CASE OF THE MONTH

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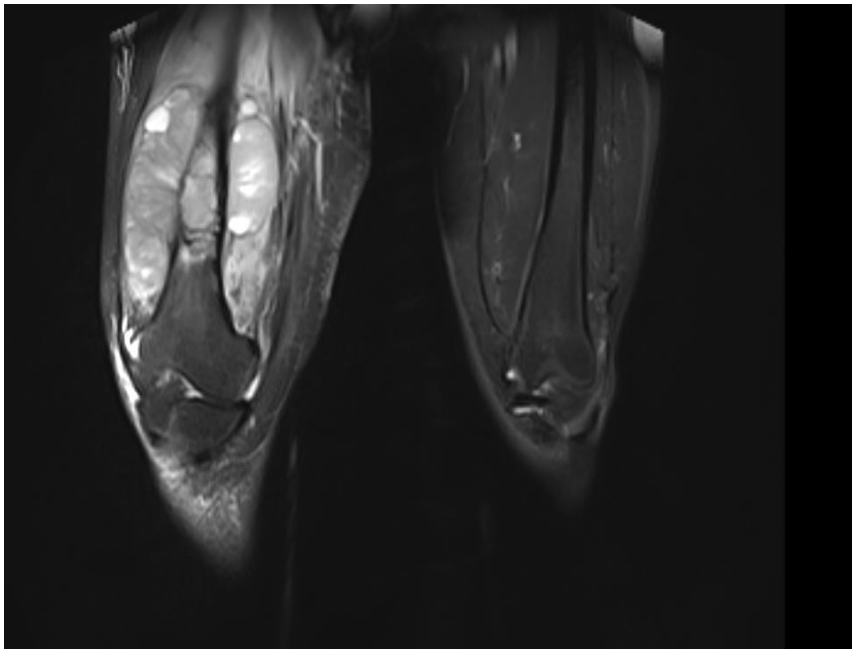
Senior Consultant

Clinical Details

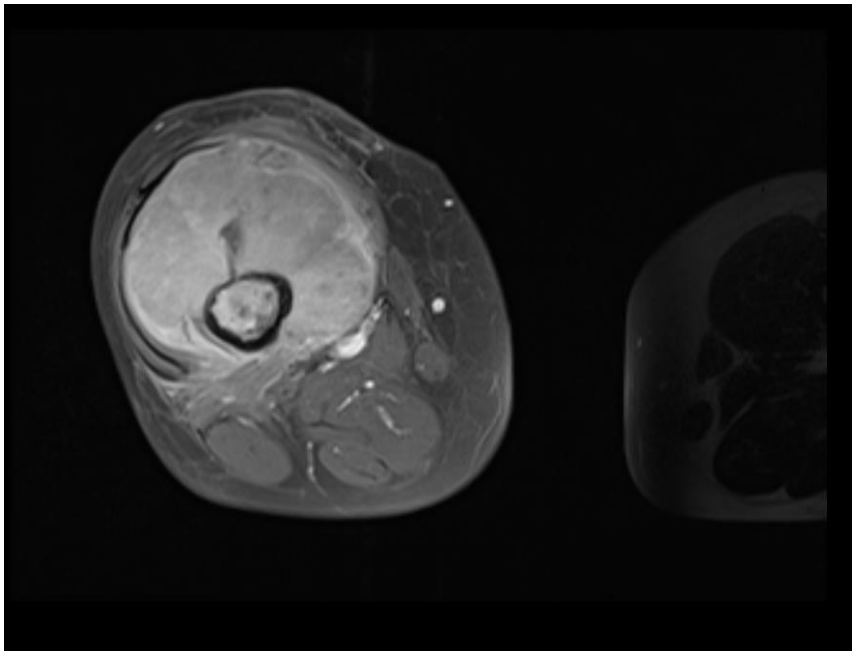
- 41 year old woman, presented with complaints of pain and swelling right thigh for 3 months
- Fever on /off present
- Underwent radiological evaluation
- Outside biopsy report: Spindle cell sarcoma

MRI – Right Thigh

Coronal STIR sequence



Axial T1 weighted fat suppressed sequence

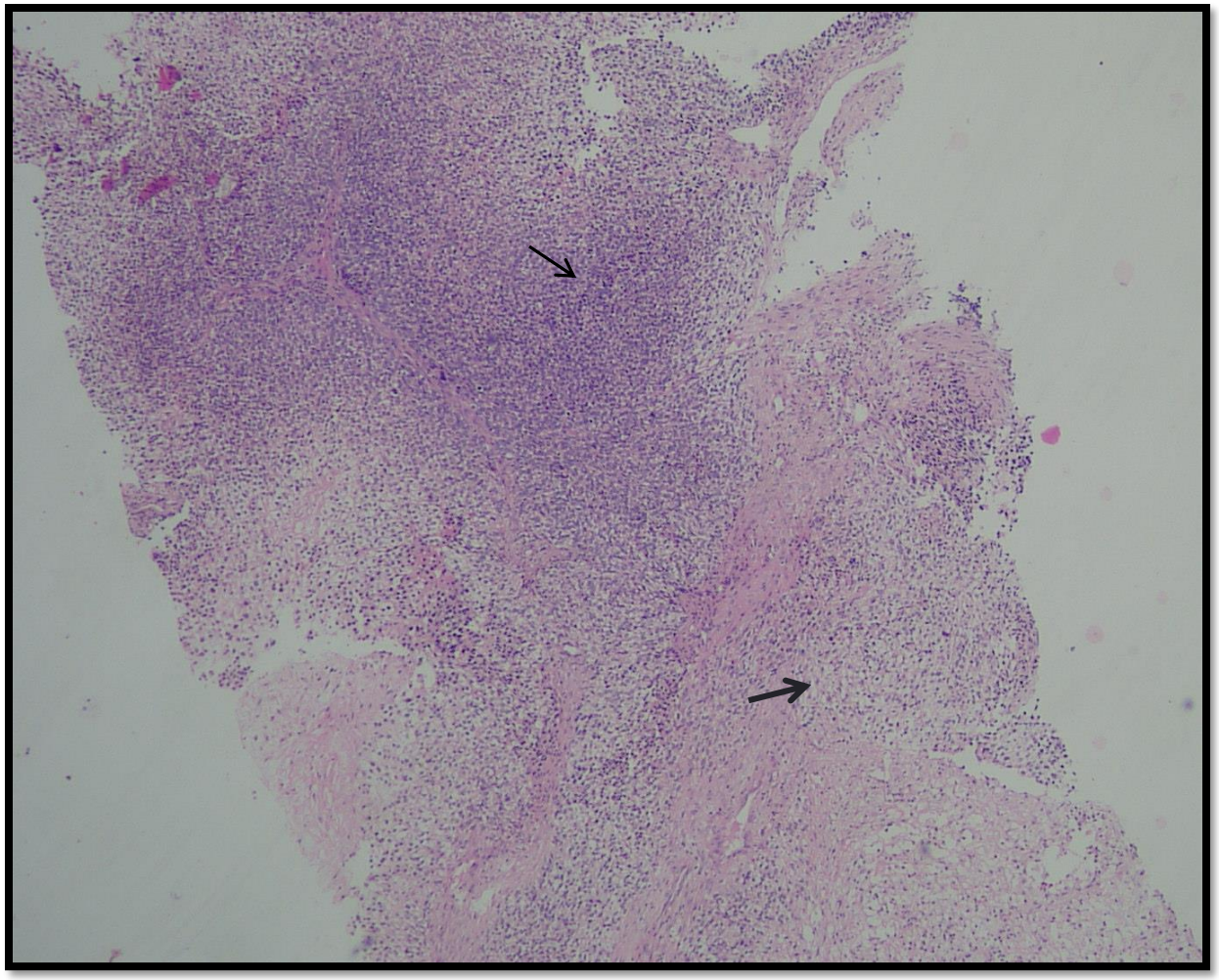


Lower third of femoral diaphyses enhancing altered marrow signal intensity, CC-15cm, expansile lesion with cortical thinning and infiltration into adjoining antero-lateral muscle compartment of thigh.

