



Germ Cell Tumors Ovary "Dysgerminoma" With Mayer-Rokitansky-Kuster-Hauser Syndrome

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Article Info	Abstract
<p>Article history: Received 29 April 2023 Revised 21 July 2023 Accepted 26 July 2023 Available online 13 Agustus 2023</p> <p>Keywords: dysgerminoma; ovarian cancer; germ cell tumors; MRKH syndrome; female genital congenital malformation</p> <p>Correspondence: rijantoagoeng23@gmail.com</p> <p>How to cite this article: RA Basoeki, A Nabiila, A Narulitia, YE Saputra, T Olfah, E Nursucahyo, M Anas. Germ Cell Tumors Ovary "Dysgerminoma" with Mayer-Rokitansky-Kuster-Hauser Syndrome MAGNA MEDIKA Berk Ilm Kedokt dan Kesehat. 2023; 10(2): 239–251</p>	<p>Background: Ovarian Germ Cell Tumors originate from primitive germinal cells and can be malignant or benign. MRKH syndrome is characterized by congenital hypoplasia of the uterus and upper vagina and can occur due to disrupted fusion of the Mullerian ducts. Diagnosing ovarian tumors in MRKH patients is difficult but can be characterized by abdominal pain and distended.</p> <p>Objective: This case report aims to explain the diagnostic methods and interventions performed in patients with ovarian tumors and MRKH syndrome.</p> <p>Case Presentation: A 25-year-old female came to the hospital complaining of a lower abdominal lump three months ago. It was followed by severe pain, weight loss, shortness of breath, and yellowish vaginal discharge. Physical examination showed anemia, obesity, and a vagina size of 7cm with a probe. Chest X-ray showed a mass in the mediastinum and pleural effusion, and USG showed suspicion of an ovarian cyst and uterine agenesis.</p> <p>Conclusion: Ovarian tumor with MRKH syndrome is a rare case. The diagnosis was based on the patient's history, clinical findings, and radiologic examination and confirmed with laparotomy and histopathology. Regular examinations are recommended to prevent and identify genital tract problems and pelvic diseases in women, especially adolescents.</p>

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INTRODUCTION

Germ Cell Tumors ovarium is derived from primitive germinal cells of embryonic or germinomatous gonads, a type of ovarian neoplasm mainly affecting young women (20-30 years old). *Germ Cell Tumors* ovarium can be malignant or benign. The incidence is estimated at 20-25% of all ovarian neoplasms and 5% of all malignant neoplasms. In general, the cause and histogenesis of *germ cell tumors* ovarium is unknown, but some ovarium are related to *dysgenetic gonads*. 5% of *dysgerminoma* patients have cytogenetic abnormalities, including partial or entire Y chromosomes, 46 XY (*testicular feminization*), gonadal dysgenesis, and mixed *gonadal dysgenesis* (45 x, 46 XY). Diagnosing germ cell tumors ovarium is challenging to establish early on because the disease often does not show symptoms (asymptomatic) in the early stages. The symptoms usually complained of are abdominal pain or adnexal torsion, but it can also be asymptomatic. Most *germ cell tumors* ovarium are benign and unilateral. However, they can proliferate; most are at stage IA, which is limited to the ovaries. If affected on both ovaries, it is usually a benign cystic teratoma, *dysgerminoma*, or a tumor with a *dysgerminoma* component (*mixed germ cell tumor*). The tumor mass can cause acute pain caused by torsion, rupture or bleeding, abdominal distension, vaginal bleeding, and fever ¹

The Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH) is characterized by congenital hypoplasia of the uterus and upper part of the vagina. The incidence of MRKH syndrome is estimated to be 1 in 4500 women. Most research suggests that MRKH syndrome is considered a genetic disease, with genes such as

