Case of the Month January 2021

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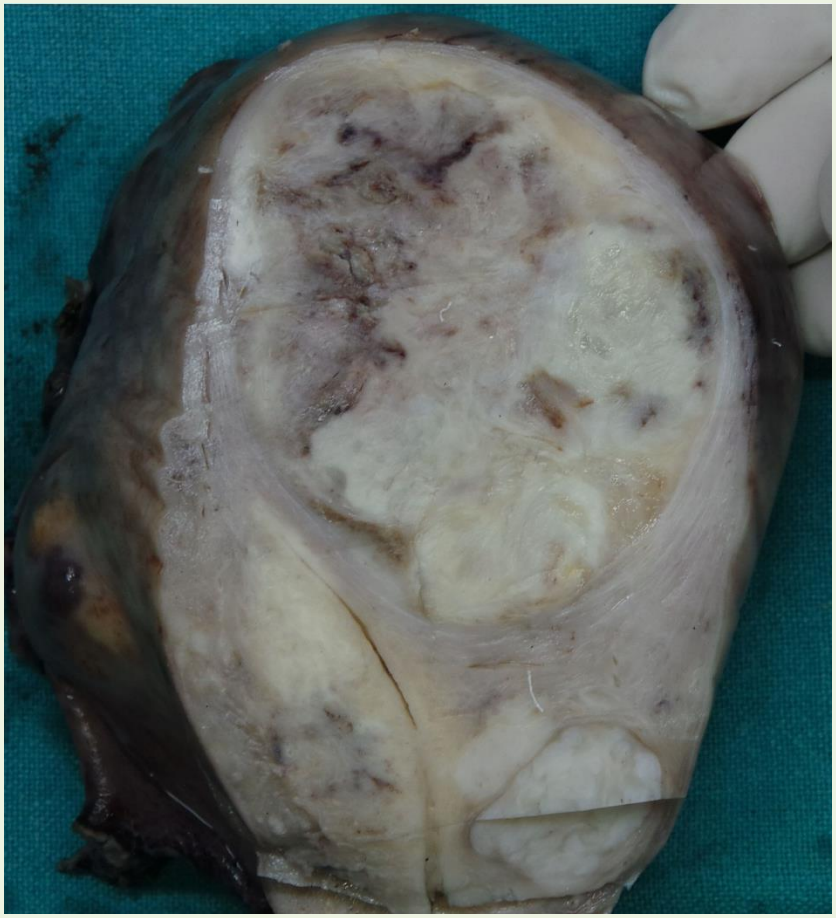
RGCIRC

