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A rare case of DICER 1 Syndrome with malignant mixed germ cell tumour of ovary in an adolescent girl with skeletal dysmorphism

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ABSTRACT

Introduction- Mixed ovarian germ cell tumours (MOGCTs) are rare entities, accounting for less than 5% of all ovarian malignancies and under 1% of ovarian germ cell tumours. We present a case in which a malignant mixed germ cell tumour manifested as an uncommon and atypical presentation of DICER-1 syndrome—a condition more frequently associated with Sertoli-Leydig cell tumours.

Case presentation-An 18-year-old female with skeletal dysmorphism had presumptive diagnosis of acute febrile illness, a neoplastic left adnexal mass, bilateral pleural effusion, and congenital dislocation of the right femoral head. She underwent successful surgical intervention followed by combination chemotherapy, resulting in favourable clinical outcomes. On histopathological examination the mass turned out to be mixed germ cell tumour(yolk sac + immature teratoma grade 1).

Conclusion- Early detection and appropriate management are critical for optimizing outcomes in adolescents with ovarian malignancies associated with Cancer Predisposition Syndromes (CPS). While treatment strategies in this age group typically emphasize fertility preservation, it was regrettably not feasible in our case due to congenital absence of contralateral ovary and fallopian tube with hypoplastic uterus.

Keywords: *Malignant mixed germ cell tumour, yolk sac tumour, immature teratoma, DICER-1 syndrome..*

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1. INTRODUCTION

Globally ,ovarian cancer is the eighth most common cancer in women and one of the leading causes of cancer related deaths. In 2022 ,there were 3,24,000 new cases of ovarian cancers and more than 2,06,000 related deaths all over the world(1) It is a significant health concern for women in India ,ranking as the third most common cancer among them.

In the same year India reported 47,333 new cases and 32,978 deaths from ovarian cancers(2)

The World Health Organization has classified ovarian tumors as 1.Epithelial tumour, 2.Mesenchymal tumor, 3.Mixed epithelial and mesenchymal tumours, 4.Sex cord stromal tumor 5. Germ cell tumour 6.Monodermal teratoma and somatic type tumors arising in dermoid cyst 7.Miscellaneous tumours 8.Mesodermal tumours 9.Soft tissue tumours 10.tumor like lesions 11. Lymphoid / myeloid tumors 12.Secondary tumors(3)Germ cell tumors originate from the primordial germ cells of the ovary . In individuals under 20 years of age, approximately 70% of ovarian tumors are of germ cell origin, with nearly one-third classified as malignant(4) Malignant mixed germ cell tumors are characterized by the presence of two or more malignant components. The most frequently observed combination includes dysgerminoma and endodermal sinus

tumor (EST), while the rarest comprises embryonal carcinoma and immature teratoma[5]

Mixed ovarian germ cell tumors (MOGCTs) remain rare, comprising less than 5% of all ovarian cancers and less than 1 % of all ovarian germ cell tumors[6] [7]

Few rare syndromes are associated with tumors of paediatric and adolescent age group. One such syndrome is DICER-1 syndrome also known as DICER-1 tumor predisposition. It is a rare genetic condition caused by mutations in DICER-1 gene[8]

In present case, MOGCTs represented a rare and atypical manifestation of DICER-1 syndrome, which is more commonly associated with Sertoli-Leydig cell tumors of ovary.

Over the past three decades, survival outcomes for patients with germ cell tumors have significantly improved, largely due to advances in surgical staging and the implementation of combination chemotherapy[7]Importantly, these malignancies are often curable with fertility-sparing approaches, a critical consideration given the young age of most affected patients[9]

Here we present a case report of MOGCTs a combination of immature teratoma (grade 1) and yolk sac tumor in a young girl with skeletal dysmorphism and DICER -1 syndrome.

2. CASE SUMMARY

An 18-year-old female was referred to emergency department of our tertiary care centre with a provisional diagnosis of acute febrile illness, neoplastic left adnexal mass, bilateral pleural effusion and congenital dislocation of the right femoral head. On admission, she reported intermittent fever over the past four months, breathlessness for the last 4–5 days, and progressive abdominal distension due to a rapidly enlarging mass. The mass was later identified as a mixed germ cell tumor—a rare entity, prompting the presentation of this case.

On physical examination she was short stature, thin built, pale and secondary sexual characteristics found to be underdeveloped with tanner stage 2. She exhibited facial dysmorphism and multiple skeletal deformities, including kyphoscoliosis, pectus excavatum, and black-stained, crowded teeth.(figure 1,2)

On admission, she was tachycardic (170 bpm), tachypneic (30 breaths/min), and had an oxygen saturation of 94% on room air, with bilaterally decreased air entry suggestive of lower respiratory tract infection.

Menstrual history - attained menarche very late at 18 years until now had 3 cycles with flow very less in amount .

Personal history-undergone corrective surgery for bilateral congenital talipes equinovarus (CTEV) in 2006.

Family history – there were no skeletal deformities or malignancies involving the ovary, breast, or uterus in family.

Abdominal palpation revealed a mobile, non-tender mass with regular margins and firm consistency, corresponding in size to a 24-week gravid uterus, accompanied by gross ascites.

Patient already had Contrast-enhanced CT report of the abdomen revealing a large, heterogeneously enhancing, multilobulated solid-cystic lesion measuring 13.6 × 12.1 × 14.2 cm in the left adnexal region with gross ascites and absent right sided ovary . Additionally, there was posterior dislocation of both femoral heads with a dysplastic right femoral head.

Diagnostic ascitic tapping was negative for tuberculosis and malignancy. On evaluation thoracic ultrasound showed bilateral minimal pleural effusion and patient got treatment for LRTI. Laboratory investigations revealed a markedly elevated CRP level of 195.8, CA-125 - 490, alpha fetoprotein-405.3, beta HCG-53,600 and LDH-320. Blood cultures were positive for *Pseudomonas aeruginosa*, and sputum cultures grew *Klebsiella pneumoniae*, although tuberculosis was ruled out.

After resolution of her lower respiratory tract infection which took about 15 days, the patient underwent exploratory laparotomy . Intraoperatively, a left-sided ovarian mass measuring 18 × 18 cm with regular margins and solid consistency, encapsulated was excised along with the left sided fallopian tube. There was absence of right ovary and right fallopian tube. As left ovary being malignant decision of hysterectomy was taken. Infracolic partial omentectomy done. Moderate ascites was noted, and the undersurface of the spleen and liver appeared smooth.

On gross examination of tumor, the cut section of the ovarian mass revealed a solid and hemorrhagic appearance with variegated texture and smooth encapsulation (figure 3,4). Following surgery, patient experienced significant relief from abdominal distension and breathlessness, with marked improvement in her quality of life. Postoperative histopathological examination confirmed a malignant mixed germ cell tumor comprising yolk sac tumor and immature teratoma (Grade 1) (figure5,6,7). The fallopian tube, uterus and omentum were free of tumor invasion, and no lymphovascular or perineural invasion was observed. Immunohistochemistry findings later corroborated the histopathological diagnosis. She had undergone whole exome sequencing on the illumina Novasq 6000 NGS platform which classified RAF1 gene and DICER 1 gene with germ line mutation.

Gene and transcript	location	variant	Zygosity/inheritance	OMIM Phenotype
RAF1 (-) MN_002880.4	Exon 17	c.1922C>T	Heterozygous/autosomal dominant	Cardiomyopathy dilated 1NN
DICER1(-) NM_177438.3	Exon 14	c.2197G>A	Heterozygous/autosomal dominant	Goiter, multinodular 1,with or without Sertoli Leydig cell tumours /Pleuropulmonary/tumour predisposition syndrome

Postoperatively, she received 3 cycles of cisplatin-etoposide regimen chemotherapy(EP). Significant resolution of lesion with decline in serum markers level has been noted. Hence the patient has been advised 3-monthly follow- up with serum markers, CECT abdomen and pelvis for 2 years . Her general condition has improved significantly after surgical intervention and chemotherapy.

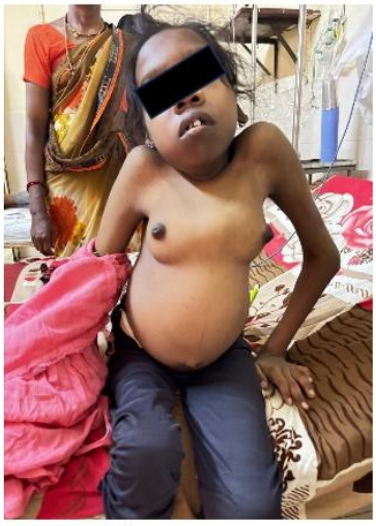


Figure 1

Figure 2

Figure 1

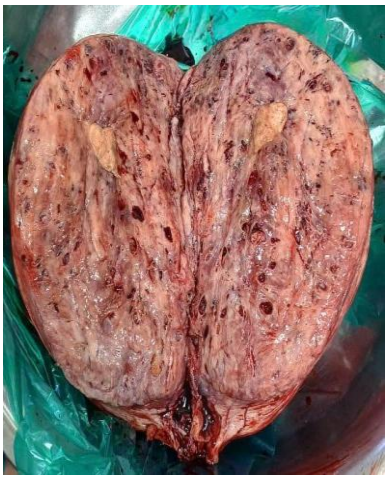
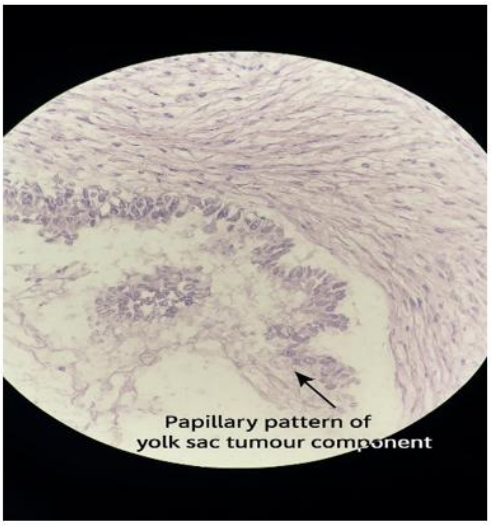


Figure 2



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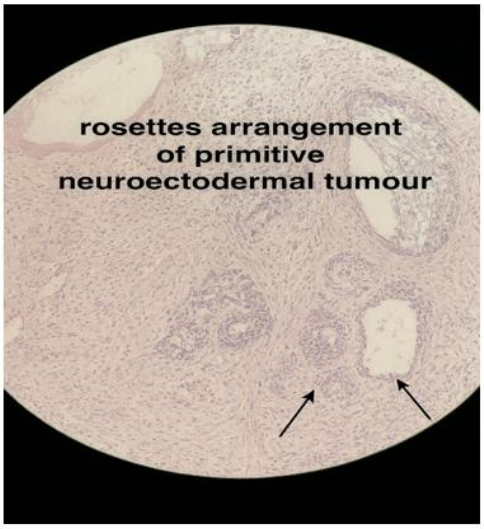

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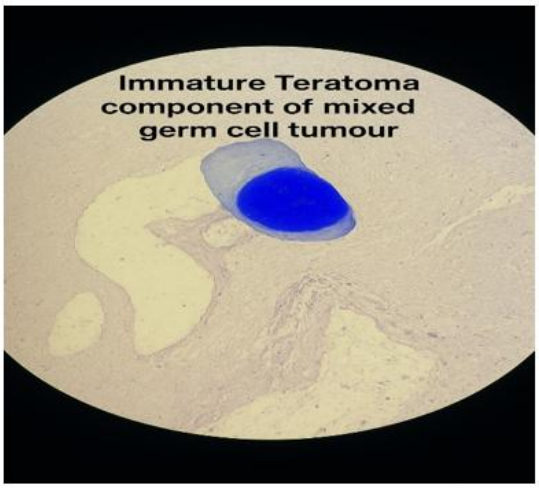

Figure 7

3. DISCUSSION

Malignant mixed germ cell tumours of ovary are rare, aggressive and rapidly growing tumours, commonly found in young adolescent girls [5] [9]As seen in our patient ,18 years old noticing the lump in abdomen which was speedy in onset, therefore it could be diagnosed early.

Clinically majority of these patients present with abdominal pain and rapidly growing abdominopelvic mass, as also seen in our patient. Acute abdominal pain is generally due to rupture, haemorrhage or torsion of ovarian tumour[10]

In present scenario, the patient had dysmorphism in form of short stature, multiple congenital skeletal anomalies, late onset menarche, hypoplastic uterus with single fallopian tube and single cancerous ovary. Her chromosomal analysis in form of whole exome sequencing exhibited RAF 1 gene and DICER 1 gene of germline mutation. DICER-1 gene had definite association with Cancer Predisposition Syndrome (CPS). Paediatric/teenage ovarian malignancies, while rare can be associated with certain CPS, like Constitutional Mismatch Repair Deficiency Syndrome, Activated P13K Delta Syndrome (APDS), SMARCA4-related Rhabdoid Predisposition Syndrome (RTPS2), Peutz-Jeghers Syndrome, and DICER1 Syndrome which was diagnosed in our patient [8] [11]

DICER 1 Syndrome is a rare tumour predisposition disorder in which there is presence of an abnormal mutation of DICER 1 gene in affected children and it is inherited as heterozygous autosomal dominant syndrome. This syndrome can manifest in form of various benign and malignant tumours including those in the ovary. Although Sertoli Leydig cell tumours are the commonly associated ovarian tumours, [8] [11] as per literature, other tumours associated with this syndrome till date are embryonal rhabdomyosarcoma of cervix and ovary gynandroblastoma and juvenile granulosa cell tumour [12], in present

situation it was malignant mixed germ cell tumour, a very rare and unique highlight of this case. Therefore additional in depth studies are needed to strenghthen this novel association.

As per the European Society for Medical Oncology, the National Academy of Clinical Biochemistry and the current Royal College of Obstetrician and Gynaecologists guidelines, in ovarian germ cell tumours, diagnostic evaluation includes chest Xray, abdominopelvic ultra sound, CT scan(abdominopelvic) and positron emission tomography in selected cases. In preoperative work up, tumour markers like serum beta HCG, serum alfa fetoprotein, LDH and CA-125 in young patients are recommended. Regression of tumour marker is of great help in prediction of better prognosis. [11] [13]

As per laparotomy staging, the stage of disease in this case, was 1C (limited to one ovary and with ascites), she had better disease free survival after receiving combination chemotherapy. These cancers are highly sensitive to combination chemotherapy and have favourable prognosis [5] [9] [13]

Fertility preservation was not feasible in present case as the patient had only one diseased ovary and hypoplastic uterus, contralateral ovary was absent. But almost always these patients are young, adolescent, unmarried and nulligravidae so fertility preservation is of prime importance. Diagnosis at early stage is common in germ cell tumours, therefore optimal debulking surgery followed by adjuvant chemotherapy with complete treatment and good follow up guarantee future preservation of ovarian function and ability to reproduce [13]

In the present study, malignant mixed germ cell tumour had a combination of immature teratoma and yolk sac tumour, which is extremely rare, only few cases being reported in literature till date[5][9]But this combination has proven excellent prognosis provided early diagnosis and treatment with surgery followed by adjuvant chemotherapy[13]

4. CONCLUSION

This study highlights the importance of diagnosis of ovarian neoplasm in adolescents at early stage, which can be the first sign of Cancer Predisposition Syndromes (CPS). Identifying CPS allows for genetic counselling and surveillance of patient and family. Early detection and appropriate management are crucial for improving outcomes in teenagers with ovarian malignancies associated with CPS. Treatment strategies for adolescent ovarian malignancies often prioritize fertility preservation. More researches are essential to understand better molecular and genetic characteristics of ovarian germ cell tumours and their relationship to CPS.

Declarations

Consent for publication- Informed written consent has been obtained from the patient for the publication of case details, clinical images, and relevant medical information. All reasonable measures have been taken to protect patient's confidentiality, and any identifying information has been thoroughly anonymized.

Conflict of interest-none declared

Funding-no funding sources

Ethical approval- not required as per institution protocol.

5. ACKNOWLEDGEMENTS-

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