Differential diagnosis (based on clinico-radiological evaluation)

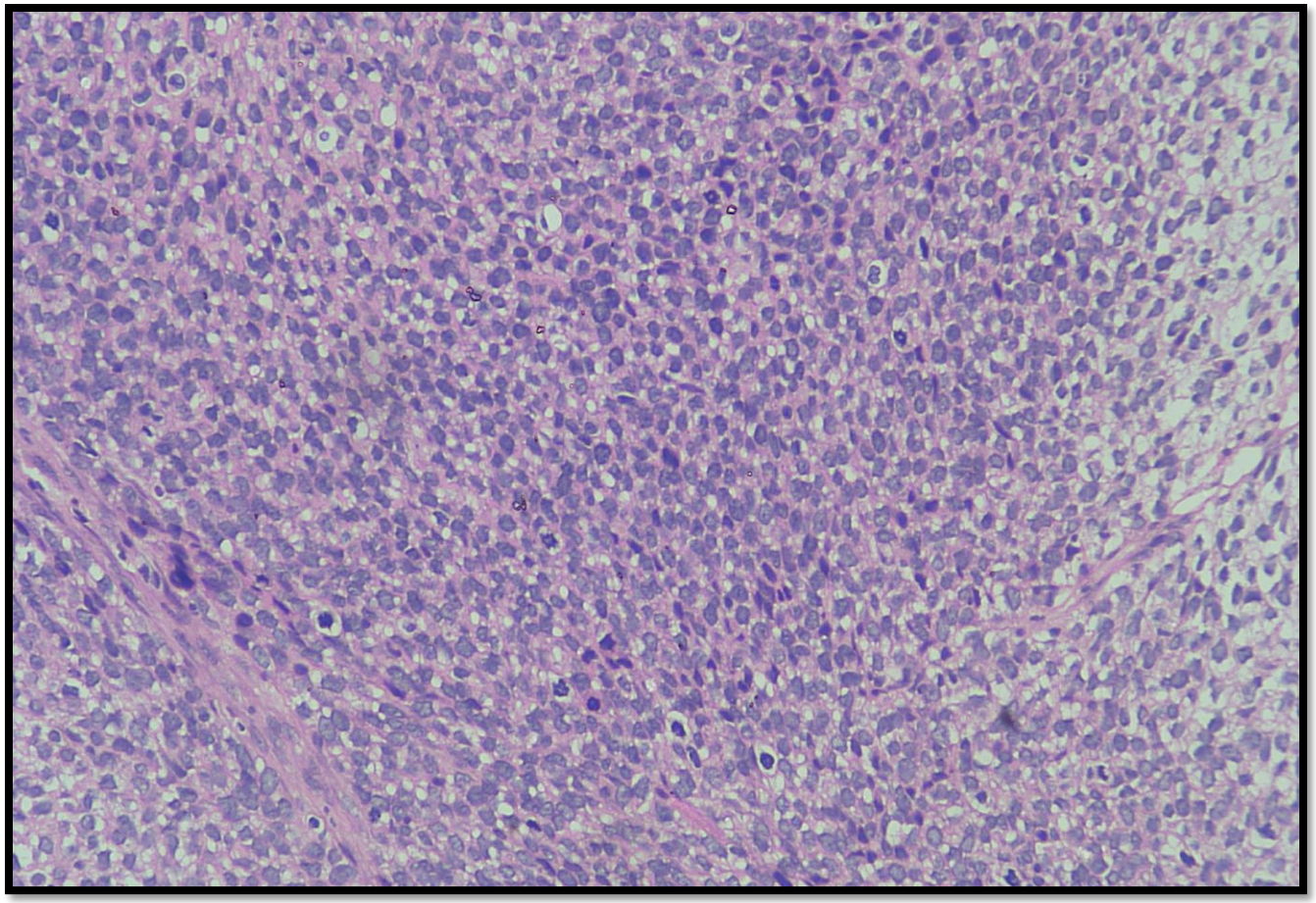
?Ewing's sarcoma, Right femur

Pathological evaluation (Core needle biopsy)



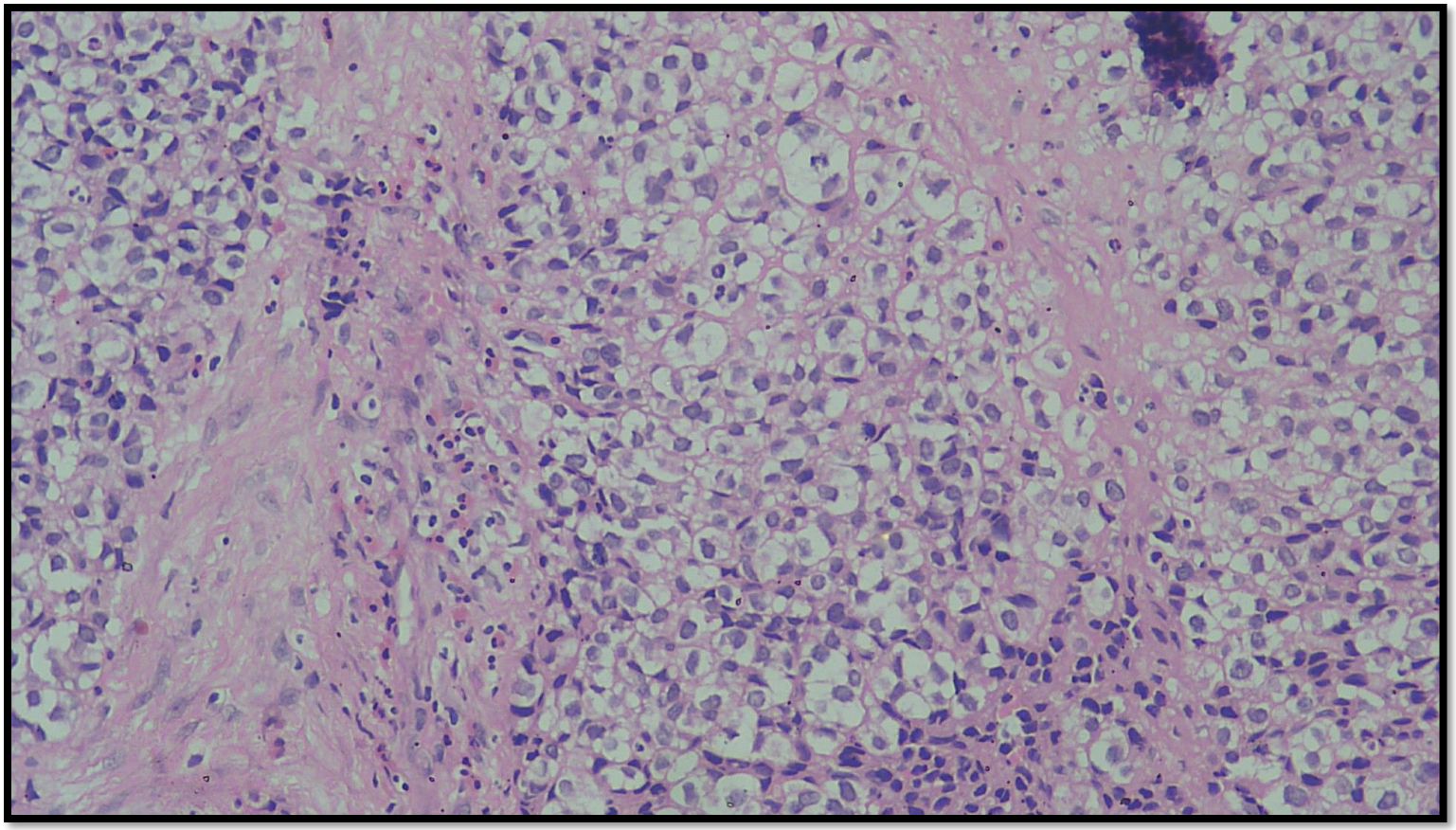
Tumor cells arranged in sheets with darker appearing round cells (arrow) and clear appearing polygonal cells (thick arrow) (H & E , 40X)

Pathological evaluation (Core needle biopsy)