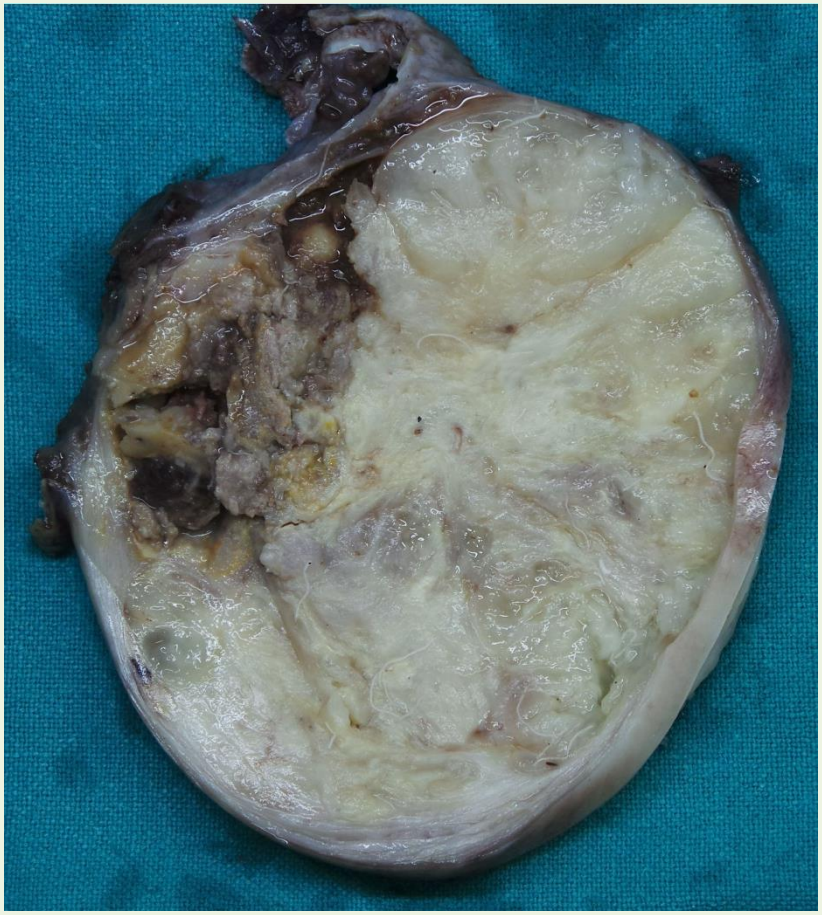
CASE DETAILS

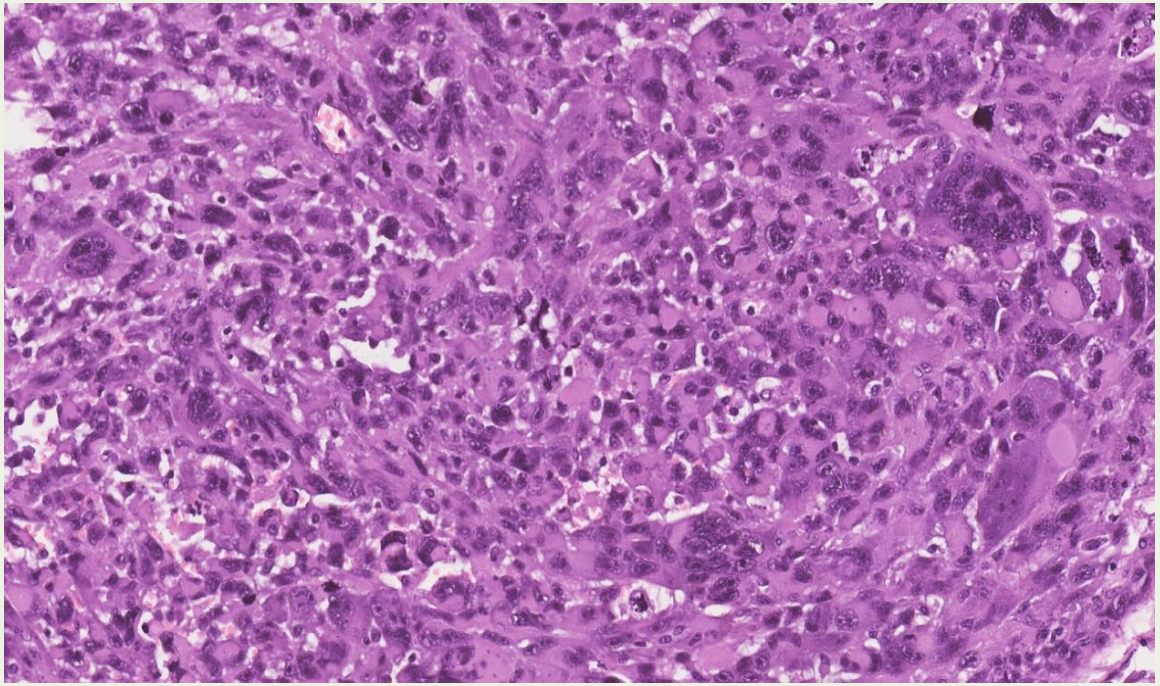
- A 53 year-old-female presented with complaints of pain lower abdomen and bloating from 15-20 days.
- USG and MRI showed bulky uterus (9.8 x 4.7 x 6.1)cm with two intramural fibroids along left lateral wall of uterus measuring 2.6 X 2.2cm and 2.5 x 2.2cm. Endometrial thickness was ~4.9mm,
- Moderate ascites was present with peritoneal nodules and diffuse omental thickening.
- Right adnexa showed a cystic mass (~13.3 x 12 x 12.6cm) indenting posterior surface of uterus and inseparable from uterus.
- Left ovary is normal ~2 x 1.4cm.
- No lympadenopathy
- CA 125: 369.0U/ML

Underwent Radical Hysterectomy

- On gross examination, uterus showed a large intramural tumor measuring 11.5 x 11.5 x 9cm, in the fundus region. Cut surface showed solid, grey-white tumor with focal yellowish areas.
- An intramural fibroid measuring 2.5 x 2.2 x 1.5cm is also noted, separate from the tumor.
- Right ovary measures 3.5 x 1.5 x 1cm, with intact capsule, and left ovary measures 3.8 x 2.2 x 0.8cm with intact capsule intact