HOXA7, HOXA9-13, HOXD9-13, and WNT4 among possible causes ². However, the etiology of MRKH syndrome is still unclear; embryologically, this may occur due to disrupted fusion of the Mullerian ducts during the eighth week of pregnancy. Clinical symptoms in MRKH syndrome are usually marked by the absence of menstruation (primary amenorrhea) but with normal *thelarche* and *adrenarche*, sexual dysfunction, and infertility. Primary amenorrhea can occur when a person has not yet experienced menstruation until the age of 14, accompanied by a lack of development of secondary sexual characteristics, or until the age of 16 without menstruation but with normal development of secondary sexual characteristics. MRKH classification is divided into three types: Type I, where there is a reproductive organ abnormality (*uterovaginal aplasia*); Type II, where there is asymmetrical uterovaginal aplasia or hypoplasia, accompanied by hypoplasia or absence of one or both fallopian tubes and malformations of the ovaries and/or renal system; and Type III or MURCS (*Mullerian duct aplasia, Renal dysplasia, and Cervical Somite Anomalies*), where anomalies are often associated with urological (15-40% of cases) and skeletal (20-40%) anomalies while hearing, cardiac, and digital (syndactyly or polydactyly) defects are rare. In patients with MRKH syndrome, ovarian tumors are challenging to examine, mainly if vaginal reconstruction is not performed ³. In these patients, there is abdominal pain and swelling accompanied by primary amenorrhea caused by a malignant ovarian tumor mass called *dysgerminoma* and the absence of a fully formed ovary, uterus, and vagina suspected to be due to aplasia or failure of Mullerian duct fusion. This review aims to explain the diagnostic methods and interventions performed

for ovarian tumors in Mayer-Rokitansky-Kuster-Hauser Syndrome, focusing on clinical findings and relevant case illustrations.

CASE PRESENTATION

A 25-year-old woman came to Fatimah Lamongan Hospital complaining of a lower abdomen lump and severe pain. The lump has been present for the past three months. Lower abdominal pain has been felt to worsen since two months ago. The pain is felt like stiffness in the lower abdomen. The patient often complains of yellow discharge, itching, and odor. The patient has visited the nearest midwife twice to treat abdominal pain, but no change has occurred. Other complaints include weight loss and shortness of breath. Then, the patient was taken to Muhammadiyah Lamongan Hospital for examination, and an ultrasound showed a suspected ovarian cyst was found. The patient was referred to Dr. Soetomo Hospital for further examination of the abdomen and lungs. At Dr. Soetomo Hospital in Surabaya, the patient underwent a procedure to take lung fluid to reduce shortness of breath. However, no action has been taken for suspected ovarian cyst treatment. The patient has never menstruated until now. The patient has been married once and is divorced because of the inability to penetrate during coitus. The patient has never given birth and has no history of using contraception. Past medical history includes no diabetes mellitus, hypertension, allergies, or history of breast cancer. Family history

from the patient's mother, who died, had a history of brain and ovarian cancer. The patient had attempted suicide after a divorce.

On physical examination, vital signs: blood pressure was 120/80 mmHg, pulse was 82 beats/minute, respiratory rate was 18 breaths/minute, SpO₂ was 99% on room air, axillary temperature was 36.6°C, with a VAS score of 8. Physical examination revealed anemia in the head, neck, and face (+) but was otherwise unremarkable. Lung and heart examinations were within normal limits. Abdominal examination showed distension (+); palpation: tumor mass at the center, tenderness on the suprapubic area, liver and spleen not palpable; percussion: tympanic (+); auscultation: normal bowel sounds. All four extremities were within normal limits and showed no abnormalities. The patient's breasts did not develop normally; *Tanner stage 3* showed enlarged breasts and areolas with no contour separation. Pubic hair growth distribution was not formed in *tanner stage 1*. In addition, there was fat growth in the buttocks and thighs. Body weight was 75kg, height was 160cm, with an IMT of 29.2 (Obesity 1).

Gynecological status showed normal labia majora, normal labia minora, normal size and shape of the clitoris, and the vagina was only 2cm long from the labia minora. The anal tone was expected, the anal mucosa was smooth, the uterus was suspected of hypoplasia, and there was no mass on the right or left parametrium.



Figure 1. Patient's physical examination

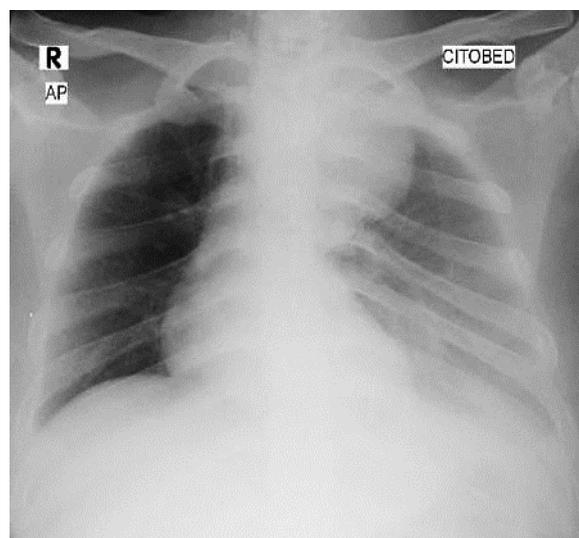


Figure 2. Thorax X-ray examination

The routine blood laboratory examination showed: Hb 10.3 g/dl, leukocytes 6,000/UL, diff count: 0-0-0-70-24-6, PCV 37.5%, platelets 716,000/ml, negative HbsAg, and HIV. No examination was performed on the hormone levels of estrogen, FSH, LH, testosterone, and prolactin.

