ANSWERS AND ADDITIONAL INFORMATION FOR ORTHOPAEDIC CLINICAL QUIZ
SKELETAL AND EXTRA-SKELETAL TUMOURS REVISITED

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Quiz 1

a. A typical chronic non-healing ulcer with two abnormal findings: roll-out ulcer edge and nodular lesions in scarred tissue, may indicate malignant transformation to either squamous cell carcinoma (SCC) of the skin or osteosarcoma of the bone.

b. SCC arising from chronic non-healing osteomyelitis (Marjolin ulcer) is the most likely diagnosis based on the presence of roll-out edge and symptom of pain is probably due to perineural invasion of the tumour (skin nodules). Plain radiographs show chronic OM changes without evidence of tumor osteoid formation. Gross specimen of the excised tissue indicates typical chronic osteomyelitis bone.

c. Four-quadrant biopsy or punch biopsies of the ulcer margin for histological examination. A Marjolin ulcer typically lacks basement membrane and should be differentiated from another pre-malignant lesion, squamous pseudoepitheliomatous hyperplasia.

d. Following a wide resection margin which includes either intercalary segment of the tube or proximal tube, normal soft tissue and fcm normal skin around the ulcer if the ulcer is deep. By contrast the wound is filled best before containing an infected tissue and proximity of resection margin to the metaplastic junction, a staged combined reconstruction using a vascularized free flap and revascularization orthopaedic or knee resection allograft is preferred. If joint preservation intercalary resection is feasible, a staged procedure consisting of free flap and defect filling with bone cement to initiate the initial stage of membrane-induced osteosynthesis is an option. The bone is stabilized with either circular external fixator or antibiotic-coated locked nail. In the second stage, bone cement is removed through an incised membrane and the defect is reconstructed with either cancellous bone graft or bone graft substitute. This technique is known as membrane-induced osteosynthesis of Masquelet.

SQUAMOUS CELL CARCINOMA (SCC): ARISING FROM CHRONIC PRE-EXISTING LESIONS

Although the association between chronic burn scar and delayed malignant transformation was documented by Celsus 2000 years ago, Jean Nicolas Marjolin (1628) was credited for observing and classifying cellular changes ‘ulcer cancrosi’ in burned skin. Today, the lesion that bears the eponym Marjolin ulcer is interchangeably used to any malignant neoplasm that show similar histology to SCC arising in association with a variety of pre-existing chronic precursor lesions: scars including burned scars and vaccination scars, draining sinus of Chronic OM and pilonidal sinus, and venous ulcers.

The pathophysiology of Marjolin ulcer is presumed to involve a two-step process of initiation phase of formation of dormant neoplastic cells in an immunologically privileged site of relatively ischaemic and dense scar tissue with fragile epithelium and promotion phase into active neoplasm after exposure to repeated injuries or stimulation by co-carcinogens leading to cell mutation and eventual neoplasms. This transformation occurs in less than 5% of such lesions, typically after a latency period of 20-40 years of exposure to mutagenic hits/carcinogenic stimuli in pre-existing precursor lesions. The co-carcinogens include toxin released from repeatedly damaged tissue by trauma, infection and UV from sun exposure. However, acute variant of Marjolin ulcers developing rapidly within few months to years have been described. Progression into SCC can be delayed by avoiding or minimizing these factors. This secondary SCC displays an aggressive clinical behavior. Perineural skin changes forms of new nodular lumps and role-out ulcer edge or pathological fungating surface surrounding or adjacent to an easily identifiable draining sinus. Invasion (2.4%-14%) typically manifests as increasing pain, has a prognostic initiation phase of formation of dormant neoplastic cells in an immunologically privileged site of relatively ischaemic and dense scar tissue with fragile epithelium and promotion phase into active neoplasm after exposure to repeated injuries or stimulation by co-carcinogens leading to cell mutation and eventual neoplasms. This transformation occurs in less than 5% of such lesions, typically after a latency period of 20-40 years of exposure to mutagenic hits/carcinogenic stimuli in pre-existing precursor lesions. The co-carcinogens include toxin released from repeatedly damaged tissue by trauma, infection and UV from sun exposure. However, acute variant of Marjolin ulcers developing rapidly within few months to years have been described. Progression into SCC can be delayed by avoiding or minimizing these factors. This secondary SCC displays an aggressive clinical behavior. Perineural skin changes forms of new nodular lumps and role-out ulcer edge or pathological fungating surface surrounding or adjacent to an easily identifiable draining sinus. Invasion (2.4%-14%) typically manifests as increasing pain, has a prognostic.