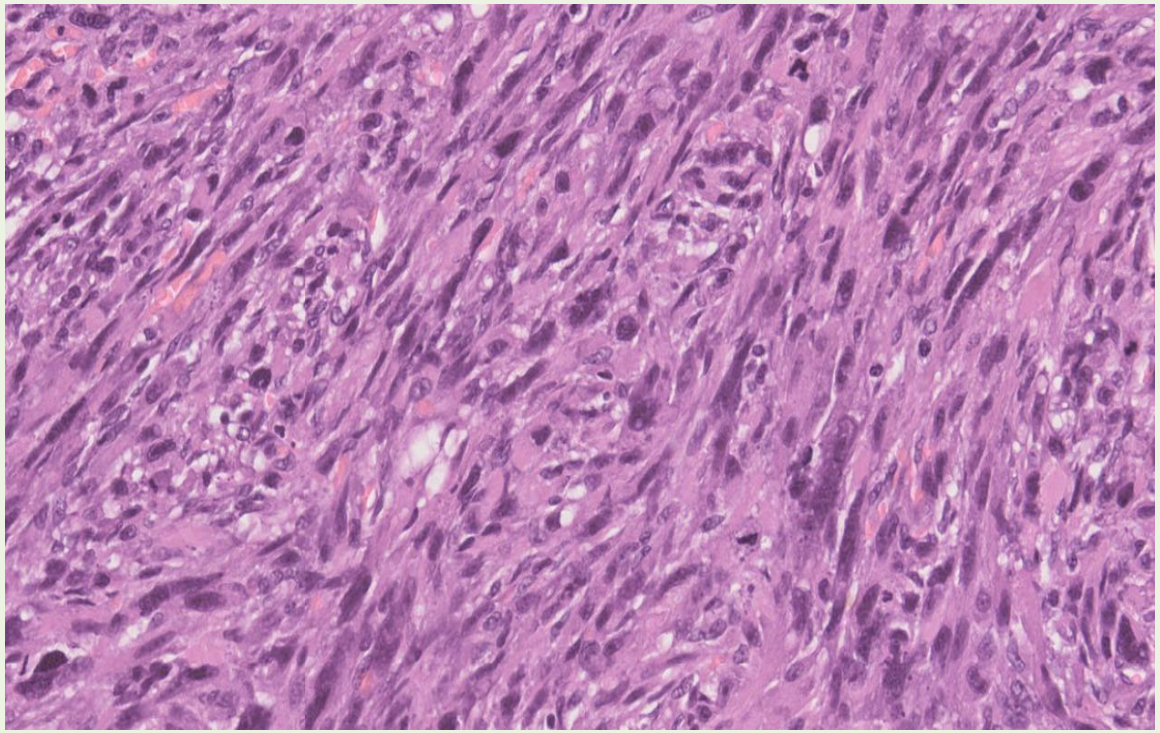


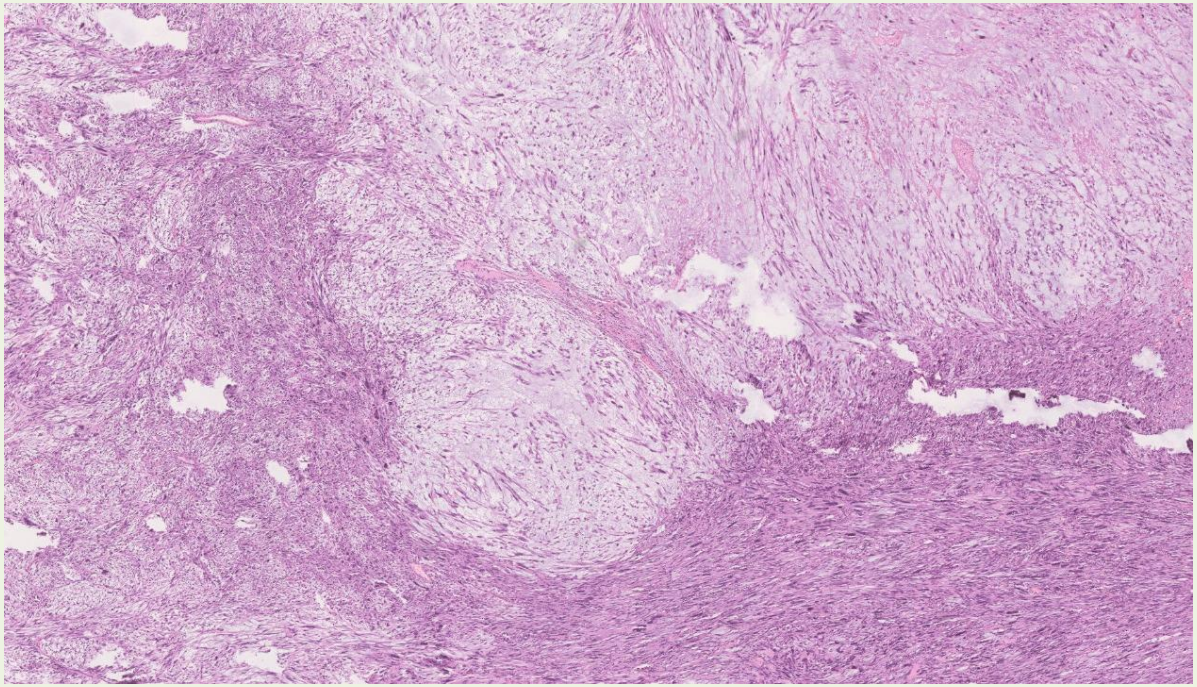


Microscopic Examination

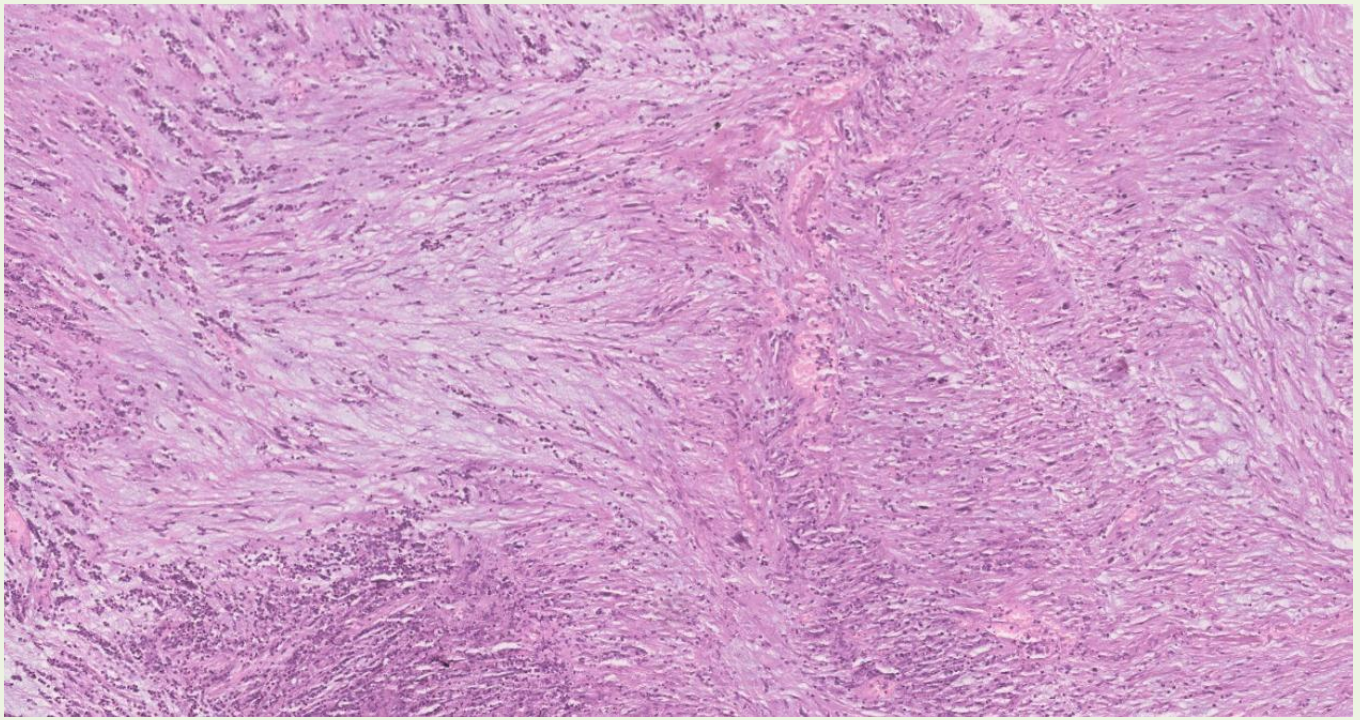
<u>Sections from tumor mass in uterus</u>
Tumor cells arranged in sheets and fascicles

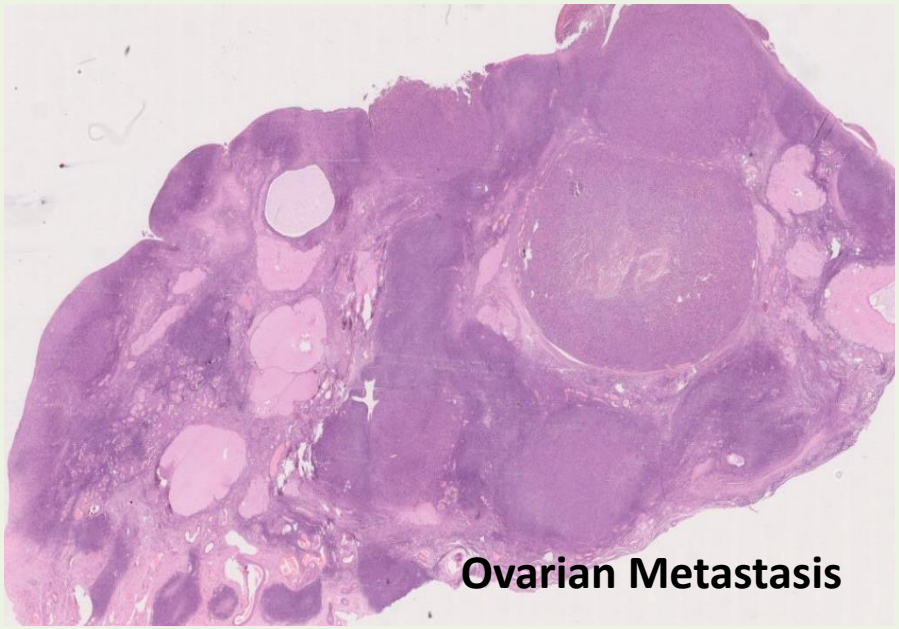
- predominantly epithelioid with spindle cell areas
- round to oval shaped plump nuclei exhibiting marked pleomorphism, prominent nucleoli & eosinophilic cytoplasm.
- Many bizzare and multinucleated tumor giant cells seen.
- Many cells show rhabdoid morphology.
- Frequent mitotic activity seen including atypical forms.

