A RARE CASE OF ACUTE ABDOMEN IN AN ADOLESCENT GIRL

DR.VEDANT TANDON

Under the guidance of

- **Dr. Shailaja Mane, HOD Paediatrics**
- **Dr. Sarita Verma, Paediatric Oncologist**
- **Dr. Sanjay Chavan, Professor, Paediatrics**

A ten year old girl, first born child to parents with non-consanguineous marriage came with the following complaints

FEVER
since 3 days, low grade, undocumented not associated with chills or rigors, relieved on taking medication

ABDOMINAL PAIN
since 3 days, generalised pain, severe intensity, non radiating, intermittent in nature, relieved on rest for 5-10 min, associated with abdominal distension which was progressively increasing.

VOMITING
3-4 episodes per day, aggravated by food intake, containing food particles, non billious, non-projectile, non blood tinged, non foul smelling.

No c/o loose stools, cold, cough, seizures, itching, rashes, burning micturition, dark coloured urine, constipation, polyuria, polydipsia.

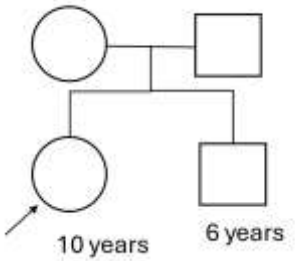
HISTORY

PAST HISTORY

- H/o surgery for Bilateral choanal atresia on Day 1 of life
- H/o strabismus in right eye since 9 months of life.
- H/o hospital admission at 6 years of age for pneumonia and was treated with iv antibiotics for 3-4 days and was discharged on oral medications for 1 week. The child was apparently normal since then.

FAMILY HISTORY

- No history of similar complaints in family.
- There was no history of tuberculosis, cancer, diabetes in family.



DEVELOPMENTAL HISTORY

She was developmentally normal and average in scholastic performance.

BIRTH HISTORY

Born at 34 weeks of gestation, by Normal Vaginal Delivery with birth weight 1.8kg, underwent surgery for bilateral choanal atresia on DoL1 - admitted in NICU for 25 days for the same

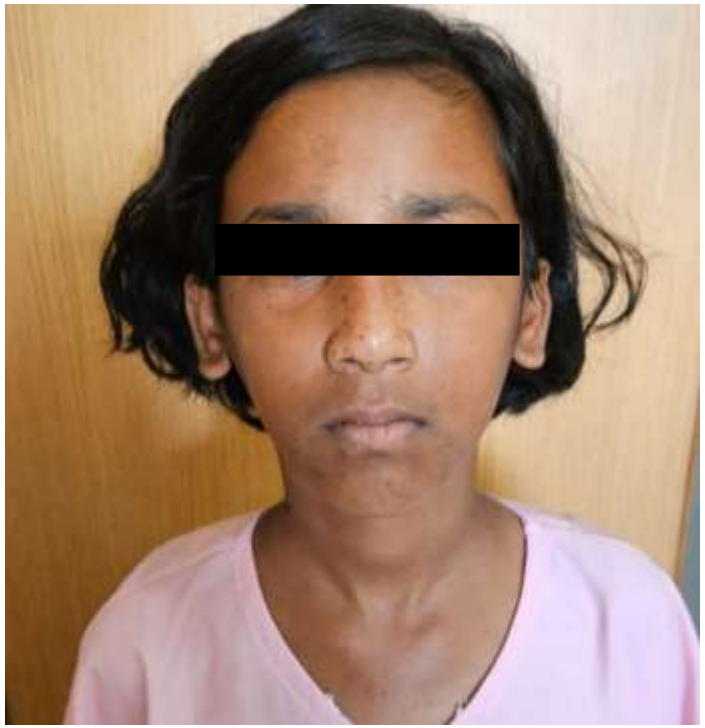
EXAMINATION ON ADMISSION

General Examination

- Temperature-100F
- HR-140/min
- RR -26/min
- sPo2- 98% on Room Air
- Peripheral pulses-low volume
- BP-98/50 (hypotensive)

- Pallor present
- Cyanosis Absent
- Icterus Absent
- Lymphadenopathy- No palpable cervical, axillary and inguinal lymph nodes present. Edema- Absent

- 7 café au lait spots of varying sizes from 5mm to 7 cm all over her body.
- Hairy Nevus present over sacral area.
- Right convergent strabismus.
- No other Neurocutaneous markers present.



Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

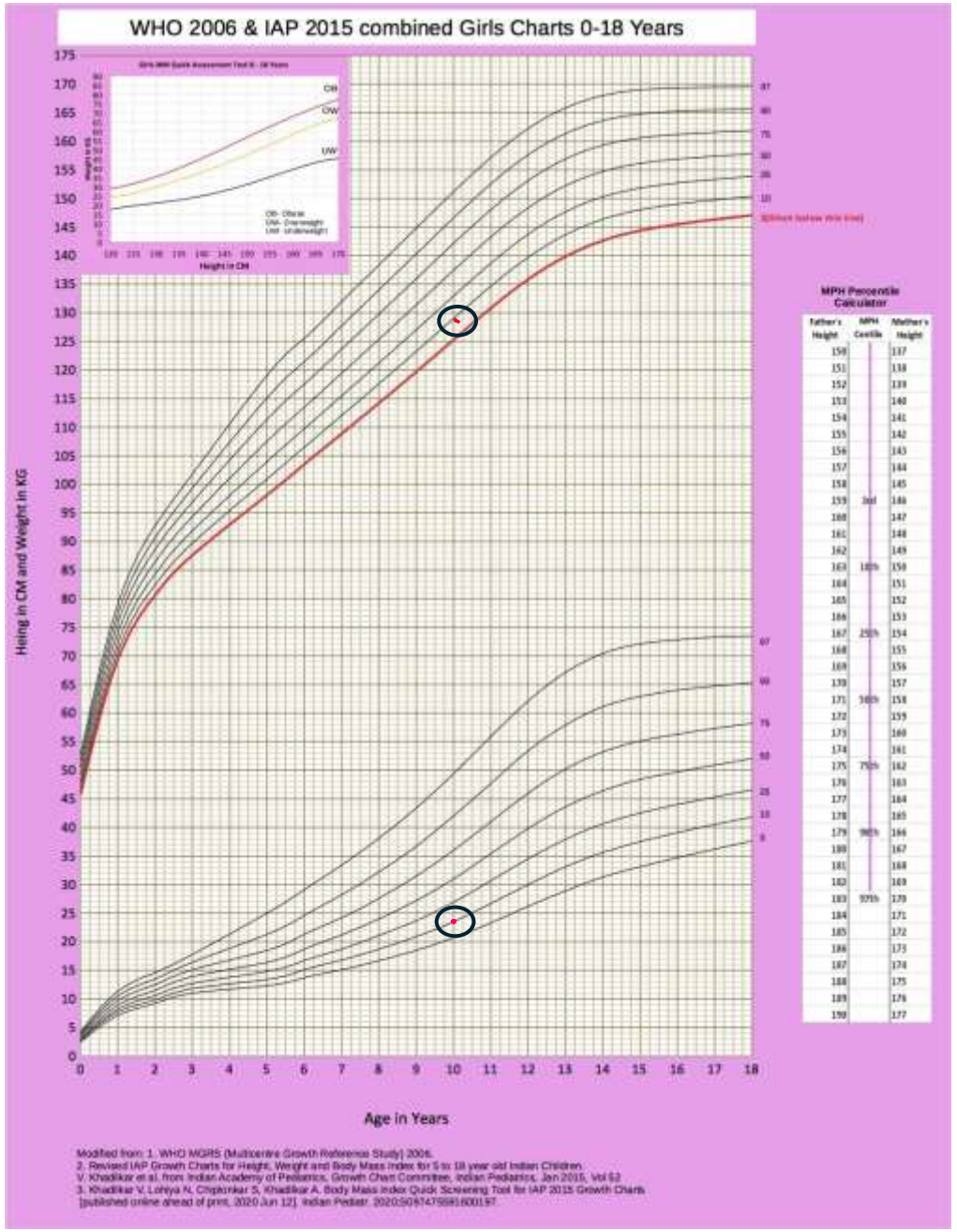
Anthropometry

Weight: 23.9 kg (10thth-25thth centile)

Height: 136 cm(25th- 50th centile)

BMI: 12.92(3rd-5th centile)

Impression – UNDERWEIGHT for age



PER ABDOMINAL EXAMINATION

Inspection: Distended.
Umbilicus: Retracted and inverted.
No visible veins seen.
No scar marks present.

Palpation: Tenderness at Right Iliac Fossa, hypogastrium and Periumblical region.
Abd. Girth: 69 cms
No local rise of temperature.
No guarding rigidity present.
No hepatosplenomegaly present.
No other lump was palpable

Percussion: No evidence of peritoneal fluid
Auscultation: Bowel sounds normal.
No audible bruit heard.

SYSTEMIC EXAMINATION

CVS-S1 and S2 normally heard.
NO additional murmur heard

Respiratory System-B/L Airway Entry Equal with no significant auscultatory findings.

CNS- The child was oriented to time place and person.
GCS- E4V5M6
Pupils: B/L Equally Reactiveto light
No meningeal signs present.
No cerebellar signs present.
Tone and Bulk- Normal
Power- 5/5 in all 4 limbs

Differential Diagnosis

- Acute Appendicitis
- Pancreatitis
- Ovarian Torsion/ Cyst

COURSE IN HOSPITAL

Child admitted to PICU

IV NS BOLUS GIVEN AT 10ML/KG

IV ANTIBIOTICS STARTED after taking blood culture

Inj Piperacillin + Tazobactam at 100mg/kg/dose
Inj Metronidazole at 30mg/kg/day
Inj Paracetamol at 15mg/kg/dose
Inj Pantoprazole at 1.25mg/kg/day

Urine R/M was normal

Investigation	Value	Normal Range
Hb (g/dl)	*8.9*	14-17
TLC (/ul)	*15056*	4-11
N/L	66/24	40-80/20-40
Platelets (/ul)	610000	150-450
MCV (fl)	67	80-100
MCH(pg)	22	27-31
MCHC (g/dl)	35.1	32-36
Serum bilirubin (mg/dl)	0.8	0.22-1.20
Conjugated bilirubin (mg/dl)	0.3	0.1-1.0
Unconjugated bilirubin (mg/dl)	0.5	Upto 0.5
SGOT (U/L)	45	8-48
SGPT (U/L)	33	7-55
Serum urea (mg/dl)	33	7-20
Serum creatinine (mg/dl)	0.41	0.6-1.35
Serum amylase (U/L)	45	25-115
Serum lipase (U/L)	50	0-160

USG ABDOMEN AND PELVIS DONE after initial stabilisation

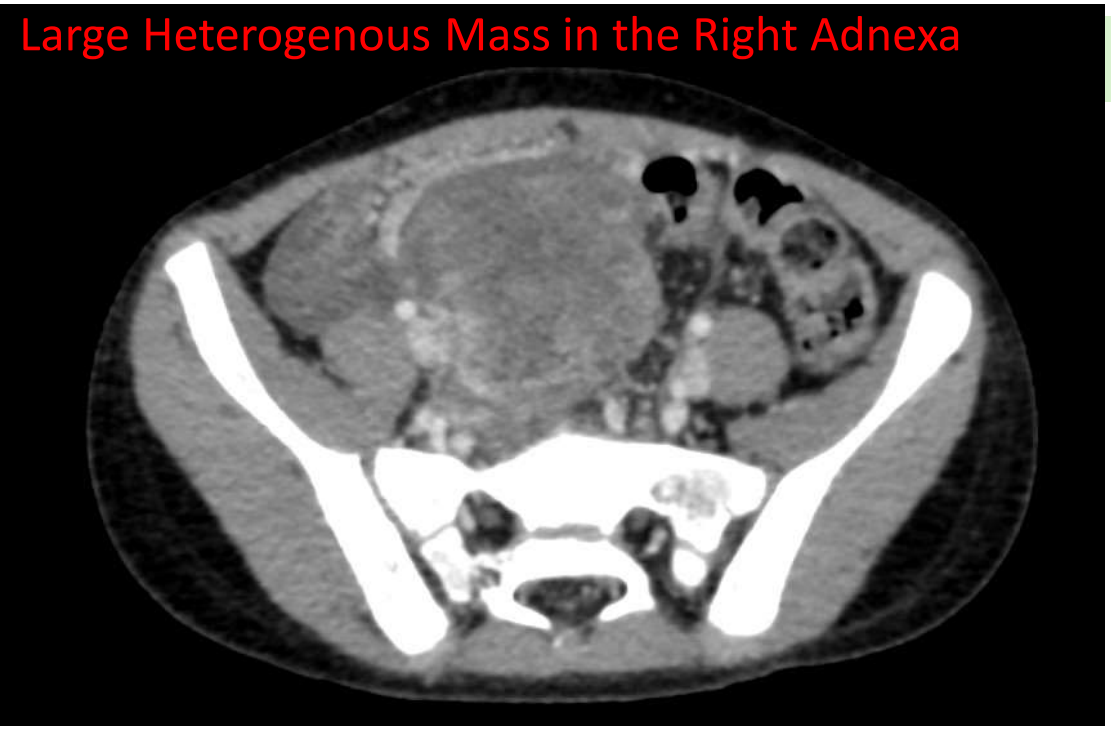
- Well defined rounded **hypoechoic lesion 4.2 x 3.5 cm noted in the right adenexa**, no vascularity noted.

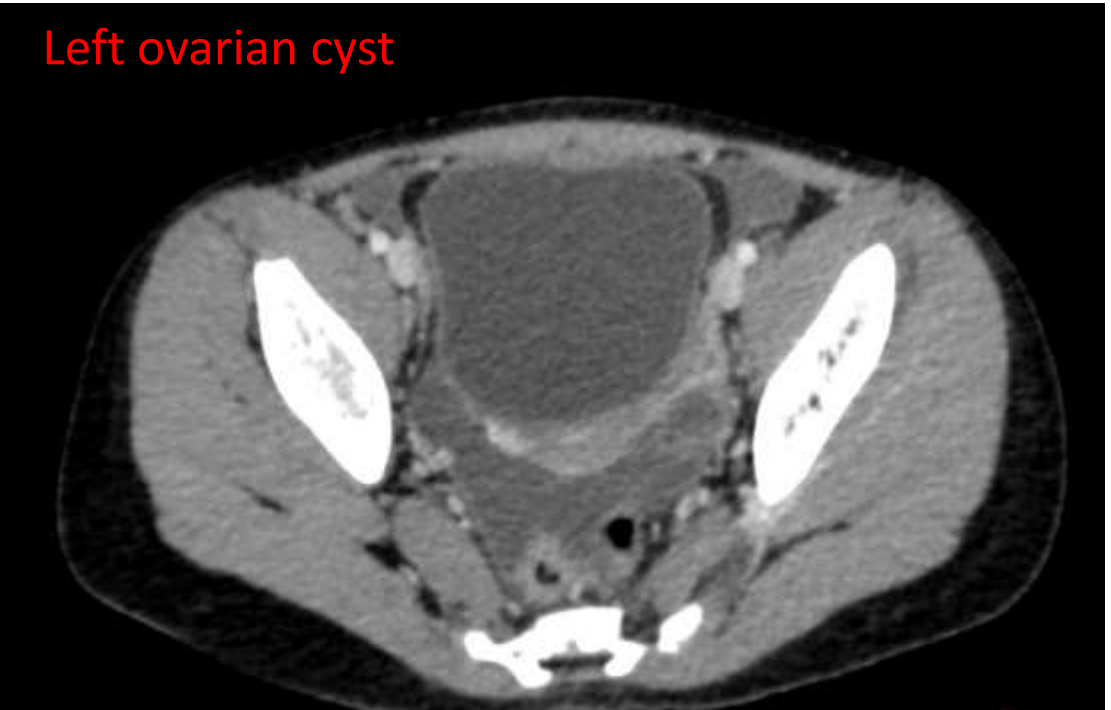
- Right ovary not seen seperate from lesion. May represent **Right ovarian haemorrhagic cyst.**

- Mild ascites (approximately 100cc free fluid in abd and pelvis)
- Left ovary and Uterus appear normal.

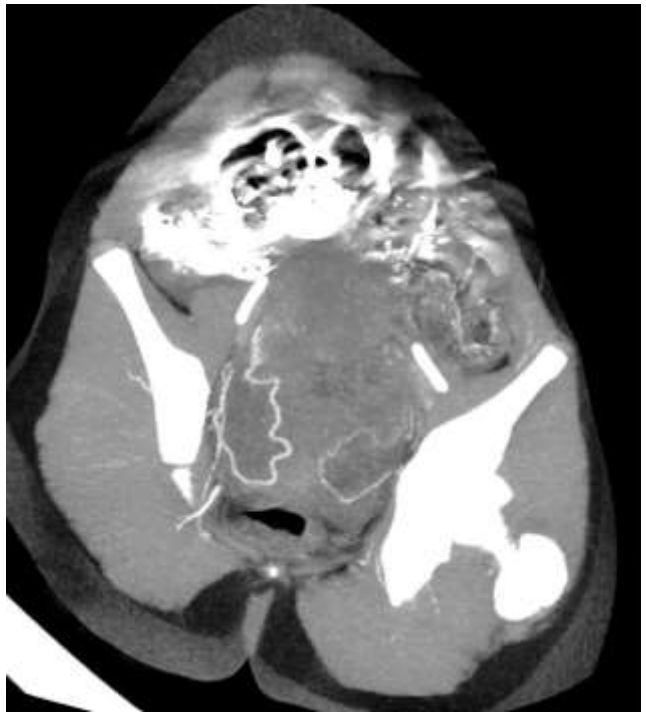
- Findings S/O possibility of **Right ovarian / adenexal torsion**

CT Scan of Abdomen and Pelvis





Arterial Phase shows vascular supply by right uterine artery



Large well defined predominantly solid mass with few cystic components with heterogenous post contrast enhancement seen in the midline arising from the right adnexa - most likely s/o neoplastic etiology of ovarian origin with no obvious evidence of torsion.

Heteregeneous peripherally enhancing left ovarian cyst noted.

Moderate Ascites.

Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

COURSE IN HOSPITAL

4 hours after CECT

Child's Abdominal Pain and Distension worsened

Emergency USG – Abdomen and Pelvis done

Impression :
Rupture of the right ovarian tumor and recent torsion -de-torsion phenomenon with features consistent with mild hemoperitoneum

Urgent Paediatric surgery consultation done
Paediatric Oncology Consultation done
Paediatric Endocrinologist Consultation done

Advice to send Tumor Markers

Tumor Markers

Tumor Markers	Observed Value	Normal Range
Alpha Feto Protein(ng/ml)	**>2000**	0 to 8.78
Beta HCG(mIU/ml)	1.42	0-5.3
CA-19.9(U/ml)	13.33	
CA-125 (U/ml)	**134**	0-35
CEA (ng/ml)	0.89	0 to 5

Emergency diagnostic laparoscopy

After taking Consent

↓

INTRA – OP FINDINGS

Right Ovarian Tumor + Tumour rupture with hemorrhagic ascites
Cyst in the left ovary

↓

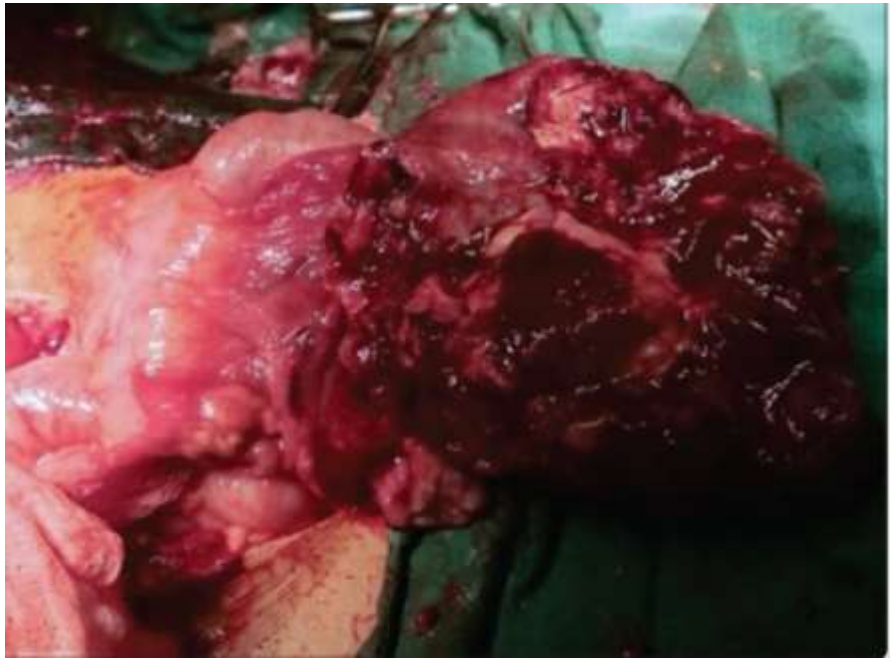
DECISION TO DO EXPLORATORY LAPROTOMY

Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

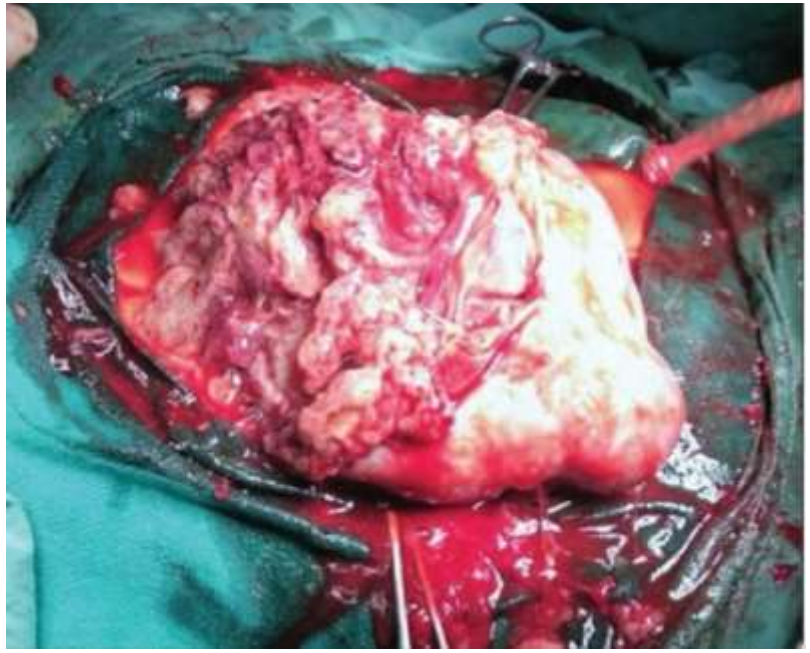
EXPLORATORY LAPROTOMY

Frozen section from Right ovary sent- s/o <u>High grade Malignant Neoplasm</u>- Salpingoopherectomy done

+ Deroofing of cyst in the left ovary + + Hemorrhagic fluid Suction done & sent for Cytology



Omentum adherant to large mass occupying midline and right lower abdomen.



Right Ovarian Tumor

Frozen Section of Right Ovary

High grade malignant neoplasm.

Right Salpingoopherectomy done

Final histopath confirmed
Yolk sac tumor (80%)
Dysgerminoma(20%)

Ascitic fluid sent for malignant cytology:

- **Reactive mesothelial cells**
- **Few atypical cells**

Cell block slides
Left Ovary

- Hemorrhagic background with many neutrophils , some lymphocytes.
- **Few reactive mesothelial cells seen.**
- No evidence of any malignant cells in cell block slides

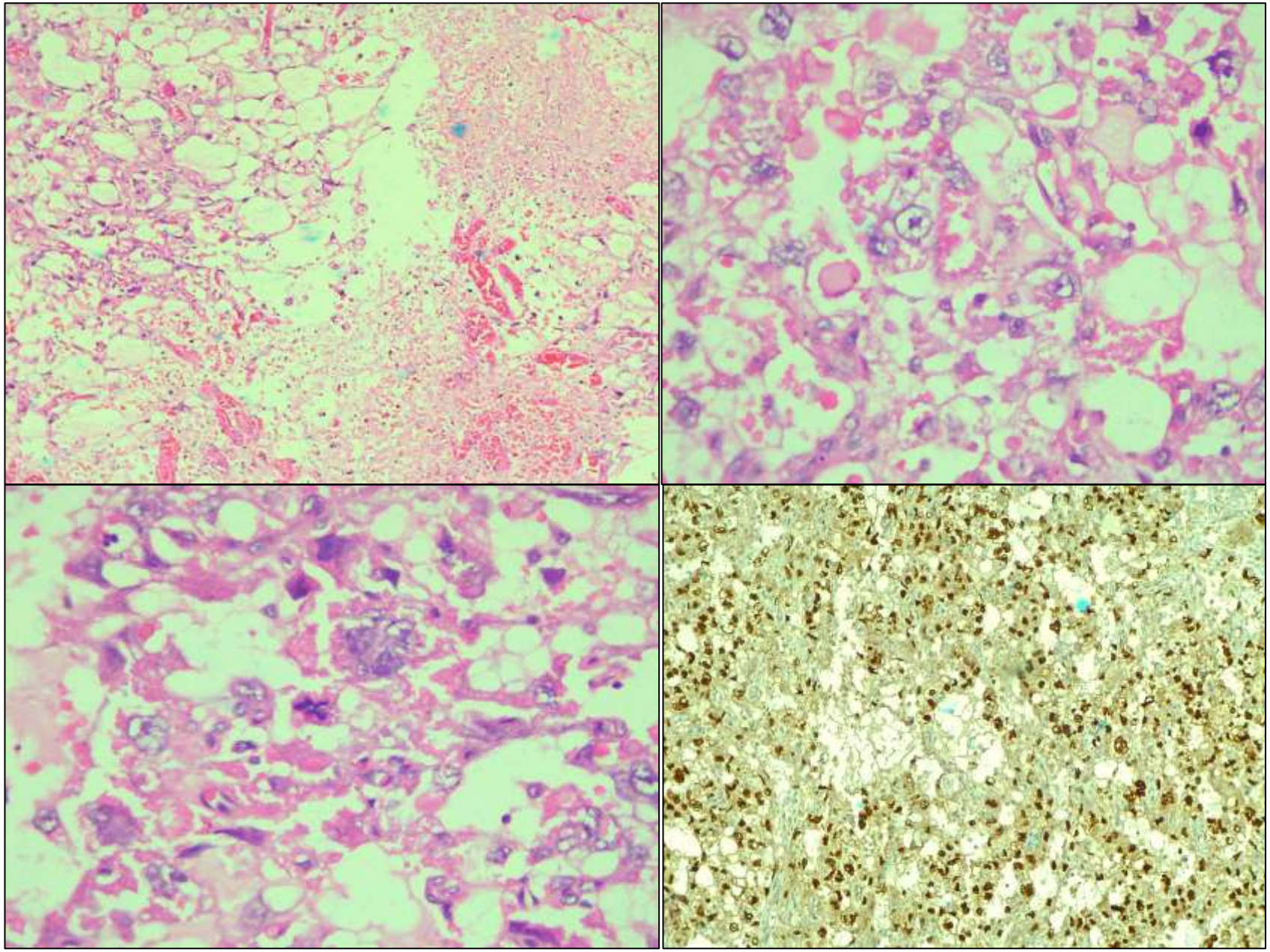
Histopath:
Sex cord stromal tumor.

Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

GROSS EXAMINATION:

Received two specimens.