An aggressive surgical approach has become the gold standard management for Marjolin ulcers. In SCC, surgical excision is recommended 4cm margins of lesion of <2cm diameter and at least 6mm margin for lesion of >2cm diameter if 95% cure rate is targeted. Amputation with or without regional node dissection is recommended for SCC arising in a draining sinus of COM. The decision for en block lymph node clearance is based on sentinel node staging: sub-capular, sub-capular and parenchymal, parenchymal and extensive parenchymal patterns. Owing to the nature of this carcinoma in poorly vascularized scar tissue, the role of adjuvant chemotherapy and radiation therapy remains controversial. In cases with metastatic disease or tumour at surgically non-feasible site, chemotherapy or with without radiation therapy is recommended.

References:

Quiz 2

a. An eccentric predominantly lytic with few incomplete trabecula bone lesion of narrow transitional zone involving meta-epiphyseal region of the distal femur. The lesion has breached the anterior and posterior cortices of the distal femur. However MRI displays a pathologic lesion containing fibroblastic stroma with variable mineralization.

b. Considering a slow onset disease of non-progressive clinical behavior, the lesion with these imaging findings is probably representing a variant of osteosarcoma called central low-grade osteosarcoma.

c. Tumour staging involves imaging studies and tissue biopsy. Imaging studies help to determine local extensions, degree of effect on limb and distant metastases in the lungs (plain radiograph and CT thorax) and other bones (bone scans). Representative tissue biopsy is essential for tumour grading. A stage-III disease (low grade tumour with local extension or extra-compartmental disease) is the most likely pathological stage.

d. Although regarded as a low-grade malignancy, wide margin resection remains the preferred option as inadequate resection becomes associated with high rate of local recurrence displaying a higher histological grade with metastatic potential. Due to tumour proximity to the knee involving the epiphysis with cortical breaching, tumour excision is often associated with osteochondral resected bone of the femur along with cuff of normal soft tissues. Reconstruction options include
tumour megaoesophagus arthrophy, knee fusion allograft and van Nes rotationplasty. For young adult with expectant optimum functional demand, megaoesophagus arthrophy is the best option. As the tumour is responds to neither chemotherapy nor radiotherapy, the role of pre- and post-operative adjuvant chemotherapy remains controversial or unnecessary until adequate supportive data are available from large RCTs.

LOW-GRADE CENTRAL OSTEOSARCOMA

Distinct variants of osteosarcomas (OS) are based on their anatomic site of origin: medullary cavity or perosteal tissue adjacent to the metaphyseal surface of a long bone, and their histological sub-types: high-grade and low-grade malignancy, have been described. Rare anatomic variants with exclusive extra- cortical confinement or extraskeletal site have also been encountered. The majority of high-grade variants are conventional central medullary (90% of all OS), telangiectatic and extra-skeletal OS. Surface parosteal OS are typically low-grade and perosteal OS are frequently intermediate-grade. However, low-grade variants of central and extra-skeletal OS as well as high-grade variants of surface OS have also been reported.

Low-grade central OS (LGCCOS) variant is regarded as a medullary-equivalent or homologue of perosteal OS because of its fibroblastic predominant resemblance. This rare variant accounts for 1-2% of all OS. It has predilection for a decade older patients and with longer symptoms build-up in contrast to the conventional OS. The difficulty in establishing the diagnosis remains the key problem.

Radiographically, it may mimic mono-osotic fibrous dysplasia, desmoplastic fibroma, nonossifying fibroma, osteoblastoma and aneurysmal bone cyst. It appears as a more permissive lesion into the fatty marrow and native bone trabeculae, and less homogenous in comparison to ground appearance of fibrous dysplastic lesion. If ossification is scant, it may mimic a reactive exostosis. Fibrillogranular and prominent mitotic activity. Andresen et al. (2004) described four radiological types of LGCCOS: type 1-lytic with variable coarse and thick trabeculae, type 2- predominantly lytic with few thin incomplete trabeculae, type 3- densely sclerotic, and type 4- mixed lytic and sclerotic.

Grossly, it is well-demarcated whitish firm mass of fibrous stroma that appears centrally located in the medullary cavity of the metaphysis or meta-diaphyseal region with soft tissue component in some cases. Histologically, it may be indistinguishable with benign fibrous lesions particularly fibrous dysplasia and desmoplastic fibroma. A permissive growth pattern is absent in fibrous dysplasia and desmoplastic fibroma lacks matrix production. It consists of parallel trabeculae as round islands woven bone intimately intermingling with mild-to-moderate bland fibroplastic spindle cells with variable amount of osteoid production and fibrous stroma resembling fibrous dysplasia if involving the medullary canal. However, its trabeculae are longer and parallel in contrast to short and curt trabeculae of fibrous dysplasia. The spindle cells show mild mitotic activity and mild atypia. Immunohistochemically stains with cycline-dependent kinase 4 (CDK4) and murine double-minute 2 (MDM2) help to aid the diagnosis of LGCCOS. Despite this difficult differentiation with benign lesion, distinguishing low-grade central OS from high-grade surface parosteal OS variant and other benign fibrous lesions remains crucially important as this will influence surgical decision.