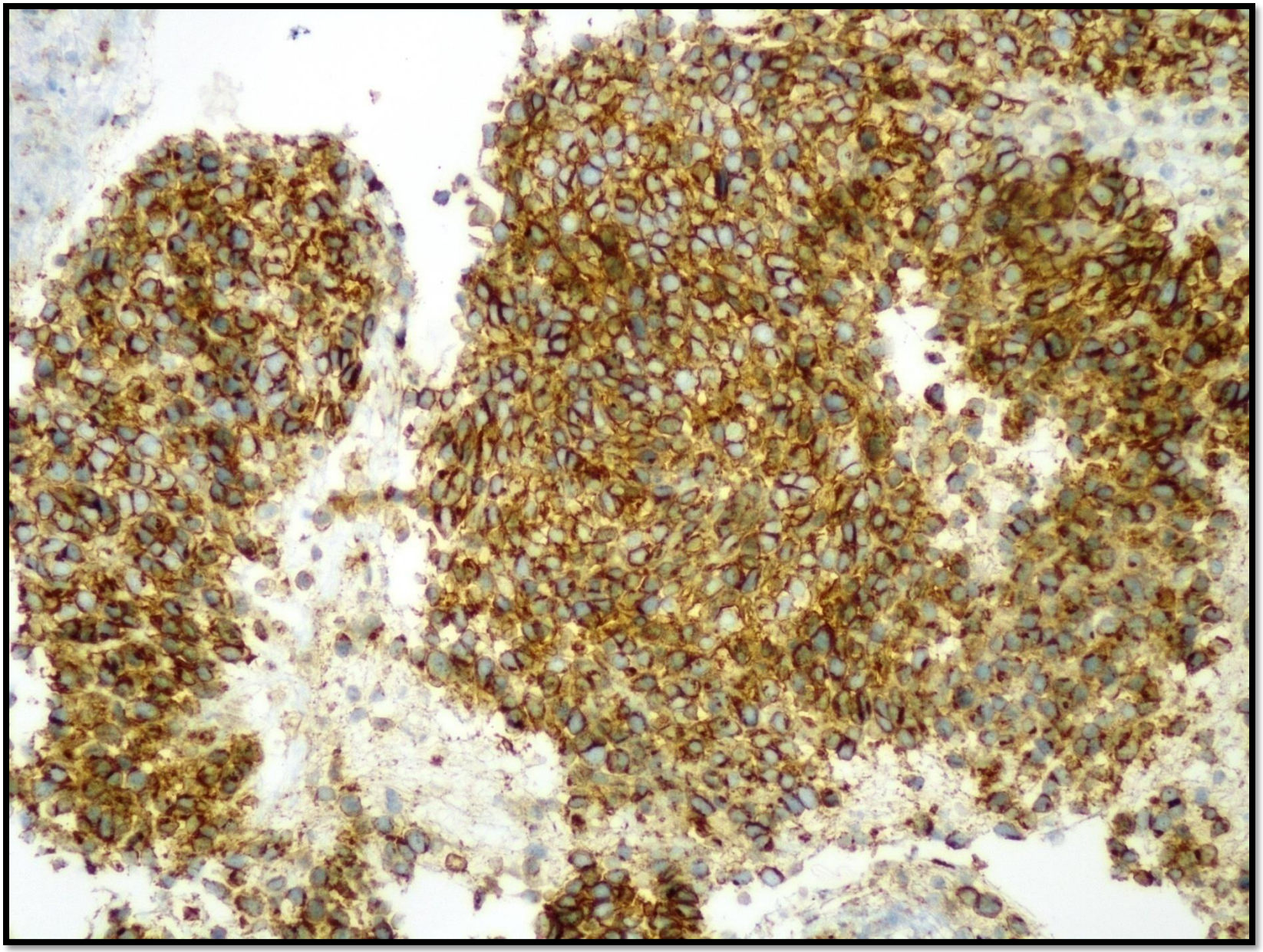


The individual tumor cells are round to polygonal with moderate clear to pale eosinophilic cytoplasm, ovoid nuclei having fine chromatin and an occasional conspicuous nucleoli. Mitosis is brisk and atypical forms are noted. (H & E, 400X)

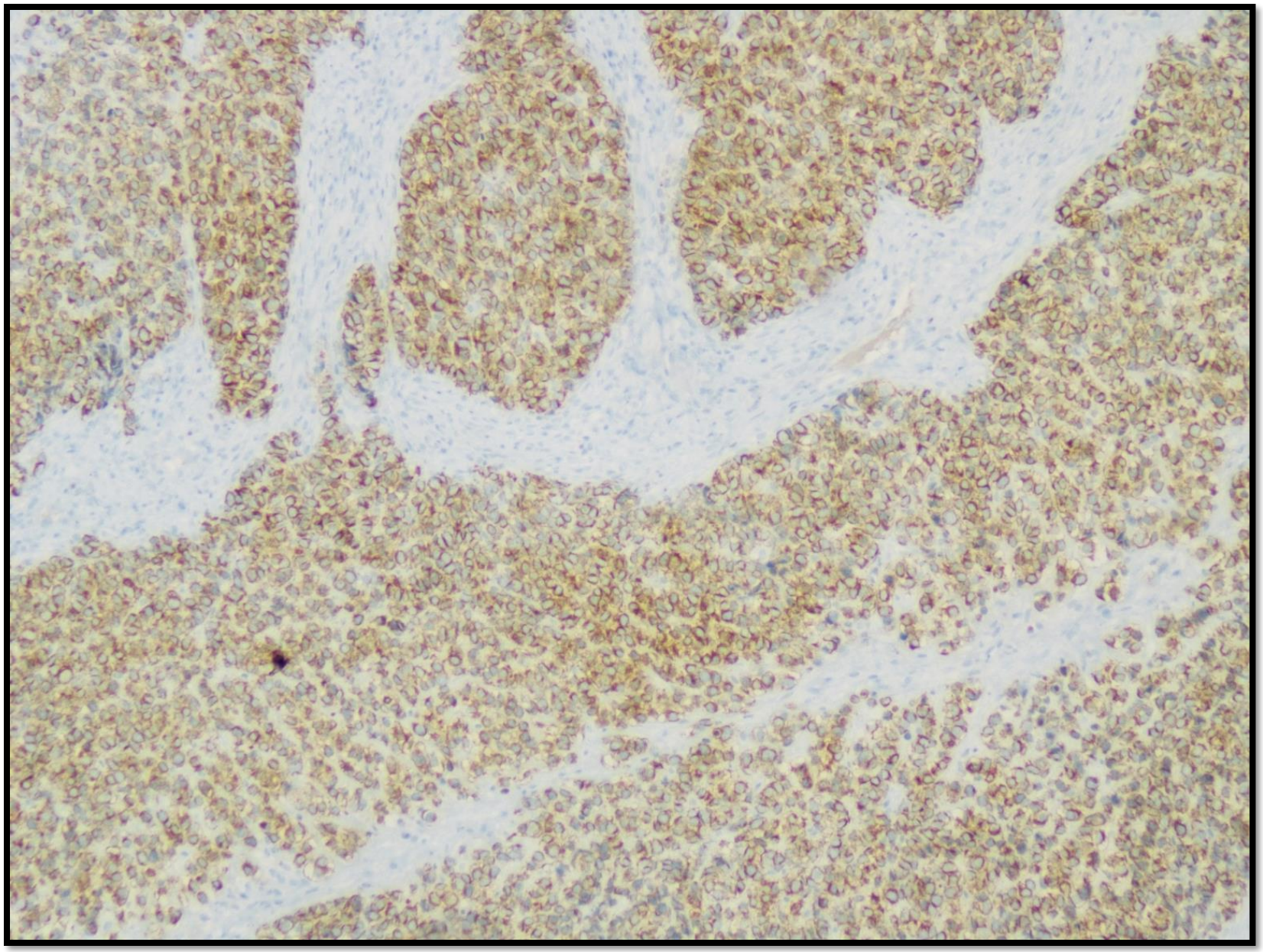
Pathological evaluation (Core needle biopsy)



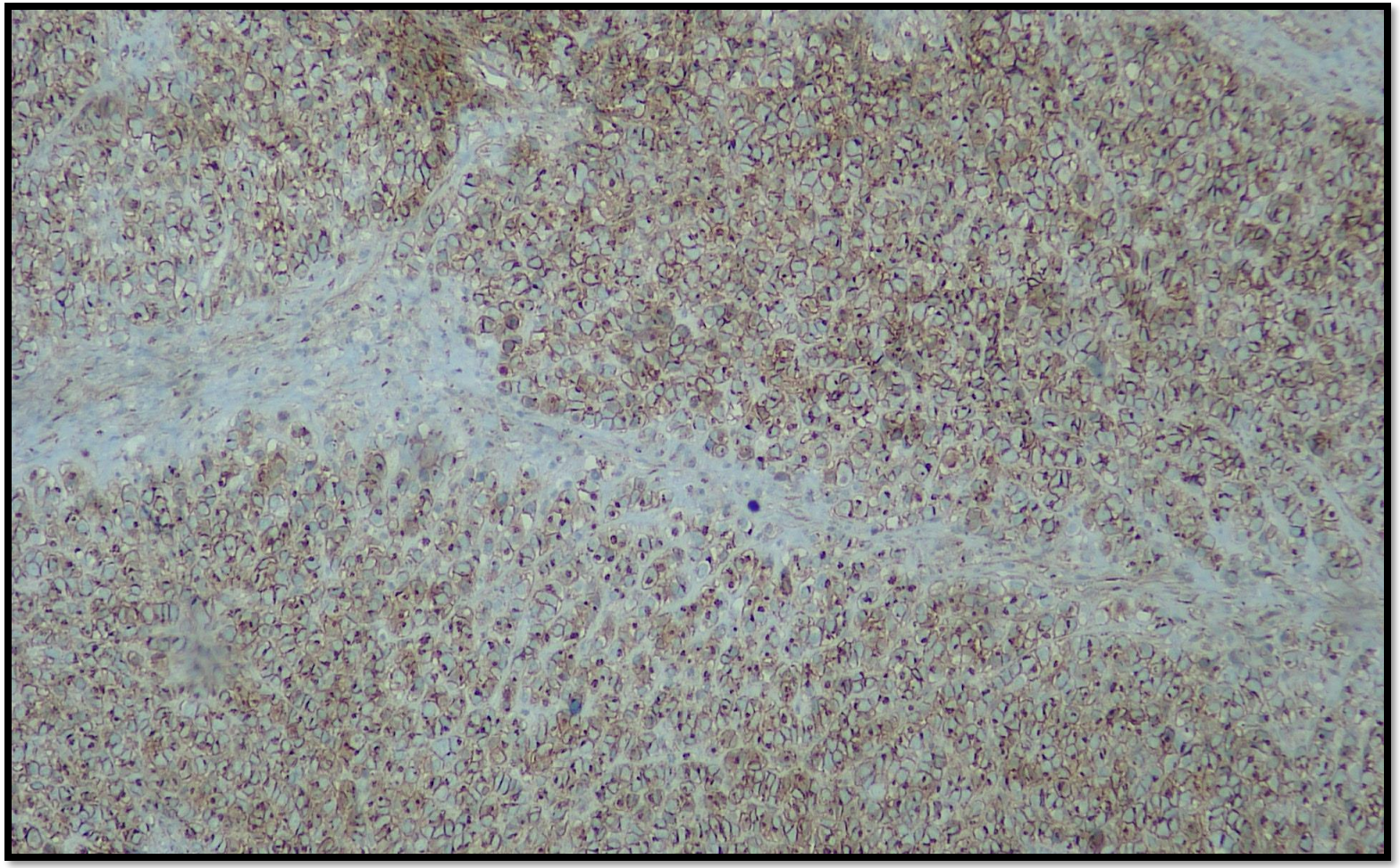
Also identified in the same biopsy was areas with large round cells having abundant clear cytoplasm
(H & E, 200X)



CD99 showed strong membranous staining of the tumor cells (200X)



Diffuse expression of CK was noticed in tumor cells (200X)



Synaptophysin showed diffuse cytoplasmic positivity in tumor cells (200X)

Diagnosis

- On subsequent IHC:
  - CK7, CK20, LCA, Chromogranin, TTF-1, p40, p63, GATA-3, PAX-8 – all were negative in tumor cells
  - NKX2.2 and SATB2 were also negative in tumor cells
- Keeping in mind the clinicoradiological features, histomorphology and immuohistochemical features were suggestive of **Ewing's sarcoma/ small round cell undifferentiated sarcoma.**
- EWSR1-FLI1 break apart FISH studies were advised.

FISH – break apart DNA probe analysis

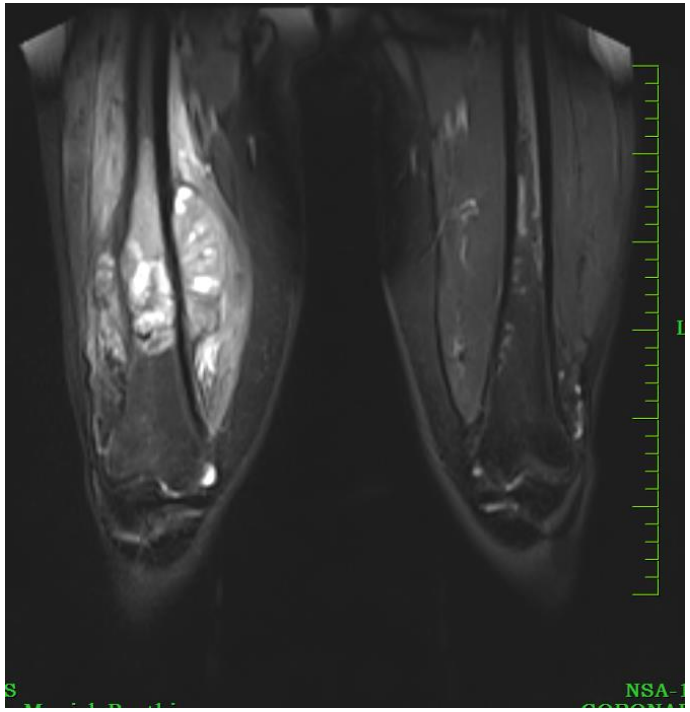
- EWSR1 Gene Rearrangement signal was not detected in cells.

Management

- Bone marrow aspirate and biopsy were done for staging, however, revealed cellular reactive marrow with no evidence of infiltration.
- Thereafter, patient underwent four cycles of chemotherapy
- After four cycles of chemotherapy, MRI and PET-CT were done for response evaluation.

MRI - Post NACT

Coronal STIR sequence



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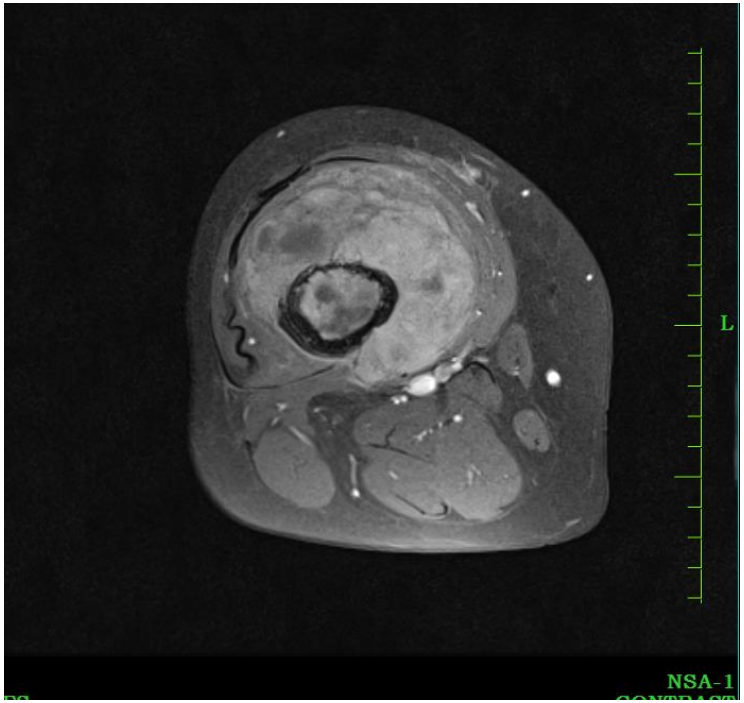
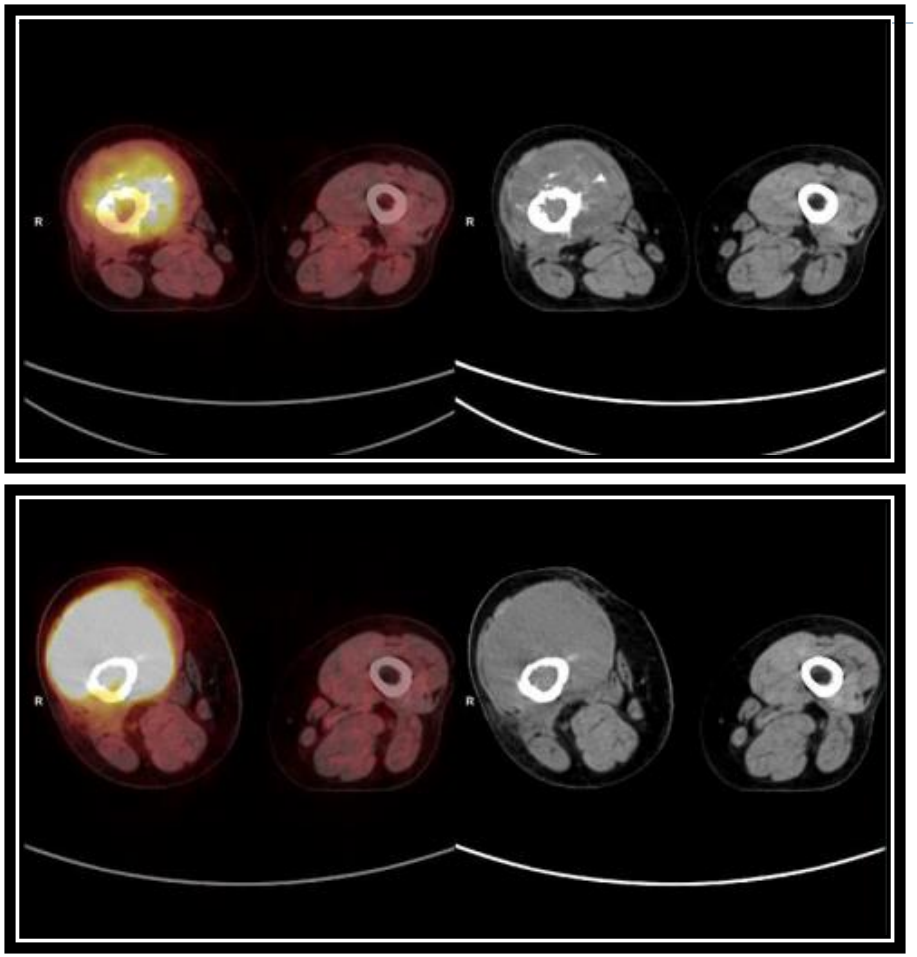


No significant response seen after 4 cycles of Chemotherapy.
Residual heterogeneously enhancing lesion with associated circumferential soft tissue component, CC-11cm. Necrotic and cystic areas identified.