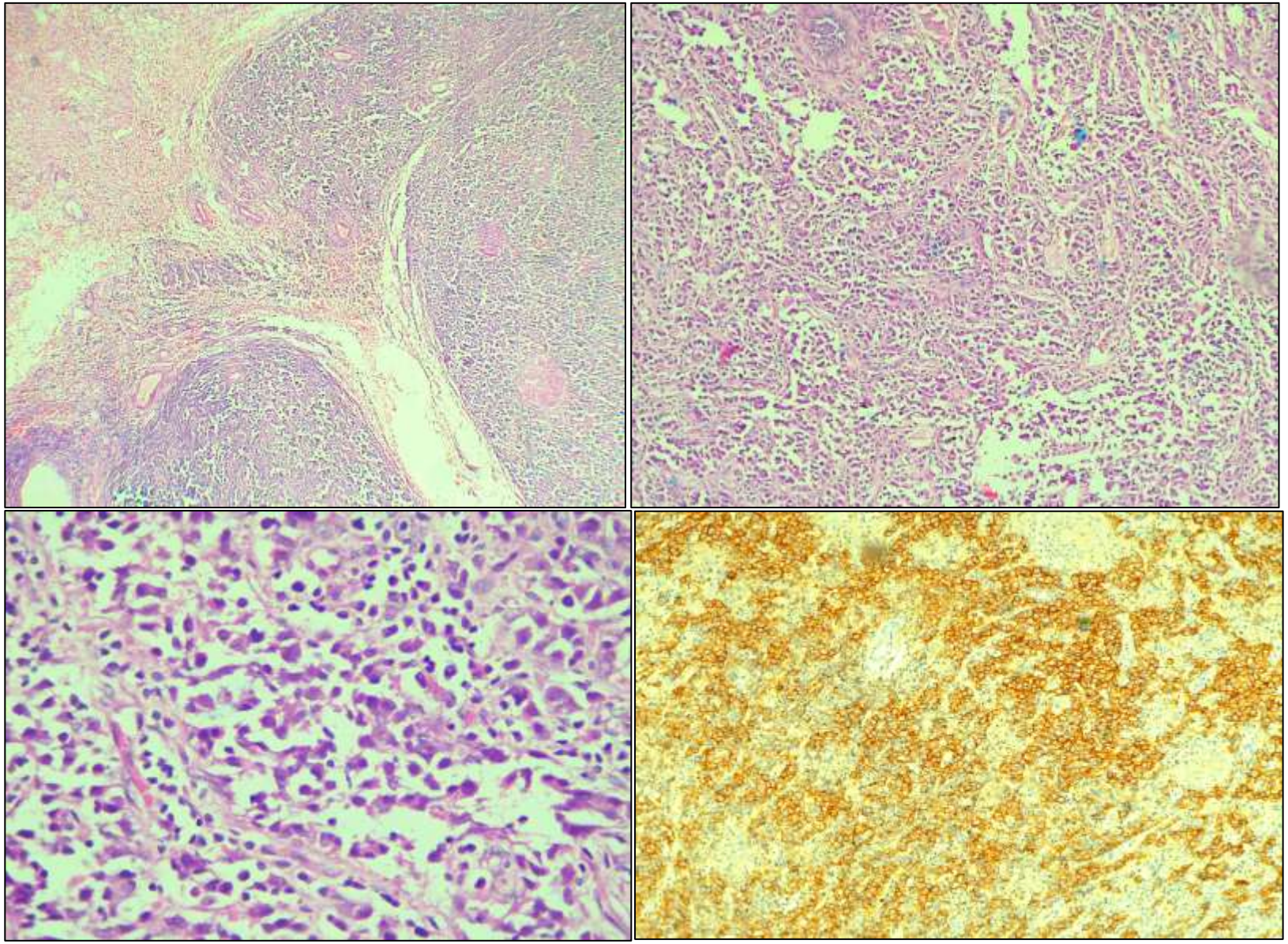
- Right ovary: Received multiple irregular tissue pieces aggregating to 5.5 x 4.5 x 3.5 cm.
- All the tissue pieces were capsulated & showed variegated appearance with solid, cystic, whitish & haemorrhagic areas. Multiple sections from various areas were taken.
- Sections from haemorrhagic & cystic areas showed tumor with predominantly microcystic pattern and areas of haemorrhage & necrosis.



Individual tumor cells were large with moderate nuclear pleomorphism, vesicular nuclei & prominent nucleoli. IHC for **SALL-4 +ve.** Diagnosis: **Yolk Sac Tumor**

- Section from the solid whitish areas showed tumor with cells arranged in lobules separated by fibrous septa.
- High power shows nests of tumor cells with clear cytoplasm and separated by fibrous septa
- Individual tumor cells show round to polygonal cells with moderate amount of eosinophilic cytoplasm , mild-moderate nuclear pleomorphism with round hyperchromatic nuclei. Lymphocytic infiltration of fibrous septa.
- **IHC – CD117** :membranous positivity tumor cells

Diagnosis: **Dysgerminoma**



Final histopath of Right Ovary

Yolk sac tumor (80%)

Dysgerminoma(20%)

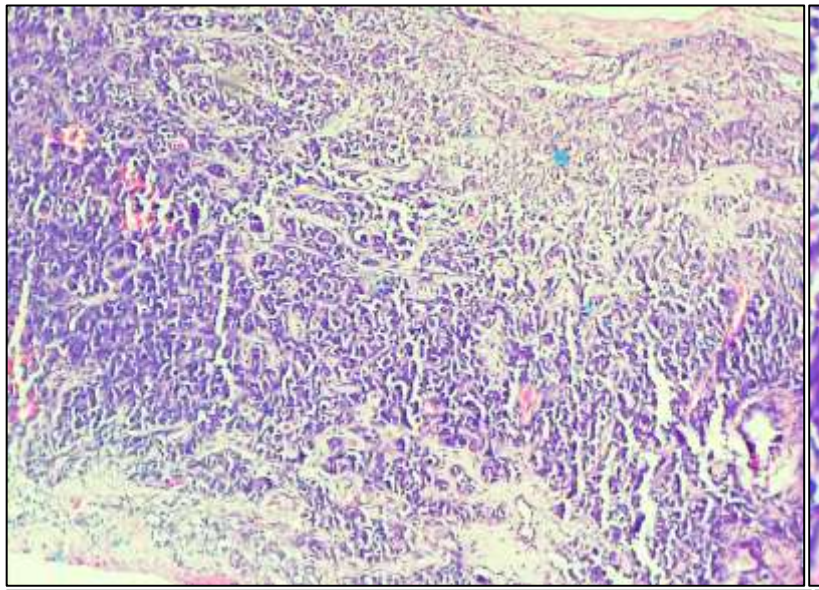
Gross examination:

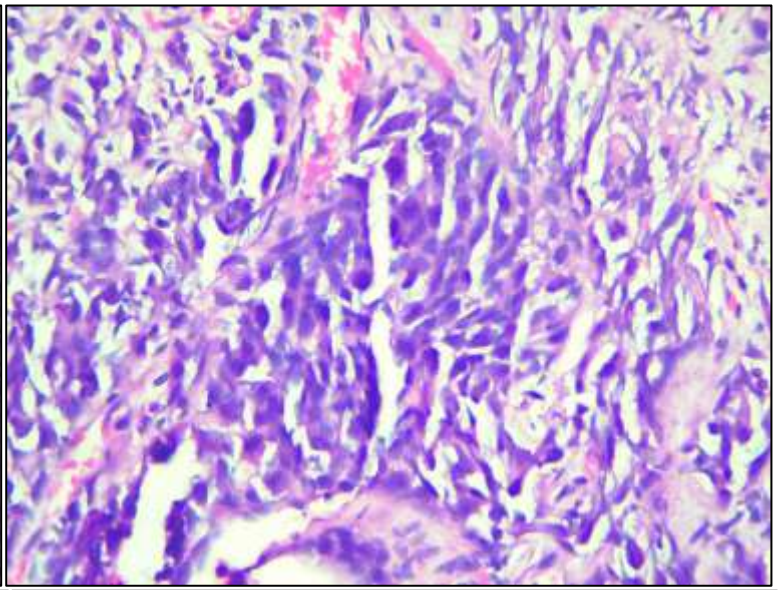
Cyst over left ovary : Received single grey white soft tissue bit measuring 0.6 x 0.5 x 0.1cm.

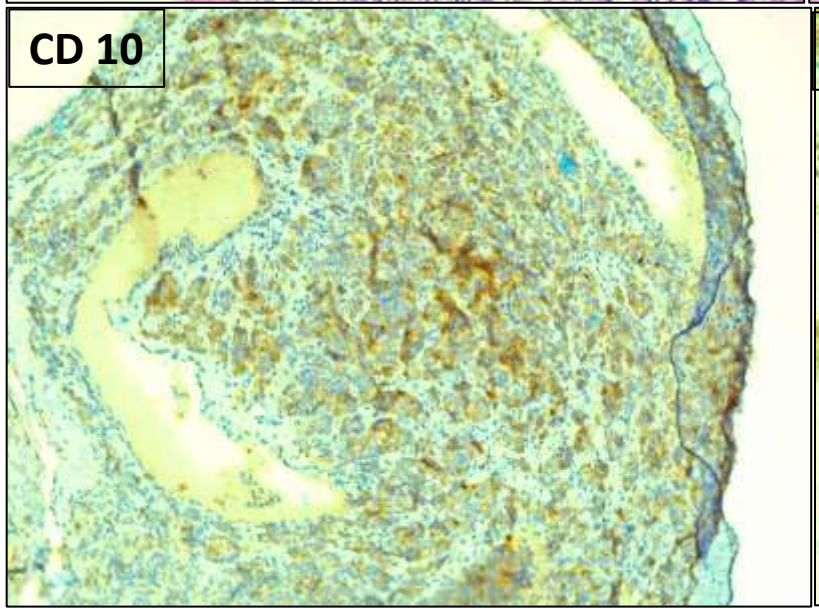
Microscopy:

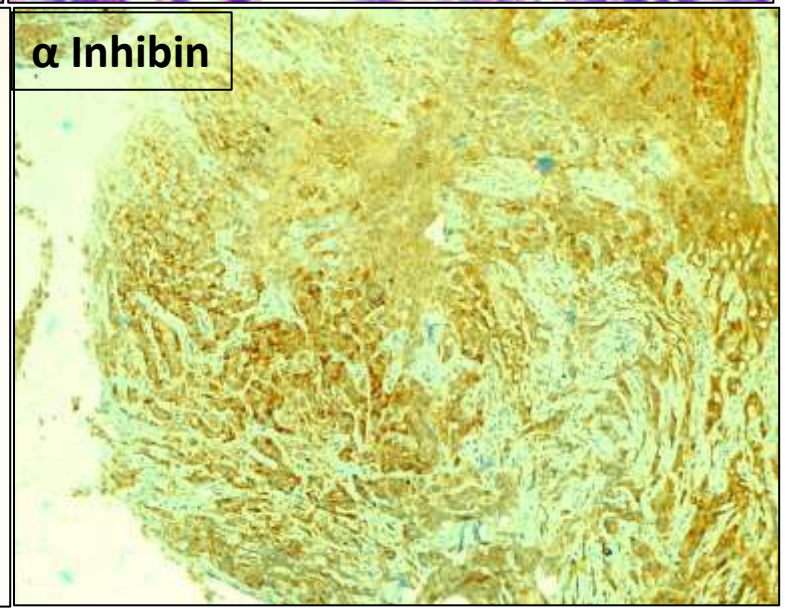
- Tumor cells were blue and primitive appearing & arranged in sheets and trabeculae.
- Individual tumor cells show round to angulated hyperchromatic nuclei with scant cytoplasm resembling primitive gonadal stromal cells.
- **IHC CD 10** : Tumor cells show membranous positivity
- **IHC alpha inhibin:** Tumor cells show strong cytoplasmic positivity.
- There was no differentiation towards Sertoli or Leydig cells or granulosa cells.

- **Final diagnosis of Left Ovary: Sex Cord Stromal Tumor, NOS type**









DPU
Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

Stage III assigned in view of rupture of the tumor as per Childrens Oncology Group (COG)

↓

Adjuvant Chemotherapy planned
Started on post operative day 15 once the surgical wound healed.

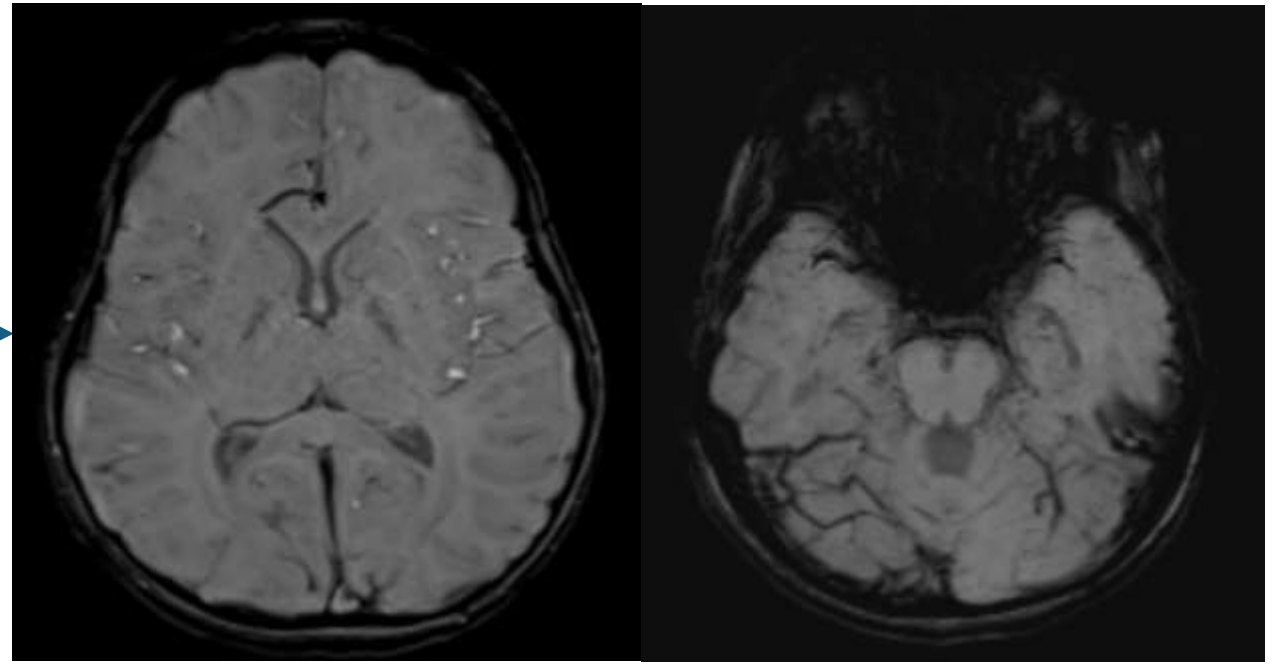
↓

Total 6 cycles of Adjuvant Chemotherapy given

- **Etoposide** at 120mg/m2
- **Bleomycin** 15mg/m2
- **Carboplatin** 600mg/m2 every 3 weekly.

Multiple phenotypic clinical clues suggestive of underlying genetic syndrome

MRI BRAIN DONE



Collection of dilated subcortical vessels noted in right cerebellar hemisphere, converging in the enlarged transcortical vessel extending along the posterior surface of the right cerebellar hemisphere.
Another dilated transcortical vein noted in the right parasagittal frontal region, reaching up to the frontal horn of the right lateral ventricle
Developmental venous anomaly.

MRI WHOLE SPINE SCREENING → **No abnormality seen**

Opthalmological Evaluation → No evidence of Leisch Nodules & Iris Hematoma
Both Eyes Fundus Examination was within normal limits.

DPU
Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

Clues suggestive of underlying genetic syndrome

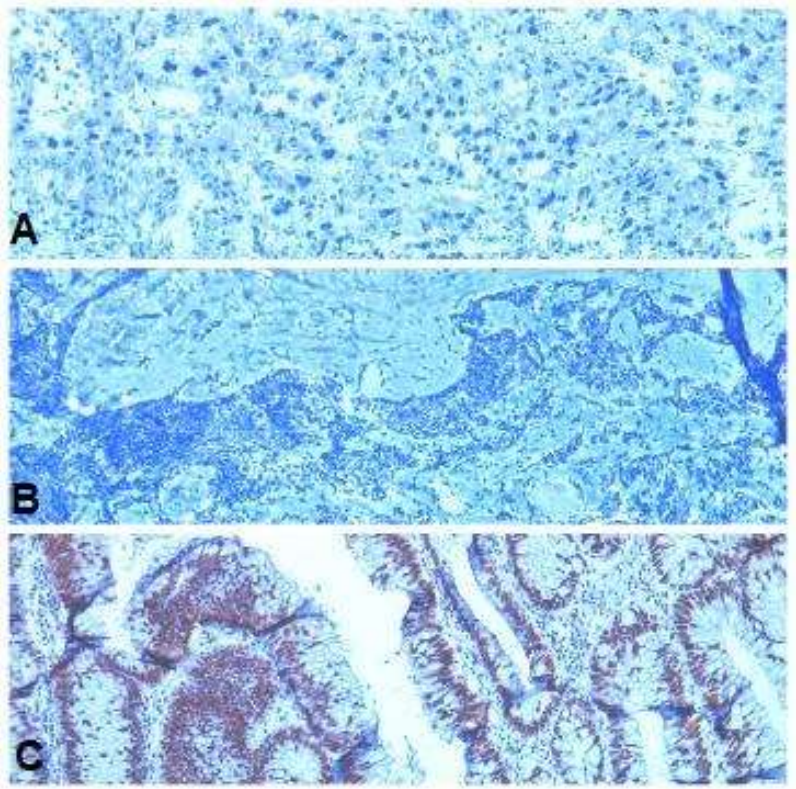
WHOLE EXOME SEQUENCING (WES) sent

Homozygous MSH6 (+) mutation - consistent with **Mismatch repair cancer syndrome 3**
also known as - **Constitutional Cancer Mismatch Repair deficiency syndrome (CCMRD).**

S. No	Gene, Variant details	Zygosity Depth (Alt allele %)	In silico tools	MAF	Literature	OMIM Disease	Inheritance	Classification
1	***MSH6* (+)** c.2550C>G p.Tyr850Ter ENST00000234420.11	Homozygous 69X(100%)	SIFT - NA LRT - NA PolyPhen - NA MT2 - NA	1000 G - NA gnomAD (V2.1) - NA gnomAD (V3.1) - NA MedVar - 0.001539%	PUBMED - NA CLINVAR ID – VCV000410471.30	Mismatch repair cancer syndrome 3 (OMIM#619097)	Autosomal recessive	Pathogenic

Tumour cells show **loss of staining** for **MSH6 protein** by immunohistochemistry

A) Germ cell tumour component
B) Sex cord stromal tumour component
C) Normal colonic mucosa - positive control



Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

ON FOLLOW UP

- Her chemotherapy is completed.
- She is on Regular surveillance for development of subsequent other malignancies.
- The parents have been explained and given the plan for surveillance as per recommended guidelines.
- Her sibling genetic testing for MSH6 mutation : **Negative**
- The parents were also advised genetic testing for heterozygous MSH-6 mutation which is a risk for Lynch Syndrome and is associated with various malignancies.
- She is currently going to school & studying in 6th Standard.
- Child shows adequate weight gain on follow up visits.

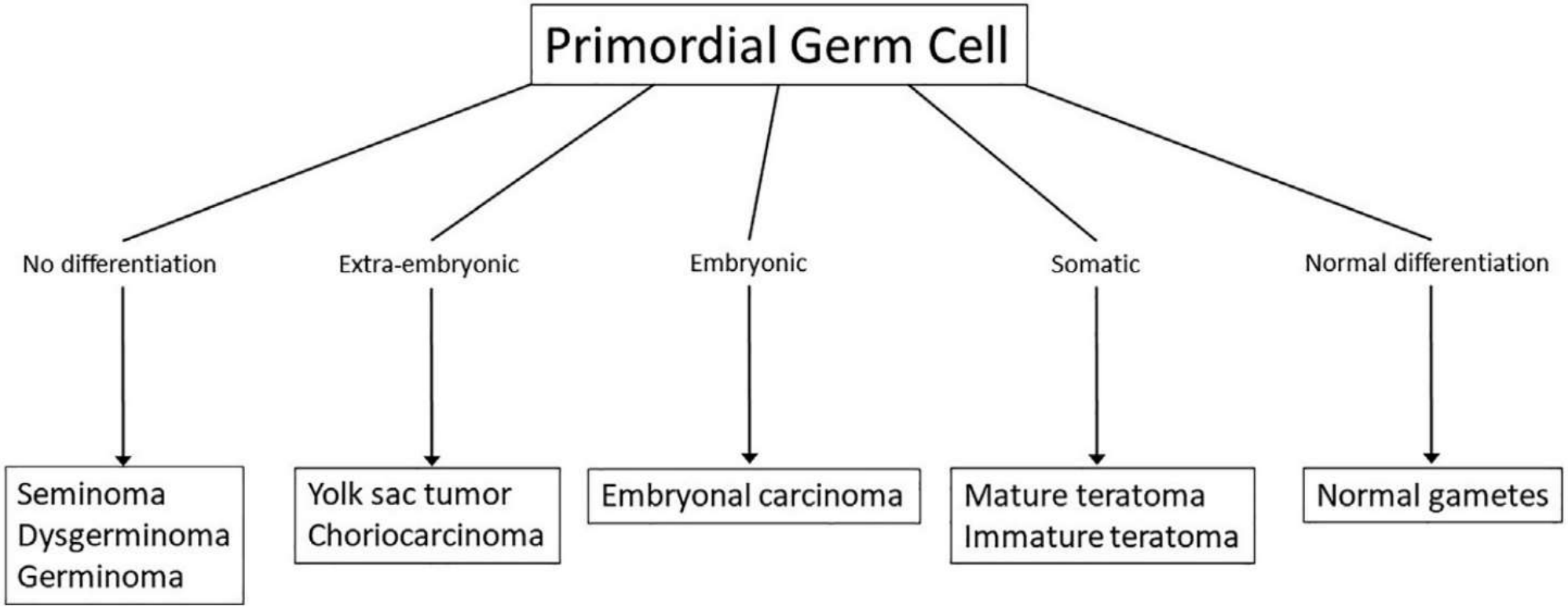
DISCUSSION

- Neoplastic ovarian tumors in children and adolescents account for **0.9 to 2 %** of tumors.
- Nearly **30 % of ovarian masses in adolescent girls** are known to present in emergency with **torsion or rupture of the tumor** similar to this case. Hence timely diagnosis is essential to prevent such life threatening complications.
- Causes of ovarian mass are **functional or physiological cysts (61%) > benign neoplasm (30%) > malignant (9 %) ovarian tumors.**
- Amongst the malignant ovarian tumors, **germ cell tumors** are the most prevalent subtype accounting for **56 %** and **yolk sac tumor is the most common malignant germ cell tumor.**

- GCTs arise from pluripotent primordial germ cells. It has various histologic subtypes.

- **Sex cord stromal tumors** constitute **12 %** of all the malignant ovarian tumors.

- GCTs secrete **alpha fetoprotein (AFP)** and **Beta-HCG**.
- AFP is elevated in 95% to 100% of patients with yolk sac tumors.
- The measurement of serum AFP is useful during the initial workup for a **suspected GCT**, for **surveillance**, and to assess the **response to therapy.**



- This case **first time reports yolk sac tumor and sex cord stromal tumor** asscociated with **Cancer Mismatch repair syndrome 3** which predisposes to various cancers like

1. **Hematological malignancies**
2. **Brain tumors**
3. **Gastrointestinal tumors**
4. **Rhabdomyosarcoma**
5. **Embryonal tumors.**

- **MSH-6** is a DNA Mismatch Repair (MMR) Gene.

- **Loss of function** or **Mutation** of this gene leads to **Microsatellite instability** (MSI) and Lynch Syndrome.

- Abnormal MSH-6 expression can be detected via **Immunohistochemistry (IHC)** or **molecular testing** like done in this case.
- CCMRD is a childhood cancer predisposition syndrome caused by biallelic pathogenic variants of four mismatch repair(MMR) genes ie **MLH1, MSH2, MSH6, and PMS2.**
- Amongst the ovarian malignancies, **sex cord stromal tumors** are very well known to be associated with cancer predisposition syndromes like **Peutz-Jeghers syndrome, Olliers disease and Maffucci syndrome.**

KEY-POINTS

- The spectrum of known **Cancer Predisposition Syndromes** is ever expanding to include malignancies previously not reported.
- Cancer Mismatch repair Syndrome 3 can have predisposition to **ovarian sex cord stromal** as well as **Germ cell tumor** and these tumors can manifest as **somatic micro satellite instability.**
- **Parents and first degree relatives** should be screened for **heterozygous MSH mutation** which leads to a condition known as **Lynch Syndrome.**
- People with Lynch Syndrome should have routine healthcare visits and screenings like colonoscopy or screen for ovarian tumors.
- The pharmogenetic and prognostic implications of micro satellite instability in sex cord stromal and germ cell tumors needs to analysed in larger and long term studies.

DPU
Dr. D. Y. Patil Medical College, Hospital & Research Centre, PIMPRI, PUNE

Acknowledgements

- Dr. Shailaja Mane HOD and Professor
- Dr. Aniruddh Bhagwat, Senior Consultant in Paediatric Surgery and team
- Dr. Sarita Verma, Consultant Paediatric Oncologist
- Dr. Charusheela Gore, HOD Department of Pathology & Team
- Dr. Himadri Bal, Professor Department of Obstetrics and Gynecology
- Dr. Sajili Mehta, Paediatric Endocrinologist
- Dr. Vineeta Pande, HOU and Professor
- Dr. Sanjay Chavan, Professor and PG Incharge
- Dr. Manoj Kumar Patil, Professor and PICU Incharge
- Dr. Shiji Chalipat, Paediatric Neurologist
- Dr. Sonal Khatavkar, Department of Anesthesia
- Department of Radiodiagnosis

Special Thanks to

Dr. Aniruddh Bhagwat, Senior Consultant in Paediatric Surgery

Dr. Mihir Wadhawan, Resident, Deptt. Of Radiodiagnosis

Dr. Abhishek Tambile, Resident, Deptt. of Pathology

References

1. Birbas E, Kanavos T, Gkrozou F, Skentou C, Daniilidis A, Vatopoulou A. Ovarian Masses in Children and Adolescents: A Review of the Literature with Emphasis on the Diagnostic Approach. Children (Basel). 2023 Jun 27;10(7):1114. doi: 10.3390/children10071114. PMID: 37508611; PMCID: PMC10377960.

2. Pastorczak A, Krajewska K, Urbanska Z, Szmyd B, Salacinska-Los E, Kobos J, Mlynarski W, Trelinska J. Ovarian carcinoma in children with constitutional mutation of SMARCA4: single-family report and literature review. Fam Cancer. 2021 Oct;20(4):355-362. doi: 10.1007/s10689-021-00258-w. Epub 2021 Apr 28. PMID: 33907931; PMCID: PMC8484133.

3. Metwalley, K.A., Elsers, D.A., Farghaly, H.S. et al. Precocious puberty secondary to a mixed germ cell-sex cord-stromal tumor associated with an ovarian yolk sac tumor: a case report. J Med Case Reports 6, 162 (2012). https://doi.org/10.1186/1752-1947-6-162

4. Nelson Textbook of Paediatrics 22nd Edition

5. Children's Oncology Group(COG) Staging Guidelines- Ovarian GCTs

THANK YOU