In general, low-grade central OS has significantly better prognosis than conventional OS. With an expected 90% disease-free life between 5 and 10 years, LGCCOS is an eminently curable malignant tumour with appropriate treatment. Treatment with surgery in form of wide local resection with clear margin alone is adequate. Adjuvant chemotherapy or radiotherapy is not routinely necessary. Local recurrences in form of high-grade malignancy and metastatic diseases are typically delayed for 5-10 years and are frequently related to inadequate surgical margins.

References:

d. Wide local resection including amputation to achieve negative margins has been considered as the preferred option as systemic chemotherapy has previously been presumed to give unfavorable response. With recent data indicating an improved overall prognosis, surgery with multimodal treatment including adjuvant chemotherapy regimens followed by surgery (limb salvage or amputation), EOS is best treated similar to conventional OS.

EXTRA-SKELETAL OSTEOSARCOMAS (ESOS)

ESOS is a high-grade malignant bone-replacing tumour arising exclusively in the muscle or soft tissue without attachment or relation to underlying bone. Despite extremely rare, low-grade variant of ESOS showing similar histology to perosteal osteosarcoma and well-differentiated central low-grade OS have been reported.

The clinical features of ESOS are not well documented as they are rare tumours accounting for less than 5% of all OS. They affect patients of age later than those OS i.e. middle-aged adults of older than 40 years of age with male-to-female ratio of 2:1 and manifest as slowly growing occasionally painful deep-seated mass of more than 5cm. Differential diagnoses include acute osteomyelitis or deep-seated inflammatory phlegmon and heterotopic ossification A low-irradiation ESOS may develop following local radiation therapy on pre-existing pathology. Imaging studies commonly display an ill-defined large soft tissue density of >5cm with irregular calcification most often central or peripheral zonal phenomenon as oppose to peripheral zonation in heterotopic ossification).

Grosdy, ESOS is a circumscribed non-encapsulated mass which appears tan fleshy tumour with areas of haemorrhage and necrosis. It is histologically characterized by highly cellular pleomorphic neoplastic cells with polygonal, epitheloid or spindle shaped nuclei and prominent mitotic activity (mitotic rate of 10-15 mitoses per 10HPF). Myxoid tumour contains lacelike osseous ramifiying between individual cells or small clusters of cells and matured mineralized bone mainly in central location. Hyaline cartilage with endochondral ossification may present (positive staining for S-100) when chondrocytes show atypia. Area with necrosis may occasionally have osteoclast-like giant cells. Histologically, differential diagnoses include conventional OS with soft tissue extension, desmofibrosarcoma and undifferentiated pleomorphic sarcoma.

The biological behavior of ESOS varies with earlier series tend to indicate that they pursue aggressive local malignant disease and high rate of lung metastasis with patients succumbing to metastatic disease within 2-3 years after the initial diagnosis. Owing to this prior poor prognostic reputation and a 5-year survival rate of 25%, wide local excision including amputation to achieve negative margins has been considered as the best option. However, recent studies from the Cooperative Oncology Study Group in Japan and the German and the Japanese Musculoskeletal Oncology Group in Japan had demonstrated that the use of multimodal treatment including multimagent chemotherapy regimens and surgery (limb salvage or amputation) similar to those used in conventional OS can improve the prognosis Multimagent chemotherapy using AP(V)A sequential regimen, which combined adriamycin (A), cis-platinum (P), and ifosfamide (I), is currently preferred in many centres. Tumour size, histologic subtype, and proliferation index have been proposed as prognostic variables.