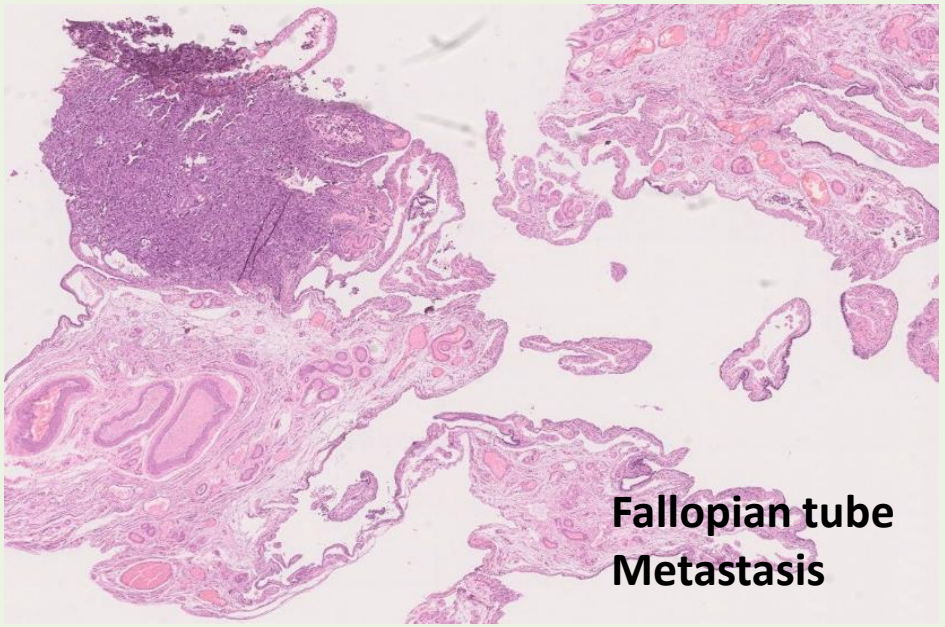


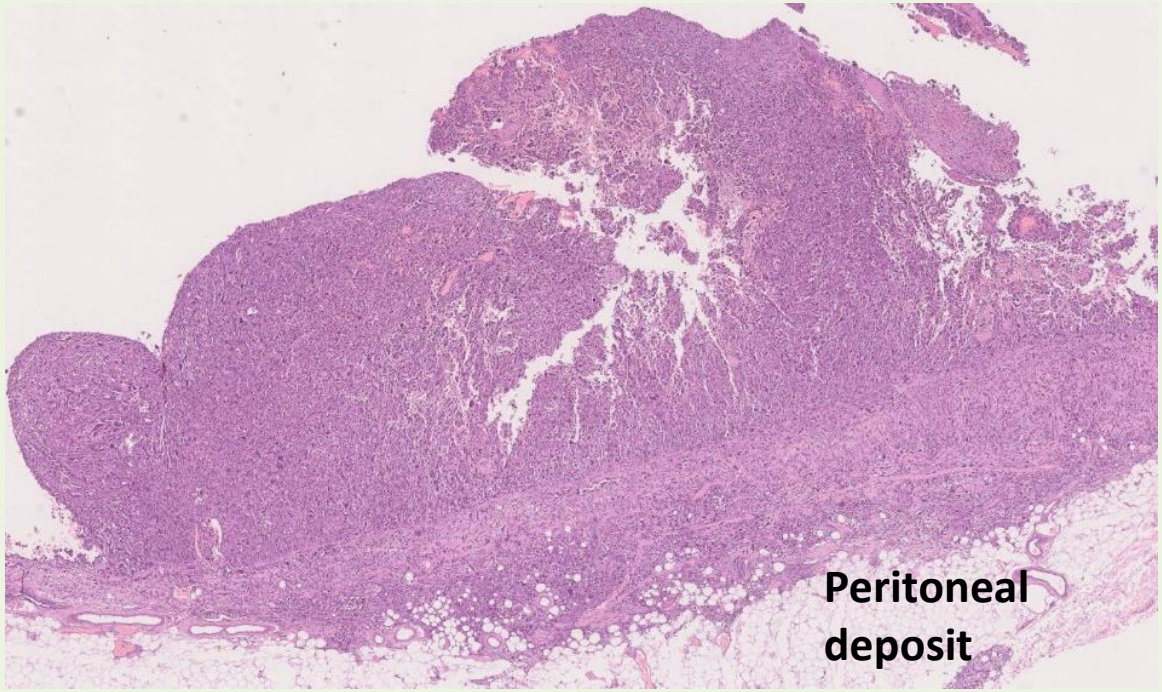


- Uterine tumor also showed spindle cell areas in a myxoid background




Ovarian Metastasis


Fallopian tube
Metastasis


Peritoneal
deposit

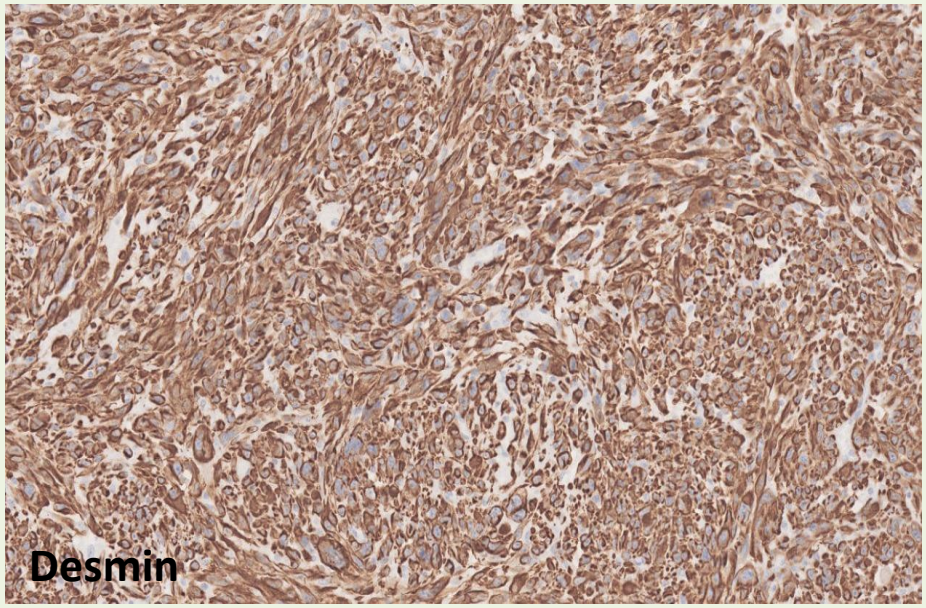
- **Lymphovascular invasion :** present, extensive
- Endometrium : atrophic, free of tumor
- Myometrium :
  - intramural leiomyoma present
  - multiple lymphovascular emboli identified

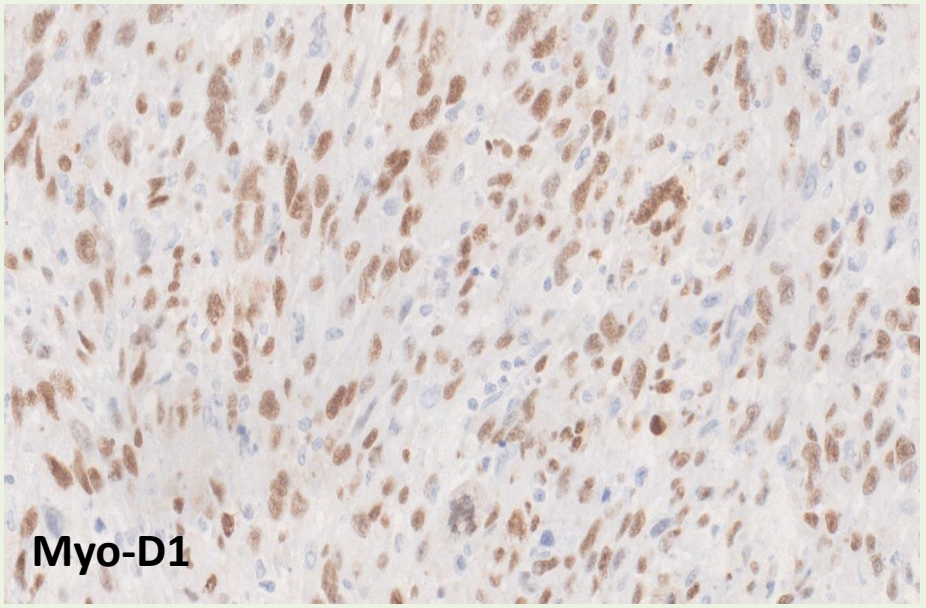
- Tumor involves:
  - Bilateral ovaries
  - Bilateral fallopian tubes
  - Bilateral parametrium
  - Omentum
  - Pelvic deposit, Bladder peritoneum , POD deposit
  - Deposits on sigmoid mesentery
  - Bilateral pelvic lymphnode metastasis with extranodal extension
  - Multiple peritoneal and mesenteric deposits
  - Appendiceal serosa & subserosal deposits