PET-CT – Pre & Post NACT

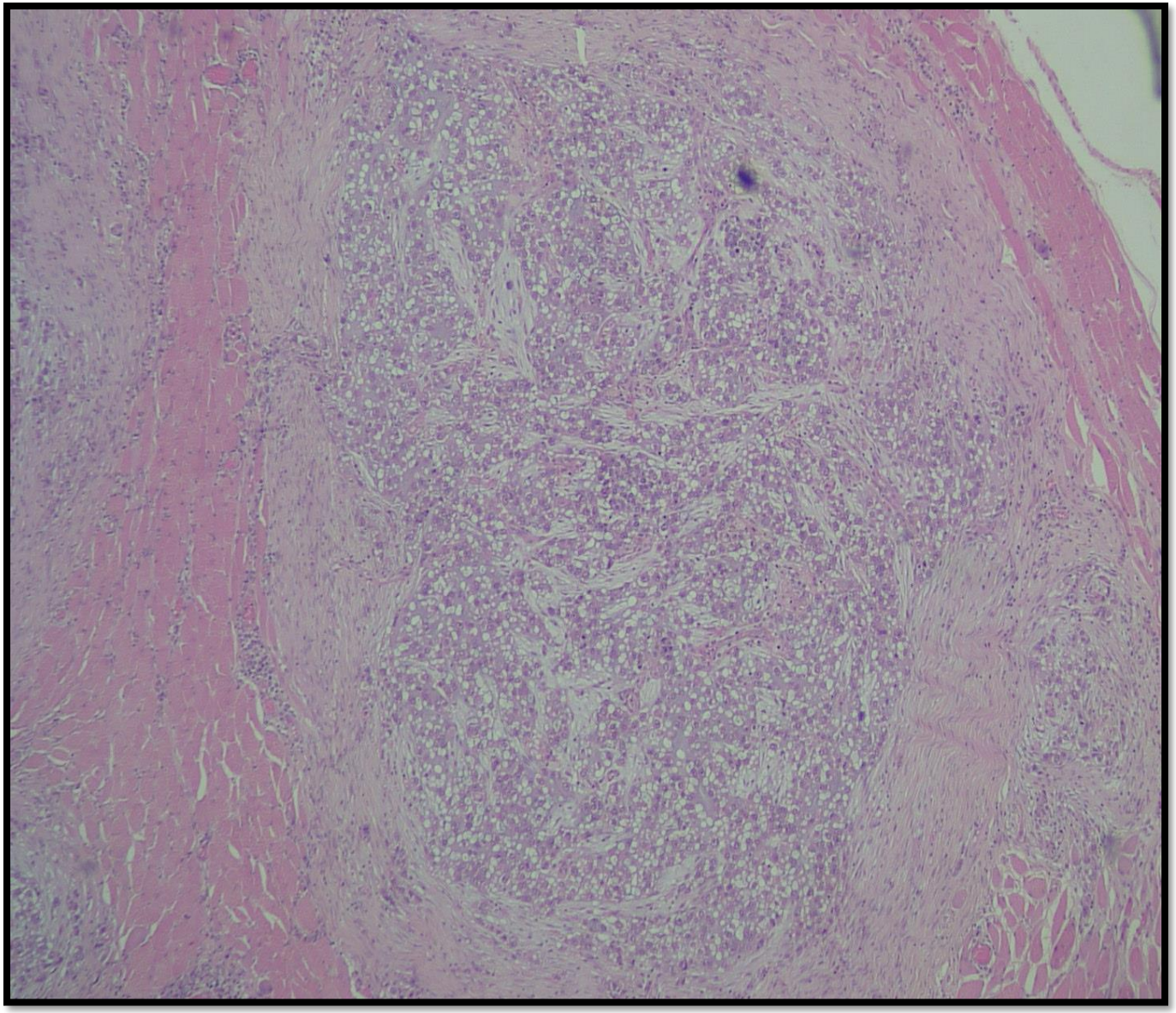


PET CT study dated January, 2018 (top row), right femur lesion showed mild decrease in extent and metabolic activity in comparison to the previous PET CT done in Oct. 2017(bottom row), suggestive of partial response.

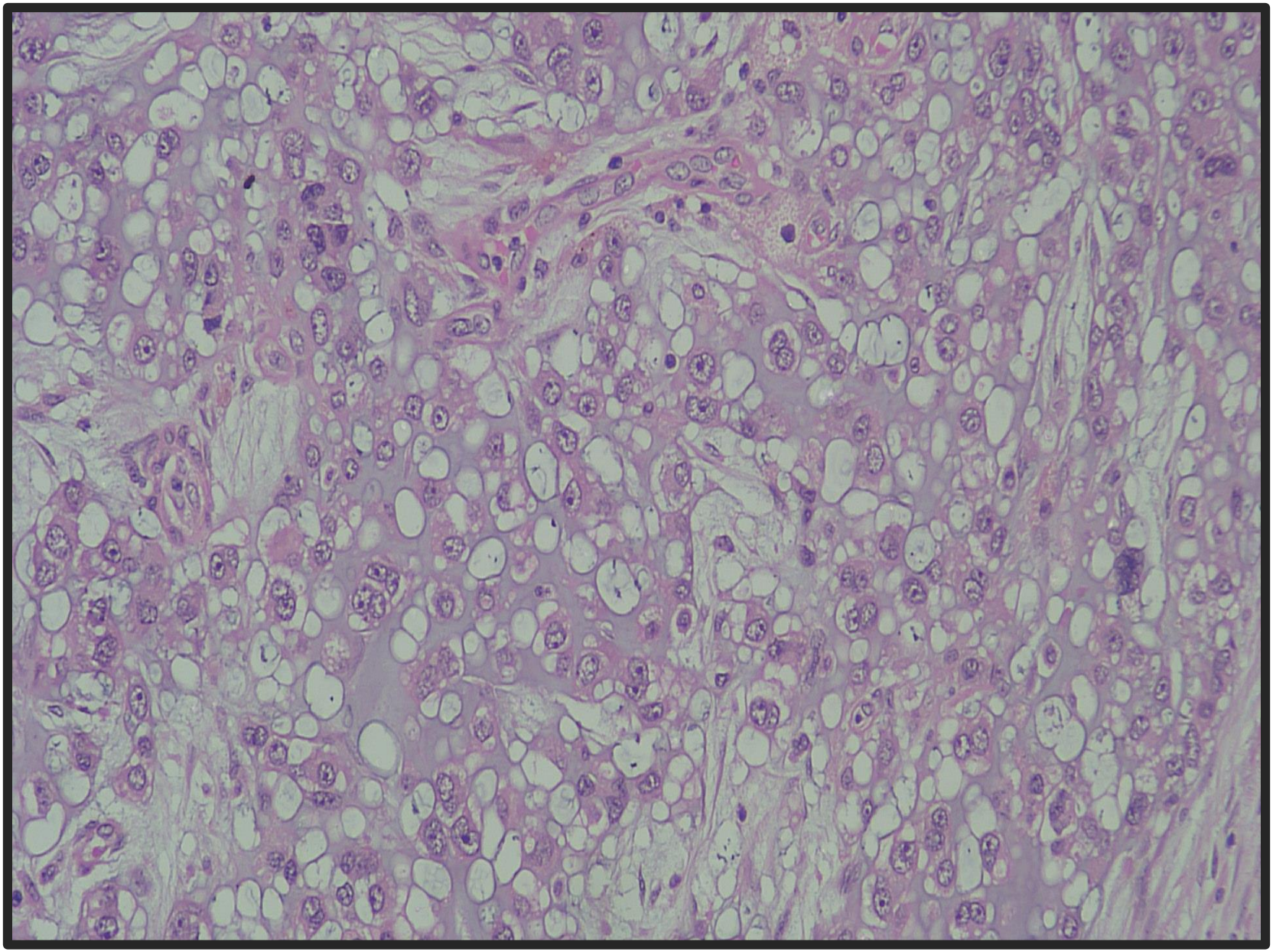
Pathological evaluation

Resected Specimen Right Distal Femur – Post Nact

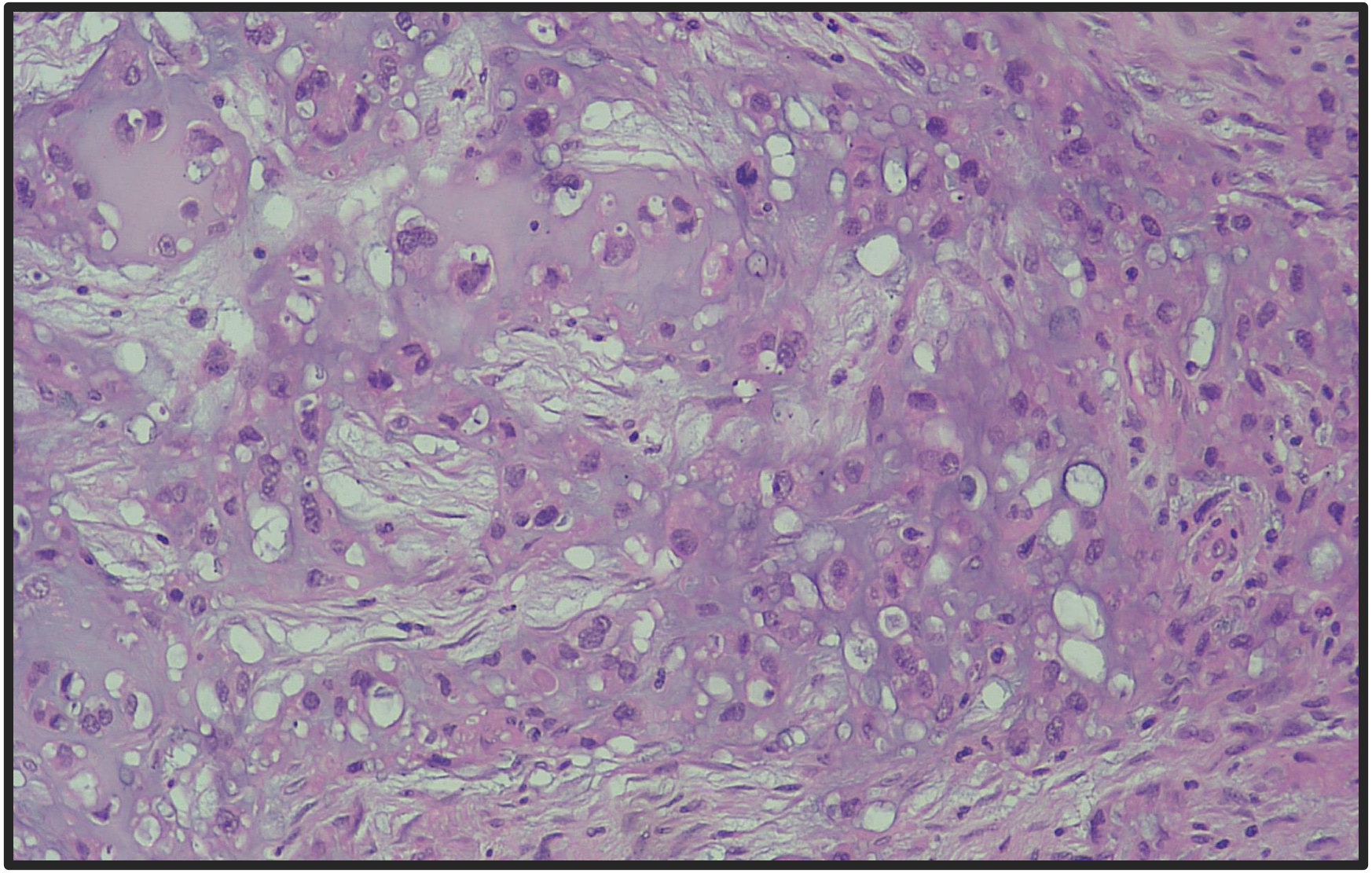
A gray-white variegated, glistening tumor measuring 16 x 10 x 6.5 cm involving the diaphysis and metaphysis, cortical and medullary cavity with significant soft tissue extension.



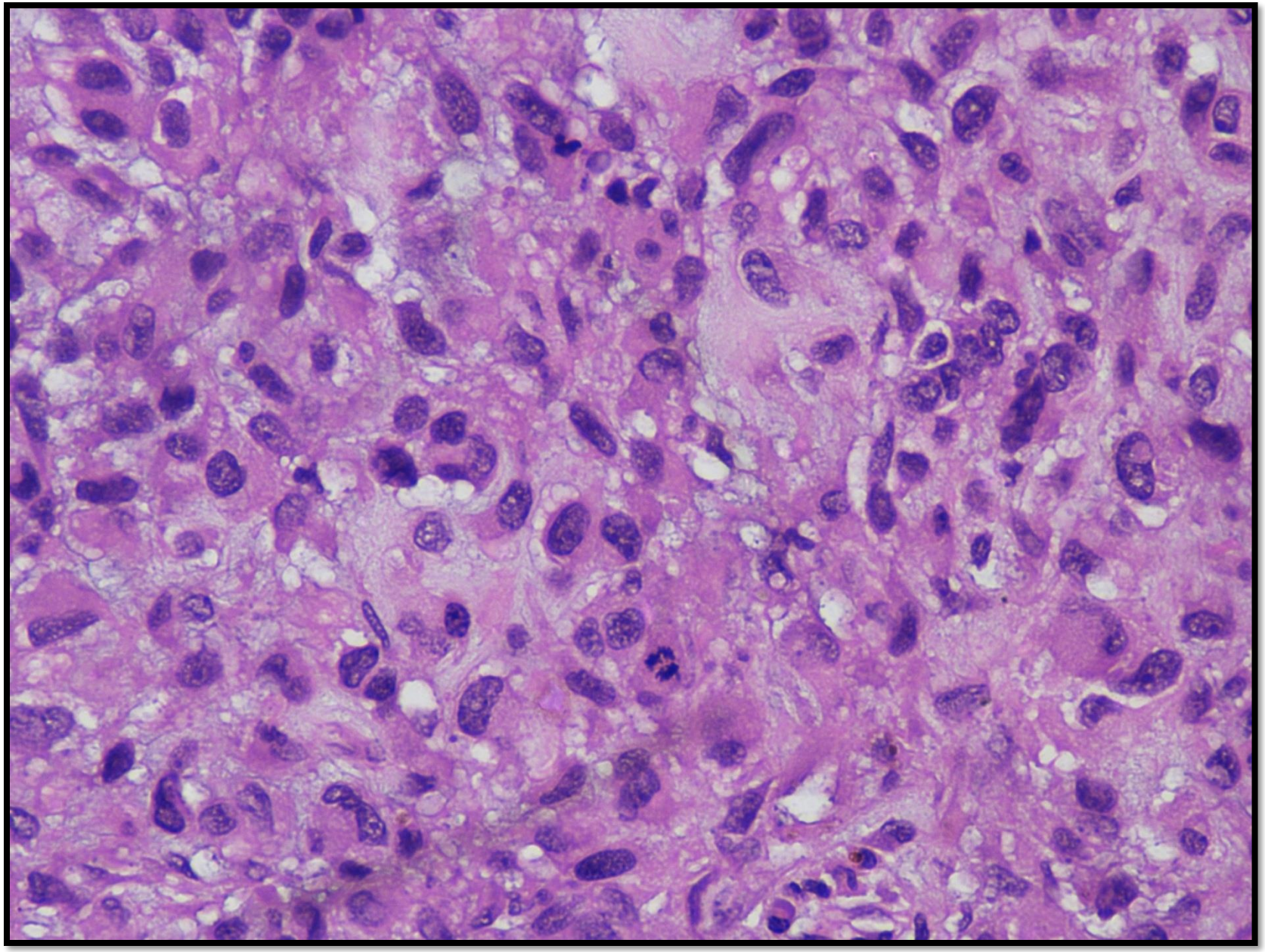
Lobulated tumor nests showing clear cells and conventional chondrosarcoma (H & E, 200X)



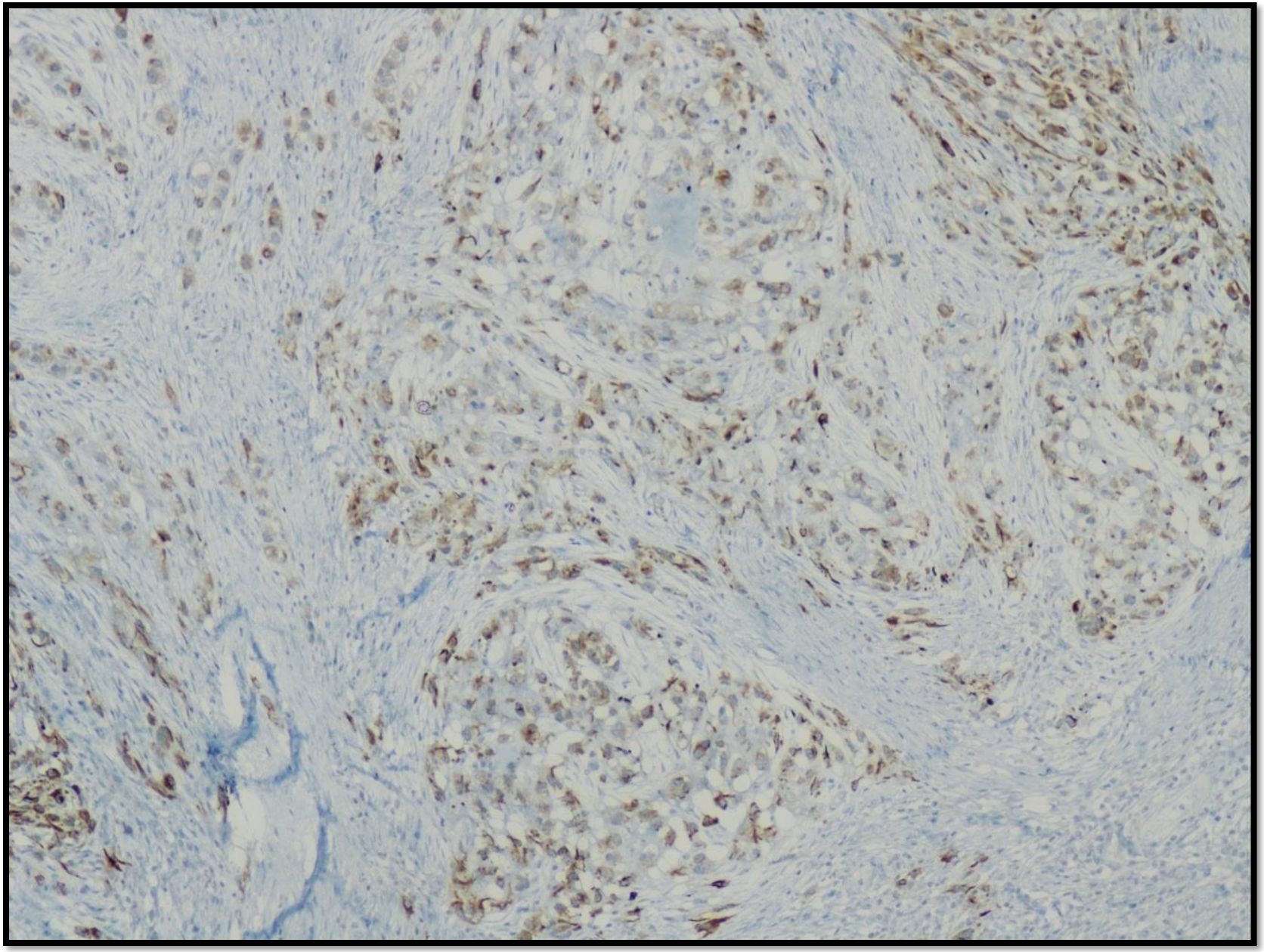
Sheets of clear cells with abundant pale eosinophilic to clear cytoplasm
(H & E, 400X)



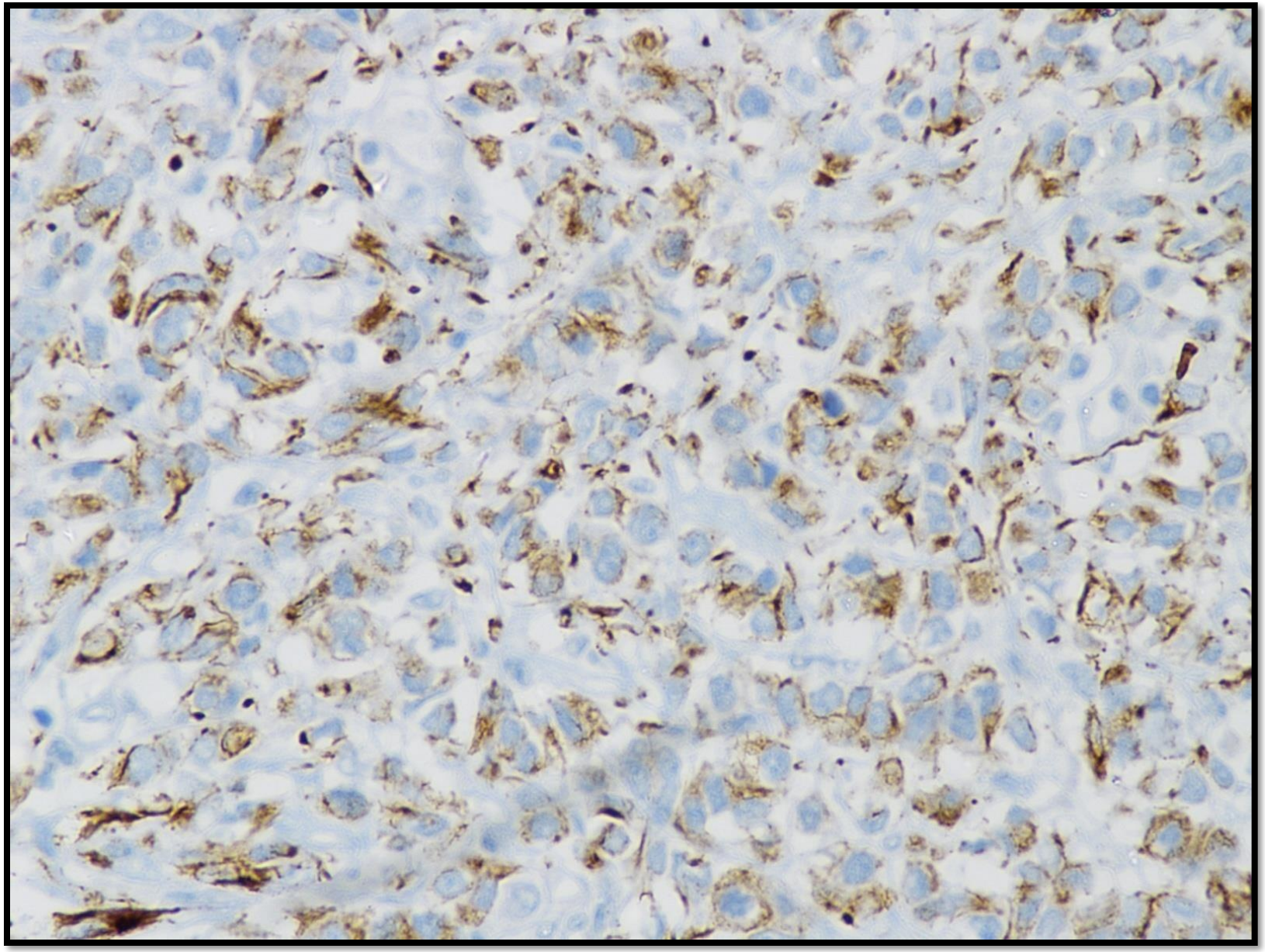
Zones of conventional chondrosarcoma with hyaline cartilage(H & E, 400X)



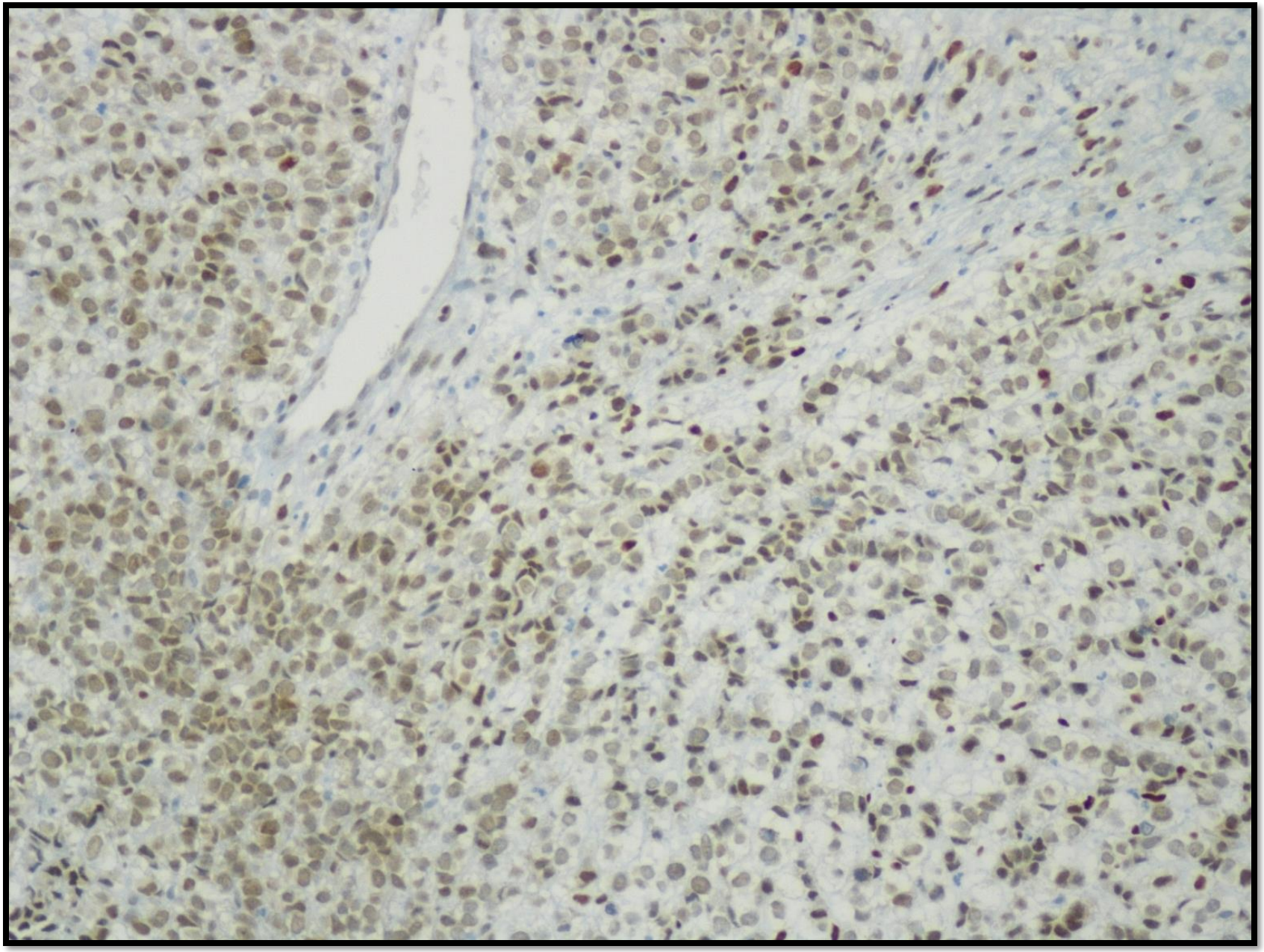
Areas of high grade spindle cell sarcoma were juxtaposed to chondrosarcoma areas, suggestive of dedifferentiation (H & E, 400X)