References:

Quiz 4

a. Infection (abscess or acute osteomyelitis), inflammatory-like condition (myositis ossificans) and primary malignant bone tumour (osteosarcoma). Imaging studies either plain radiographs or MRI scan exclude myositis ossificans and abscess.

b. With plain radiographs depicting a typical triad of a diaphyseal location of permeative lytic bone destruction with reactive peristomial lamination and Codman triangle, and a large soft tissue component, the diagnosis of Ewing sarcoma is more likely. However, the diaphyseal location of the lesion is also characteristic feature for other round-cell tumours that permeate bone particularly lymphoma and eosinophilic granuloma/Langerhans cell histiocytosis). Tissue biopsy is required to narrow down the diagnoses to a definitive diagnosis. At biopsy, the pathological tissue appears as whitish grey and soft in consistency. A diagnosis of Ewing sarcoma is most likely.

c. Treatment of Ewing sarcoma involves multimodal therapy following proper staging procedures: MRI scans and/or CT to define local extension or soft tissue component and degree of cortical destruction, chest CT to detect lung metastasis, bone scans to detect osseous metastasis and tissue biopsy. Modern treatment with Ewing sarcoma consists of neo-adjuvant pre-operative chemotherapy, followed by limb-salvage surgery or amputation and consolidation chemotherapy. Current chemotherapy protocols are based on ifosfamide and etoposide in addition to a combination of vincristine, dacarbazine, cyclophosphamide and doxorubicin (VACA). The final assessment of histological response to chemotherapy and the analysis of post-resection surgical margins are important determinants used to decide for adjuvant therapy. Amputation is now exclusively reserved for bulky tumour involving vital structures.
EWING SARCOMA (ES) AND EWING SARCOMA FAMILY OF TUMORS (ESFTs)

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ESFTs accounted for 6%-8% of primary malignant bone tumors, representing the third most frequent primary bone sarcoma after osteosarcomas and chondrosarcomas. ES per se account for approximately 10% of all primary bone tumors, second to osteosarcomas in terms of occurrence. PNET is relatively rare in bone, representing 10% of all ESFTs.

Clinical presentations of ESFTs vary with the majority of patients (80%) are adolescents or young adults below 20 years of age. They are rare before the age of 5 and after the age of 30. In children below 5 years of age, metastatic neuroblastoma should be considered. In the elderly, ESFTs may be mistaken for a diagnosis of acute osteomyelitis and catastrophically delay the therapy.

The vast majority of ES originate centrally in the diaphysis and metaphysis of a large long bone, or in a flat bone. Radiographically, an aggressive permeative/infiltrative lytic lesion with narrow transitional zone often without frank cortical destruction despite the presence of a large soft tissue mass/component (best seen on post-contrast MRI) indicates the tumor has tendency to infiltrate through the bone.

The tumor cells typically appear as a tightly packed nodular growth of sheet-like cells. Grossly, the tumor may be glistening firm or soft and friable grey to white in color, mimicking pus. Hemorrhage and cystic necrotic changes may present. The tumor (PNET) is the most differentiated as regard to neuroectodermal differentiation.

Fluorescence in-situ hybridization (FISH), cytogenetics and reverse-transcriptase PCR techniques are useful to identify non-random reciprocal translocations of EWS gene with one of the members of ETS family transcription factors (FLI-1, ERG, ETV-1, and EIAF genes) on chromosome 11q22, 21q22, 7p22 or 17q12. These include t(11;22)(q22;q12) fusion of FLI-1 and EWS in 90%-95% of cases and t(21;22)(q12;q11) fusion of ERG and EWS in 5% to 10% of cases. Other gene fusions partners are rare occurrences in less than 1% of cases. Demonstration of one of these specific translocations especially FLI-1 protein within the nuclei of small round cell tumors (85-90% of cases) is considered diagnostic of ES/PNET and is also included in ES therapeutic protocol for detection of residual disease and metastasis.

The staging of ESFT is based on the AJC on cancerUAC TNM classification parameters: tumor size (8cm being the cut-off), nodal involvement, metastases and Broder tumor grading.

Primary Tumor Extent (T) Regional Nodes (N) Metastatic/ Distant Node (M)
T1 can't be evaluated can't be evaluated can't be evaluated
T2 no evidence of primary tumor metastatic metastatic
T3 tumor discontinuation in the primary bone site no metastasis no metastasis
T4 metastasis distant metastasis distant metastasis

As ES is a high-grade malignant tumor, its stage grouping begins as stage II disease.

• Stage IIA T1, N0 or N X, M 0
• Stage IIB T2, N0 or N X, M 0
• Stage III T3, N0 or N X, M 0
• Stage IVa any T, N0 or N X, M 1a
• Stage IVb any T, N1, any M any T, N1, M 1b

Classification and Prognosis:

- age below 17 years
- extremity involvement (distal/proximal)
- appendicular > axial tumor
- tumor < 8cm in greatest diameter
- no extension into soft tissues
- no soft tissue and non-metastatic disease
- type-1 EWS-FLI-1 fusion transcript
- >90% tumor necrosis after neo-adjuvant chemotherapy
- surgically excised diseased bone

References: