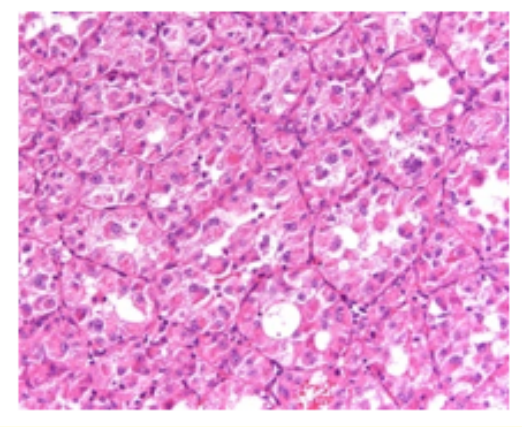

Figure 2: *Alveolar soft part sarcoma delineating uniform tumour cells imbued with abundant, eosinophilic cytoplasm, vesicular nucleus, conspicuous nucleoli and rod shaped, intracytoplasmic crystals. Tumour cells configure a nesting or pseudo-alveolar pattern [8].*

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7. Image 1 Courtesy.
8. Image 2 Courtesy.

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