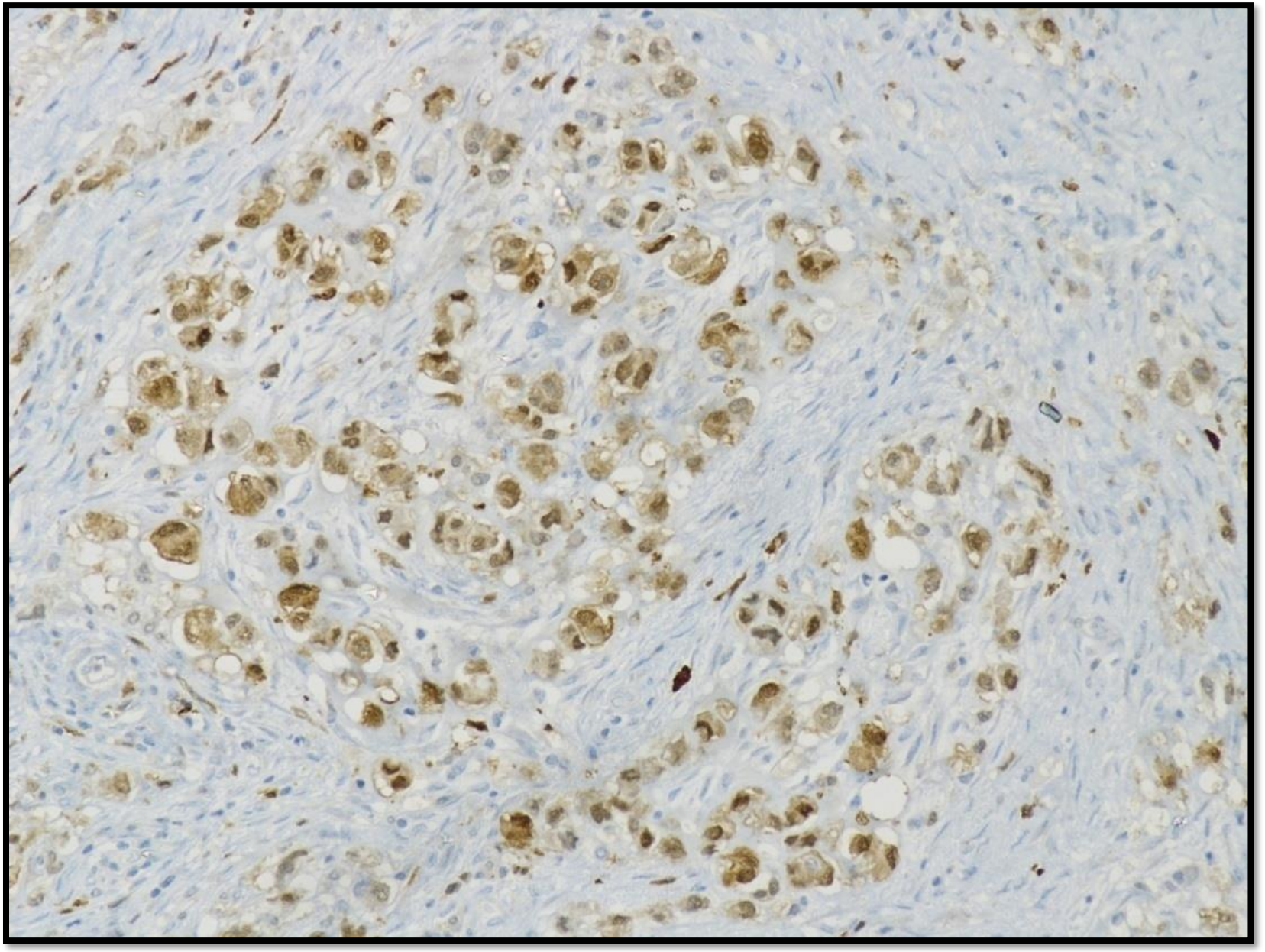
Cytokeratin showed strong and diffuse cytoplasmic positivity in chondrosarcoma areas (200X)



- Cytokeratin positivity was noted in dedifferentiated areas also (400X)



S-100 showed strong and diffuse nuclear staining of the tumor cells (200X)



Tumor cells were diffusely positive for Synaptophysin (400X)

Summarizing the IHC findings

POSITIVE

- S-100
- CK
- Synaptophysin
- CD99

NEGATIVE

- CK7
- CK20
- LCA
- Chromogranin
- TTF-1, p40, p63, GATA-3, PAX-8
- IDH1

Final Diagnosis

- Based on clinicoradiological ,histopathological picture ,and IHC findings a diagnosis of clear cell chondrosarcoma with areas of dedifferentiation was made
- Final diagnosis - DEDIFFERENTIATED CHONDROSARCOMA
- Moreover, the response to chemotherapy was minimal(4%) in the form of necrosis and fibrosis.

Discussion

- CLEAR CELL CHONDROSARCOMA (CCS)is a very rare low-grade malignant bone tumor that accounts for less than 2% of all cases of chondrosarcoma.
- The main diagnostic challenge in CCS is that it typically presents with nonspecific symptoms and the radiographic findings.
- The majority of CCS cases are characterized by a protracted clinical course with a low rate of recurrence and delayed metastasis. Rare cases of CCS behave in an aggressive fashion and require close monitoring
- Tumor characteristics found to correlate with aggressive behavior include tumor location (proximal humerus)and poor tumor differentiation on histopathology

Discussion

- Dedifferentiation is seen in 11% of all chondrosarcomas. Dedifferentiation in clear cell chondrosarcomas is reported in 3 cases uptil now

- This is a case report of dedifferentiated chondrosarcoma with aberrant diffuse positivity for CK in both chondrosarcomatous and dedifferentiated areas

- Dedifferentiated chondrosarcomas- characterized by bimorphic histological appearance with distinct and abrubtly separated areas of low grade chondrosarcomas (grade I –grade II) juxtaposed to a high grade, non-cartilaginous, undifferentiated sarcoma

- Dedifferentiated component can be osteosarcoma, high grade angiosarcoma, leiomyosarcoma, rhabdomyosarcoma and giant cell rich tumors

Discussion

- The undifferentiated area if sampled on a core biopsy can resemble an undifferentiated round cell sarcoma/Ewing's sarcoma
- Moreover, immunohistochemistry can also overlap as seen in the present case
- On IHC, dedifferentiated chondrosarcomas are positive for S-100 and IDH1 (<20%). CD99 is a non-specific marker and can be positive in chondrosarcomas
- Non cartilaginous component of dedifferentiated chondrosarcoma – immunophenotype is according to the histological line of differentiation
- Myogenic differentiation with positivity for SMA and desmin has been seen in few cases in the literature

Discussion

- This case showed diffuse and strong expression of Cytokeratin in both chondrosarcomatous and spindle cell areas.
- Cytokeratin expression in chondrosarcomas has been described in few case reports in literature.
- An aberrant expression of cytokeratin can be seen in primary bone tumors and should not be misinterpreted as metastatic carcinoma.
- Cytokeratin is positive in bone tumors which frequently have epithelioid areas like epithelioid variant of osteosarcoma, Ewings sarcoma, osteofibrous dysplasia and adamantinomas
- Chondroid bone tumors which show cytokeratin expression are chordoma, chondroblastoma and clear cell chondrosarcoma while not seen in conventional chondrosarcoma

Discussion

- Approximately 8% of chondrosarcomas have been reported to stain with EMA and CK.
- To the best of our knowledge, single case of dedifferentiated chondrosarcoma with cytokeratin positivity in fibrosarcoma like area has been described in literature.
- Distinction from epithelial malignancies like renal cell carcinoma and carcinomas with mucinous differentiation is important, especially in chondroid bone tumors like clear cell chondrosarcoma.
- CEA and lineage specific markers can help in the distinction from epithelial malignancy

Conclusion

- An extensive IHC marker panel should be employed when dealing with bone tumors keeping in mind the rare diagnosis and aberrant expression.
- Clinicoradiological correlation must be coupled with pathological examination to arrive at a correct diagnosis.
- Aberrant cytokeratin expression can be seen in bone tumors and also in chondroid bone tumors like clear cell chondrosarcomas.
- Epithelial malignancies should always be ruled out when dealing with sarcomas showing epithelioid or clear cell morphology.
- Other site/lineage specific epithelial markers should be employed to distinguish between two.