The thorax X-ray result, it was found that the size and shape of the heart looked normal, with opacities of mass density, oval-shaped, sharp

borders, and regular edges, measuring 5.4 x 7.3 cm in the mediastinum at the level of the left Thoracic Vertebrae 1-5. No pulmonary infiltrate was detected. The trachea appeared in the middle. The right costophrenic angle was slightly blunt, and the left appeared blunt, closed with opacity. The right and left hemidiaphragm looked good. The bones and soft tissues appeared normal. The conclusion of the result was a mediastinal mass measuring 5.4 x 7.3 cm with organized pleural effusion.

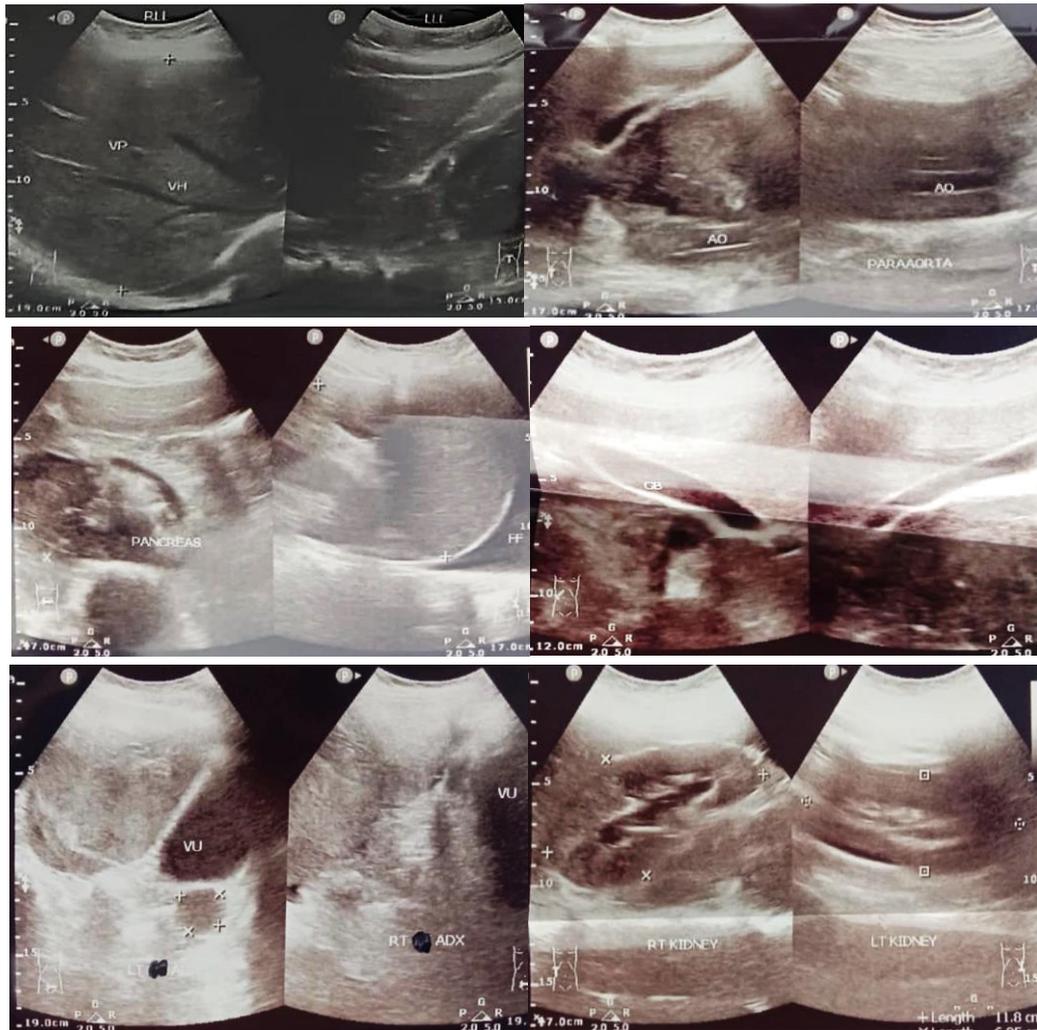


Figure 3. Ultrasound examination

The ultrasound examination result:

1. A solid hetero-echoic lobulated mass with clear borders measuring beyond the measurable probe +/- the para-aortic that encases the abdominal aorta, extending to the pelvic cavity, intra-mass vascularity (+), suggesting a lymphoma.
2. The cystic lesion in the left adnexa could be a simple cyst or a functional cyst.
3. There was mild to moderate right-sided hydronephrosis with grade II preference.
4. There was a suspicion of uterine agenesis.
5. An incidental finding was left pleural effusion.
6. The liver/gallbladder/spleen/pancreas/left kidney/bulge/right adnexa showed no abnormalities.

The patient was diagnosed with ovarian cyst torsion and suspected uterine agenesis. In the patient's management, Ringer Lactate infusion 1000cc was given within 24 hours, Ketorolac injection 3x30mg IV, Ketoprofen Suppository 1x100mg, Cefazolin injection 1x2gr IV as prophylactic antibiotics, and an emergency laparotomy was planned.

On 28 February 2023, surgery was performed, and during the operation, a twisted solid ovari-

an tumor was found with a size of $\pm 20 \times 15 \times 10$ cm on the left side of the uterus. The left proper ovarian ligament was found, while the right did not develop. Hypoplastic uterus with a size of $\pm 1 \times 1 \times 2$ cm, the uterus was generally attached to the right and left pelvic infundibulum ligament, and the right and left fallopian tubes were found, but they were tiny in shape and size, the right and left fimbriae were not found, and the right ovary was not found that showed at Figure 4.

The procedures that were performed were cystectomy and partial salpingectomy sinistra. The patient's condition was stable after surgery. The patient has undergone a follow-up examination and is in stable condition. The tissue

sample was sent to the Pathology Anatomy Laboratory of RSUD dr Soegiri Lamongan, for examination. The post-operative diagnosis was ovarian *germ cell tumors*, namely stage IIA dysgerminoma with Mayer Rokitansky Kuster Hauser (MRKH) syndrome.

Anatomical Pathology Examination, the results were obtained at Figure 5. Macroscopic findings received one piece of ovarian tissue weighing 1.764 grams, measuring 17.5x16x9.5cm. The outer surface is smooth. On the solid section, it appears grayish white with some brownish color, lobulated, and has a solid rubbery consistency as showed at Figure 6, Figure 7, and Figure 8.

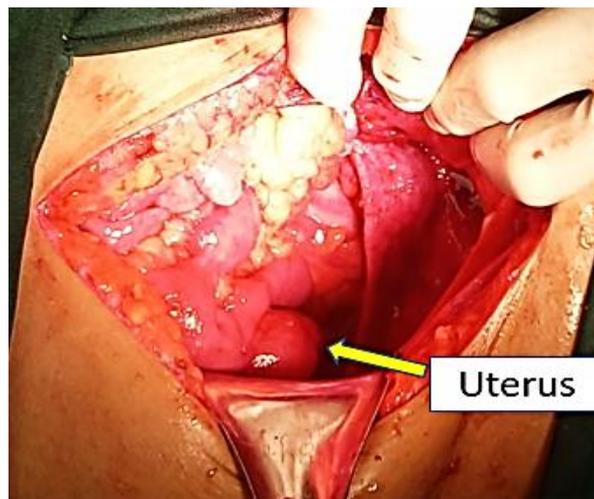


Figure 4. Durante Operation

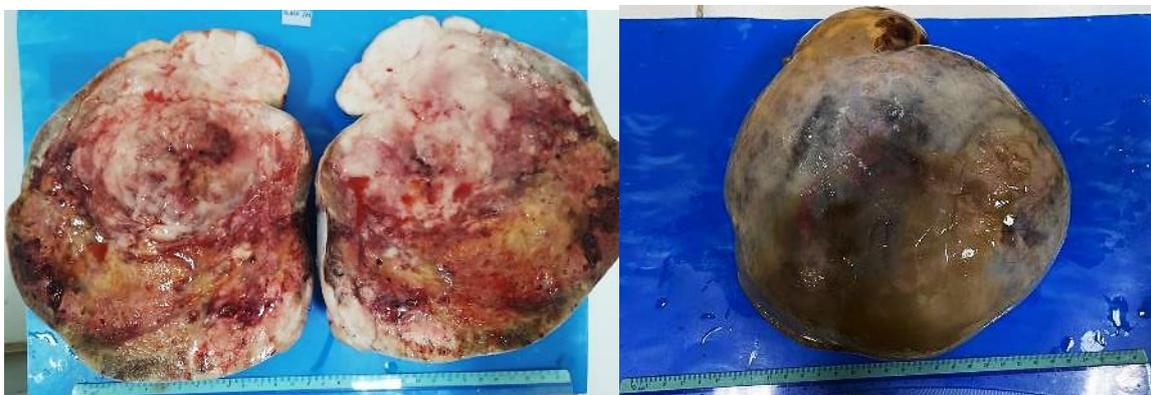


Figure 5. Macroscopic preparations

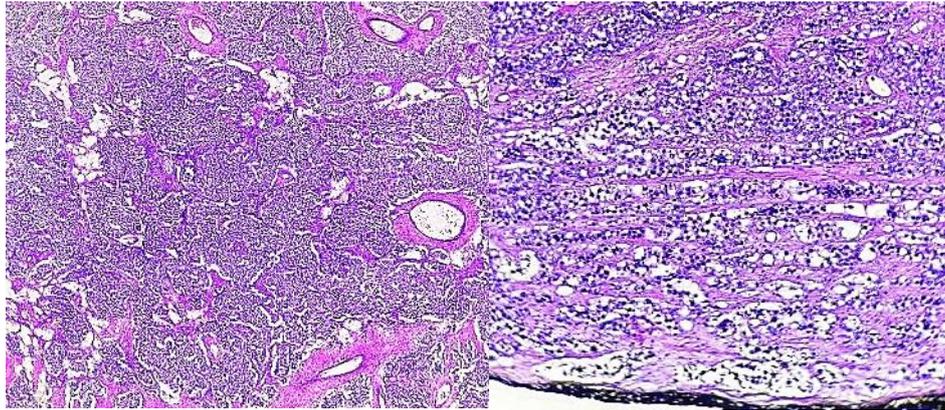


Figure 6. Microscopic cross-section 40x magnification

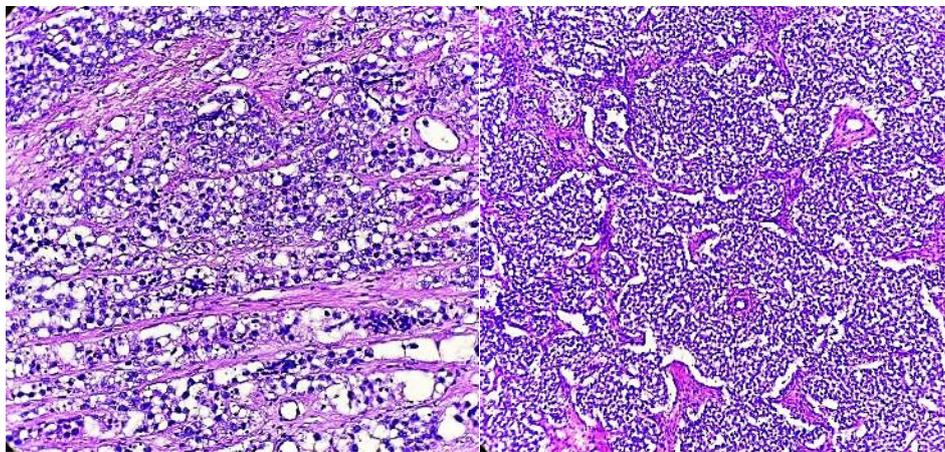


Figure 7. Microscopic cross-section 100x magnification

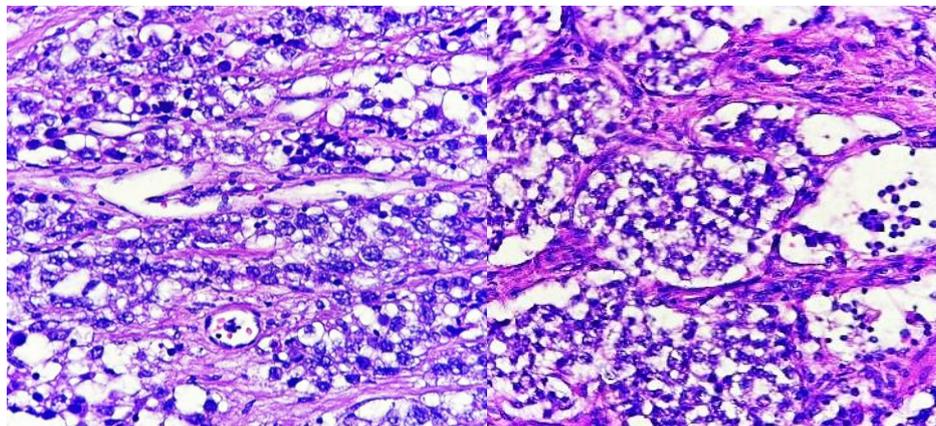


Figure 8. Microscopic cross-section 400x magnification

Microscopic results showed a section of ovarian tissue with tumor growth arranged in solid nests bordered by fibrotic connective tissue with infiltration of lymphocyte and histiocyte cells, some in rows. The tumor consists of heavily pleomorphic, hyperchromatic, oval-

shaped nuclei, prominent nucleoli, narrow-wide and clear cytoplasm, with 9/10 HPF mitosis. There are large areas of necrosis visible. The tumor grows up to the edge of the ovary. In conclusion: a malignant germ cell tumor with a dysgerminoma impression growing up

to the edge of the ovary but not penetrating the capsule.

DISCUSSION

Dysgerminoma is the most common type of germ cell tumor in the ovary, accounting for only 3% of all ovarian cancers. Symptoms may be asymptomatic or present with abdominal pain, leading to misdiagnosis as acute appendicitis, ectopic pregnancy, acute abdomen, or abdominal distension with vaginal bleeding⁴. In this case, the patient complained of a palpable mass in the abdomen, severe abdominal pain, and progressive unexplained weight loss. Patients with *dysgerminoma* may also complain of abdominal pain and enlargement accompanied by an abdominal mass caused by hemoperitoneum or torsion from tumor rupture due to rapid tumor growth. Active hormonal tumor growth can cause abnormal menstruation, which may be the final stage of the tumor⁵.

Routine blood tests in this patient showed anemia and thrombocytosis. Thrombocytosis can occur due to the influence of cytokine formation, such as IL-6 (interleukin-6), and the release of cytokines is influenced by various factors such as inflammation, infection, malignancy, or stress. This condition will result in increased thrombopoiesis and increased platelet levels. Tumor markers such as CA-125, AFP, and CEA are produced by cancer cells or in response to the presence of cancer in the body⁶. Tumor marker tests are necessary as screening and supporting diagnostic cancer tests. However, tumor marker tests have not yet been performed in this case.

Dysgerminoma is a malignant tumor that tends to spread through the perirectal lymphatic system

to the lymph nodes around the aorta. It most commonly spreads via lymphatics to the para-aortic lymph nodes, and hematogenous spread can occur in the advanced stages of the disease. Clinical manifestations can be found in rapid tumor growth, and symptoms can last from one to six months before diagnosis, as in our patient, who already had involvement in the para-aortic lymph nodes⁷.

The most common metastasis in dysgerminoma is the peritoneal cavity, omentum (86%), pelvis and abdomen, and retroperitoneal lymph nodes. Then, extra-abdominal lymph nodes, such as para-aortic, supraclavicular, and cervical lymph nodes. Hematogenous metastasis can also occur in the bone, lungs (15%), liver, kidneys, adrenal glands, mammary glands, skull, brain, dura mater, intra-axial, pancreas, liver, and skin. There are also many uncommon distant metastasis sites reported, such as the eyes, placenta, bronchial-tracheal tract, bladder (17%), pleura (33%), spleen (20%), intestines (50%), and neurological involvement such as carcinomatous meningitis⁸.

In this case, a mass measuring 5.4 x 7.3 cm was found in the mediastinum at the level of Thoracic Vertebrae 1-5 from a chest X-ray examination. This mediastinal mass is not a metastasis of the dysgerminoma tumor in the ovary because, based on the PA examination, the tumor cells did not penetrate the capsule, thus not proving a relationship between the mediastinal mass and the dysgerminoma tumor in the patient⁹.

In making the diagnosis of dysgerminoma can be done with several supporting examinations, including a radiological examination. In most cases of ovarian dysgerminoma, ultrasounds

show a multilobular tumor with a smooth contour, well-defined borders, and heterogeneous echogenicity characterized by prominent fibrovascular septa. Necrosis, hemorrhagic areas, and speckled calcifications may also be defined¹⁰. This finding is consistent with the findings in our case. However, the various radiological features lead to various differential tumor diagnoses. Hence, the need to know about ovarian dysgerminoma's pathology, symptoms, and markers to optimize radiological interpretation and enable appropriate treatment and follow-up. In addition, in diagnosing dysgerminoma, it is only possible to enforce histopathological examination¹⁰.

On histopathological examination of dysgerminoma, macroscopically *dysgerminoma* is large, solid, multinodular tumors that appear fleshy, yellow, or cream-colored. Areas of necrosis, hemorrhage, and cystic den may occur, while calcifications can also be seen in *dysgerminomas*, typically with a speckled or spotted pattern. Grossly visible calcifications only occur in *dysgerminomas* arising from a pre-existing gonadoblastoma with calcifications described as mottled or punctate. However, calcifications may also be detected in *dysgerminomas* without an underlying recognizable gonadoblastoma. Microscopically, *dysgerminomas* comprise round cell nests separated by thin fibrous septa infiltrated by lymphocytes. Tumor cells are large and polygonal, with clear or eosinophilic cytoplasm containing a prominent central nucleus. Mitoses are often abundant. Immunohistochemically, *dysgerminomas* can be positive for octamer-binding transcription factor 4, Sal-like protein 4, LIN28, NANOG, KIT (CD117), and D2-

40, and negative for epithelial membrane antigen, CD30, and GPC3, while cytokeratins may be focally positive¹¹

Managing ovarian cancer in dysgerminoma depends on the staging of the tumor. In stage 1A, conservative surgery can be performed, including staging laparotomy with unilateral salpingo-oophorectomy. Chemotherapy is not required in stage 1A unless there is a recurrence (9.2% of cases). Treatment for stage 1B includes bilateral salpingo-oophorectomy with or without a total abdominal hysterectomy and three cycles of chemotherapy with Bleomycin, Etoposide, and Platinum. Meanwhile, for stages II, III, and IV, complete tumor resection and four cycles of chemotherapy with Bleomycin, Etoposide, and Platinum are performed⁴.

In this patient, it is an ovarian tumor with stage IIA, where the tumor has spread to the uterus and/or the fallopian tube. In this case, a cystectomy and partial salpingectomy sinistra were performed, and a microscopic examination of the resected surgical specimen was conducted to confirm the diagnosis of dysgerminoma. *Dysgerminoma* is a malignant tumor, but it has an excellent prognosis. After salpingo-oophorectomy, the cure rate for unilateral tumors without invasion or capsule spread is 96%. In treating dysgerminoma, surgery is not only therapeutic but also necessary to determine the diagnosis and stage of the tumor⁵. For now, the patient with dysgerminoma is referred to the RS dr. Soetomo for chemotherapy management¹²

According to the WHO 2020 Tumor Classification, ovarian *dysgerminoma* usually occurs as part of gonadal dysgenesis. The tumor can be

found incidentally during the examination to determine the cause of primary amenorrhea in women with gonadal degeneration with karyotype disorders of 46 XY known as pure gonadal degeneration, mixed gonadal dysgenesis (45X/46XX), or partial gonadal dysgenesis (46XX). Therefore, in this explanation, dysgerminoma has a high risk of gonadal neoplasia. Previous findings have shown that patients with gonadal degeneration in the MRKH syndrome risk developing *dysgerminoma*, and bilateral gonadectomy intervention is recommended. Howitt et al. reported that the incidence of dysgerminoma in people with abnormal genital development or chromosomal abnormalities is around 5-10%. Although our patient experienced primary amenorrhea, we do not have data on genetic testing. Therefore, we suggest performing genotype testing or mutation screening that is useful for the patient and other family members ¹³.

Several studies suggest that patients with unknown MRKH syndrome are more likely to develop germ-cell tumors, such as dysgerminoma. In our case, it indicates that this patient has the potential risk of ovarian neoplasm. As for *dysgerminoma*, the patient is currently referred to RS dr Soetomo for chemotherapy management ¹².

There is no consensus regarding follow-up therapy for dysgerminoma, but follow-up therapy is recommended every three months for the first three years and every six months for the next two years. Moreover, every year, an evaluation will be carried out for the next ten years. The usual follow-up actions consist of a clinical examination; imaging; examination of bio-

markers, especially beta-human chorionic gonadotropin (B-HCG), and chest X-ray for metastases ^{14,15}.

However, treatment of these tumors is the most successful and responds well to surgical removal of the tumor, showing 60-80% survival rates in advanced stages and even 100% in early stages. Chemotherapy can increase survival rates, even in advanced stages, by up to 98%. If a patient resists chemotherapy, immunotherapy or stem cell transplantation can be performed ^{14,15}.

The MRKH syndrome diagnosis is often made during adolescence after experiencing primary amenorrhea, which is the absence of menstruation until the age of 25 years and shows one of the following three signs: (1) no menstruation until the age of 14 years, accompanied by the absence of growth or development of secondary sexual characteristics; (2) no menstruation until the age of 16 years, accompanied by average growth and development of secondary sexual characteristics; (3) no menstruation for at least three consecutive months in females who previously had menstrual periods. Patients are classified as having primary amenorrhea if amenorrhea occurs before menarche, which is the first menstrual period experienced by women. Primary amenorrhea is caused by various factors, evaluated based on the division of four compartments, namely disorders of the uterus and patency (*outflow tract*), disorders of the ovaries, disorders of the pituitary gland, and disorders of the hypothalamus/central nervous system ¹⁶.

In Mayer-Rokitansky-Kuster-Hauser syndrome, it is suspected that the cause is due to anomalies in the female genital organs resulting

from defects in the lateral and vertical fusion process of the urogenital sinus and Mullerian ducts. The fusion process of the right and left Mullerian ducts will be completed at 12 weeks of pregnancy, while the canalization process will be completed at five months. Failure of vertical fusion between the Mullerian ducts and the urogenital sinus will cause abnormalities in the canalization of the genital organs. Furthermore, failure to perform lateral fusion will cause organ duplication. Resorption disorders will result in the formation of a septum. In this case, uterine hypoplasia, absence of both right and left fallopian tubes, absence of the right ovary, and a 7 cm long vagina classified as hypoplasia or agenesis involving both Mullerian ducts are found, resulting in the absence of the uterus, both fallopian tubes, and the upper third of the vagina¹⁷.

The psychosocial impact of MRKH syndrome should not be underestimated, and clinical care mainly involves comprehensive counseling and support in a dialogue that needs to be handled carefully with patients. Vaginal agenesis therapy is provided for adult patients after going through counseling and therapeutic handling education through non-invasive vaginal dilatation as the recommended first-line therapy or vaginoplasty surgery as the second-line choice for patients who experience dilatation failure. Meanwhile, for absolute uterine infertility factors, definitive action cannot be taken, and until now, the only option for patients who want to become biological mother is through gestational surrogate mothers, which is still prohibited in most countries¹⁸.

MRKH syndrome has long-term psychological effects on patients, resulting in low self-esteem,

poor coping strategies, depression, and anxiety symptoms. Providing psychological counseling and peer support for diagnosed patients is recommended. Appropriate and timely psychological interventions can significantly improve patient psychological outcomes¹⁹.

The spread of tumors is generally through the lymphatics. Spread locally, and it can reach the pelvis, paraaortic, peritoneum, and retroperitoneal. It occurs in bone organs, lungs, liver, and kidneys during distant spread. In this case, a microscopic examination showed that the capsule was still intact without spreading after the salpingo-oophorectomy was performed. Infiltration of lymphocytic cells and histiocytes was seen, some in rows. The tumor consists of round, oval, pleomorphic, hyperchromatic nuclei, prominent nuclei with narrow and clear cytoplasm, and large areas of necrosis are seen which indicate signs of malignant cells^{20,21}.

CONCLUSION

According to the anamnesis, clinical findings, and ultrasound examination, it was found that the patient had an ovarian tumor accompanied by MRKH syndrome. Subsequently, laparotomy was performed to determine the diagnosis of the ovarian tumor with MRKH syndrome. This finding was followed by an anatomical pathology examination which helped determine the pathological type of the ovarian tumor, namely the malignant *Dysgerminoma* tumor. Therefore, early diagnosis of ovarian tumor *dysgerminoma* with MRKH syndrome can help provide prompt and accurate treatment by performing tumor excision. From the above explanation, it is recommended that women, especially teenagers who have not menstruated,

should be regularly examined to check for genital malformations and to detect pelvic diseases such as ovarian tumors, leiomyomas, and mass adhesions.

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