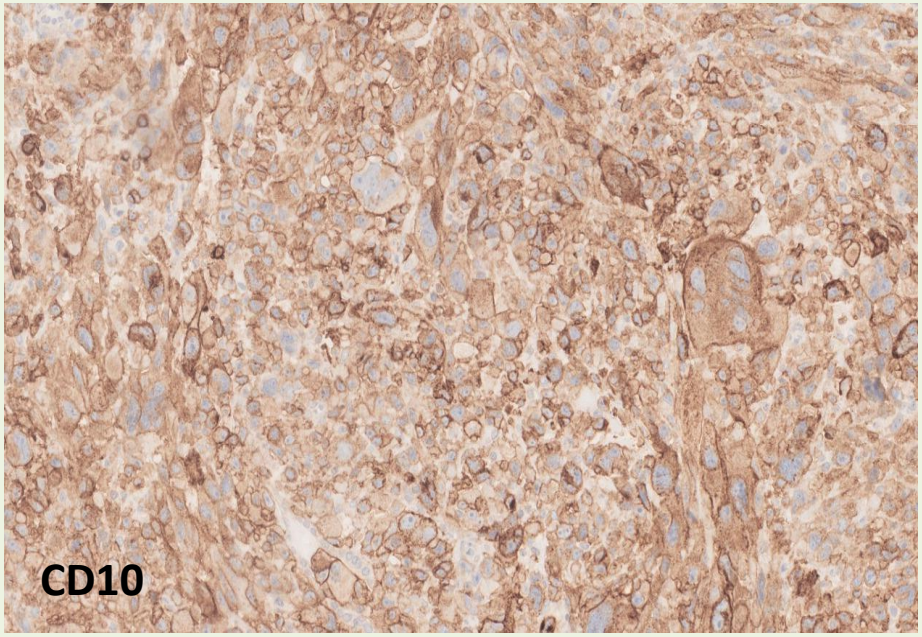
Immunohistochemistry

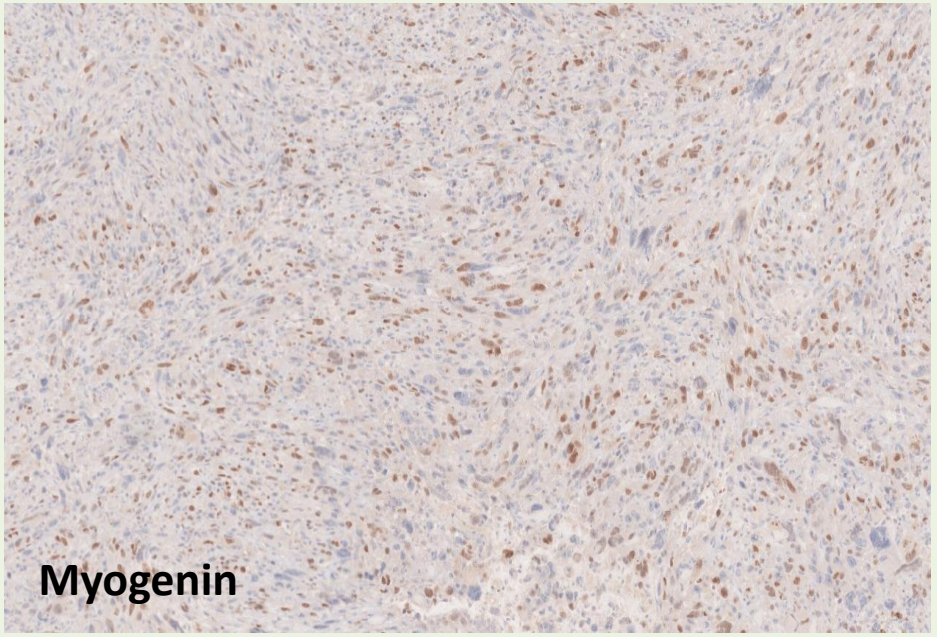
- Tumor cells are difusely positive for Desmin, Myo-D1, Myogenin, and CD10
- SMA is focal
- IHC for CK, S-100, SMMH, and PAX-8 is neagtive
- Cyclin-d1 expression seen in scattered cells

Immunohistochemistry









Final Opinion

- **Pleomorphic Rhabdomyosarcoma Uterus with metastatic involvement of bilateral ovaries, fallopian tubes, omentum and other peritoneal deposits**

  Pstage: pT3bN1
- Post operative PET CT:
  - Metabolically active peritoneal disease, lymphadenopathy, bilateral lung nodules, vault lesion, ascites and right minimal right pleural effusion
- Treatment: started on single agent IFOS

Discussion

- Rhabdomyosarcoma (RMS) is a malignant tumor that originates from mesenchymal tissues. [1]
- It constitutes 3% of all soft tissue sarcomas
- RMS is a relatively common soft tissue sarcoma among children and adolescents, nearly 50% of all pediatric soft tissue tumors. [1,2,3]
- RMS occurs rarely in adults, as it accounts for just 2–5% of all adult sarcoma cases. [1]
- It is an aggressive mesenchymal tumor [4]

- RMS can originate anywhere in the body; however, the head and neck region is the most frequent site of RMS involvement in children. [1,3]
- Rhabdomyosarcomas may arise from a wide variety of locations. [1,5]
  - extremity
  - axial tumors (most commonly from the head and neck -orbital tumors, the paraspinal region, and the genitourinary system)
  - other abdominal (retroperitoneum, abdominal wall) and thoracic (chest wall) sites of origin occur.
  - rarely, intracranial meningeal tumors
  - Rarely in Genitourinary tract lesions : urinary bladder, prostate, perineum, vagina, cervix, uterus, and paratesticular soft tissues.

- RMS share a propensity to undergo myogenesis, a well-defined biologic process that primarily occurs during embryonal and fetal development[2]
- The exact origin of extramyogenous RMS is more problematic, because myogenic transformation can be induced in non-muscle cells by genetic manipulation and might be reproduced via tumorigenic influences[2]

- RMS possess a variety of histologies, with three main types: alveolar, pleomorphic and embryonal. [2]
  - Embryonal RMS is most common in infants and young children [1,2].
  - Adolescents and young adults tend to have alveolar RMS[2]
  - Older adults tend to have pleomorphic RMS[1,2]
- It is crucially vital to correctly differentiate between the three histopathological types of RMS as they hold substantial variances in biological behavior and prognosis. [3]

- RMS is rare and unusual in adults [4]
  - generally have tumors with pleomorphic, high-grade cytologic features and differing biologic characteristics[2]
  - accounting for less than 4% of all soft tissue sarcomas in adults, and 1% of all malignancies generally.
  - Deep soft tissue of limbs is the most frequent site of involvement in adult RMS. [3,4]
- **Adult RMS involving the genitourinary system** is exceedingly rare.
- Particularly, **primary RMS of the uterine cavity is exceptionally scarce** with roughly less than 35 reported cases in the English literature. [3]

Uterine RMS

- Most uterine sarcomas fall into the category of leiomyosarcoma, endometrial stromal sarcoma, or undifferentiated sarcoma [6]
- **Pure rhabdomyosarcomas are extremely rare,** although a rhabdomyosarcomatous element may be present as a component of an adenosarcoma or carcinosarcoma (malignant mixed müllerian tumor)[6]
- Histopathological examination in addition to immunohistochemistry and cytogenetic studies aid in definitive diagnosis [4]

Uterine RMS

- Most frequent histopathological type is pleomorphic RMS (60%-70%) and correlates with poor prognosis.
- Embryonal RMS accounts for 30%-40% of all uterine RMSs [3]
- Alveolar RMS is the least common (less than 5%), characterized genetically by FOXO1 chromosomal rearrangements and associated with unfavorable prognosis.

- A study of 8 cases of uterine RMS [4]
  - 4 pleomorphic, 2 alveolar, and 2 embryonal RMS.
  - Age ranged from 22 to 70 years
  - Most common presenting symptom was vaginal bleeding
  - Most presented with advanced stage at diagnosis, including metastatic disease to lymph nodes and to distant sites
  - The masses were mostly (6/8) centered in the myometrium, while two cases arose in the cervix (2/8)

- **Pleomorphic RMS**
  - is a high-grade pleomorphic sarcoma
  - usually seen in adults, most common in the 6th to 7th decades of life (mean age ~72 years)
  - M:F=1.8:1
  - composed of bizarre brightly eosinophilic polygonal, round, and spindle cells displaying skeletal muscle differentiation

- **Pathogenesis of pleomorphic RMS**
  - Complex karyotypes
    - Numerical and unbalanced structural changes
  - Genome wide survey
    - Recurrent loss of DNA, gains and amplification

Histopathological Examination

MICROSCOPY

- Rhabdomyoblast is the a cell with an eccentric round nucleus and variable amounts of brightly eosinophilic cytoplasm. They can be like strap and tadpoles.
- Occasional tumors (less than 30%) contain terminally differentiated myoblasts with cross striation
- Sheets of large, atypical, and frequently multinucleated polygonal, spindled, or rhabdoid cells with eosinophilic cytoplasm

IMMUNOHISTOCHEMISTRY

- Desmin +
- Myogenin +
- MyoD-1 +(myogenic determination factor)
  - both show excellent specificity and sensitivity

CD10 expression in RMS

- In a study on primary uterine sarcomas including MMMT, mullerian adenosarcoma, uterine sarcomas {2 RMS (1 cervical, 1 corporeal), 2 ESS, 2 high-grade LMS, 1 high-grade ESS}.[7]
  - All were positive for CD10, showing moderate to marked staining intensity with varying distribution
- Chu and Arber in a study demonstrated CD10 expression in 60% (3/5) of extrauterine RMS, 50% of liposarcoma, 45% of schwannoma, 28% of epithelioid sarcoma, and 6% of leiomyosarcoma [8]
- This indicates that CD10 expression is not restricted to ESS [7], and might be a common phenotypic characteristic suggesting müllerian derivation of rhabdomyoblastic cells.[8]

Differential diagnosis of Uterine RMS

- Due to the rarity of uterine RMS especially in adults, other common neoplasms should be ruled out. [3]
  - Leiomyosarcoma
  - High-grade endometrial stromal sarcoma
  - Adenosarcoma
  - Carcinosarcoma
- The positive IHC for myogenin and MyoD1 and negative IHC for caldesmon and estrogen receptor can be helpful in confirming the diagnosis of RMS [3]

Prognosis

- Uterine RMS in adults is a biologically aggressive malignancy with dismal prognosis despite the multimodal therapeutic strategies.
  - Median survival 7.3 months
  - Patients with superficial tumor (~20%) have a favourable outcome
  - Metastasis to lungs is common
  - Majority of patients present with extensive disease at time of clinical diagnosis [3]
- Gerber and colleagues examined a total of 148 adult patients with RMS arising from gynecologic and non-gynecologic sites. [65-year overall survival (OS) rates for metastatic and non-metastatic patients were 45% and 26%, respectively.[9]

Treatment

- Data regarding treatment of this rare malignancy is limited, and usually extrapolated from non-uterine sites [4]
  - The optimal therapy of adult patients with RMS of gynecologic origin is not defined.
  - However, aggressive multimodality therapy comprising combination chemotherapy, radiotherapy and surgery, whenever technically feasible, yields better clinical outcomes [3]
- Ferrari and colleagues explored the treatment outcomes in 171 adult patients with RMS originating from various sites. The reported chemotherapy response and five-year OS rates were 85% and 40%, respectively[10]

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