PRIMARY AMENORRHEA AND KABUKI SYNDROME

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ABSTRACT

Introduction: Kabuki Syndrome (KS) has been reported in all ethnicities with an estimated prevalence of 1:32,000 to 1:86,000. Diagnosing and managing Kabuki Syndrome is quite difficult. Its management depends on the presenting manifestations and therefore requires multidisciplinary collaboration.
Case: A 24-year-old woman came to the hospital complaining of an enlarged abdomen and abdominal pain. In the anamnesis, information was obtained that at birth, atresia ani was found, surgery was performed when she was 2 weeks old. On examination, it was found that the growth and psychological development was still like a child (still wetting the bed, impaired attention, hearing loss). The patient had also never menstruated and was said to have ovarian cysts and hematocolpos, so she was referred to RSDS. On examination at RSDS, a malocclusion of the jaw, spaced teeth, cupped ears were found. The uterine sonde could not enter the vaginal introitus. Prader Scale 2/5 and pubic hair T2. Findings on MRI lead to a picture of Mullerian agenesis accompanied by proximal to distal vaginal agenesis. Bilateral endometriomas were also found. This patient was also suspected of scoliosis. The patient was diagnosed with Kabuki Syndrome with cervicovaginal agenesis, primary amenorrhea, hematometra, endometrioma and bicornu uterus. The patient was proposed to be given pain management by giving continuous combined oral contraceptives (COC) to reduce cyclic pain, given 3 months and evaluation of the mass increasing in size / no improvement performed hysterectomy. The results of the operation revealed the presence of pyometra and tubo ovarian abscess dextra sinistra so that TAH-BSO was performed. HRT was given because the patient had iatrogenic POI. Continual evaluation to adjust the dose and ensure adherence to therapy is essential to minimize risk and improve quality of life.
Conclusion: Early diagnosis and proper management of Kabuki Syndrome is the key to better patient survival and prognosis.

Keywords: Kabuki Syndrome, diagnosis, Iatrogenic POI

INTRODUCTION

Kabuki syndrome (KS) (also known as Niikawa-Kuroki syndrome) is a rare inherited disorder that was first recognized as a distinct entity by two groups of physicians in 1981 (Barry et al., 2022; Sattur, 2014). KS has been reported in all ethnicities with an estimated prevalence of approximately 1:32,000 to 1:86,000. KS can be found with several common manifestations such as gestalt facial features (e.g., arched eyebrows with lateral sparsening, eversion of the lateral third of the lower eyelid, long palpebral fissures, hypoplastic columella, prominent ears, cleft lip, and/or cleft palate), skeletal abnormalities, dermatoglyphic abnormalities, mild to moderate intellectual disability, postnatal growth deficiency and many more (Barry et al., 2022; Marques et al., 2023).

Kabuki syndrome is characterized by obvious facial dysmorphism, growth retardation, delayed psychomotor development and various other manifestations affecting various body systems. Its genetic etiology has been demonstrated to be the cause of this syndrome. Since then, KS has been increasingly studied in the fields of family medicine and pediatrics. Initially, the syndrome was thought to occur only in East Asian races; however, new data does not clearly indicate the prevalence of KS in any ethnic population. Clinical diagnosis of KS often requires long-term monitoring as the phenotype changes over time, with characteristic dysmorphisms and other key features tending to appear after several years of life. Prenatal, neonatal and family history is often usual or normal. The presence of facial dysmorphism may be sufficient to raise suspicion of KS, after which genetic diagnosis should be performed to confirm KS (Boniel et al., 2021; Stagi et al., 2016).

Various combinations of these major clinical manifestations should prompt clinicians to consider the diagnosis of KS; however, the major manifestations are not developed in such a way as to serve as formal clinical diagnostic criteria. A number of other congenital anomalies and functional differences have been described in association with KS, and various combinations of these features may also prompt consideration of the diagnosis. Understanding the function of the genes that cause KS, opens up opportunities for the development of targeted therapies for individuals with KS (M. P. Adam et al., 2019).

Diagnosing and managing Kabuki Syndrome is quite difficult. The management depends on the manifestations and therefore requires multidisciplinary collaboration. Currently, there is a consensus in the literature that facilitates the diagnosis of Kabuki Syndrome. This case report will present a case of a female patient with Kabuki Syndrome at RSUD Dr. Soetomo Surabaya. In this case report, case observation, how to diagnose, and management are carried out. It is hoped that this case report can provide further information and knowledge about Kabuki Syndrome.

CASE DESCRIPTION

A 24-year-old woman came to the hospital complaining of an enlarged abdomen and abdominal pain, a light weight of 20 kg, and a low height, which is only about 126 cm which can be said to be included in growth disorders. In addition, this patient is also suspected of scoliosis disorder which is a skeletal disorder, and has also been diagnosed with osteochondroma. In the anamnesis, information was obtained that at birth, atresia ani was found, surgery was performed when he was 2 weeks old. On examination, it was found that the

growth and psychological development was still like a child (still wetting the bed, impaired attention, hearing loss). The patient had also never menstruated and was said to have ovarian cysts and hematocolpos, so she was referred to RSDS. On examination at RSDS, a malocclusion of the jaw, spaced teeth, cupped ears were found. The uterine sonde could not enter the vaginal introitus. Prader Scale 2/5 and pubic hair T2.

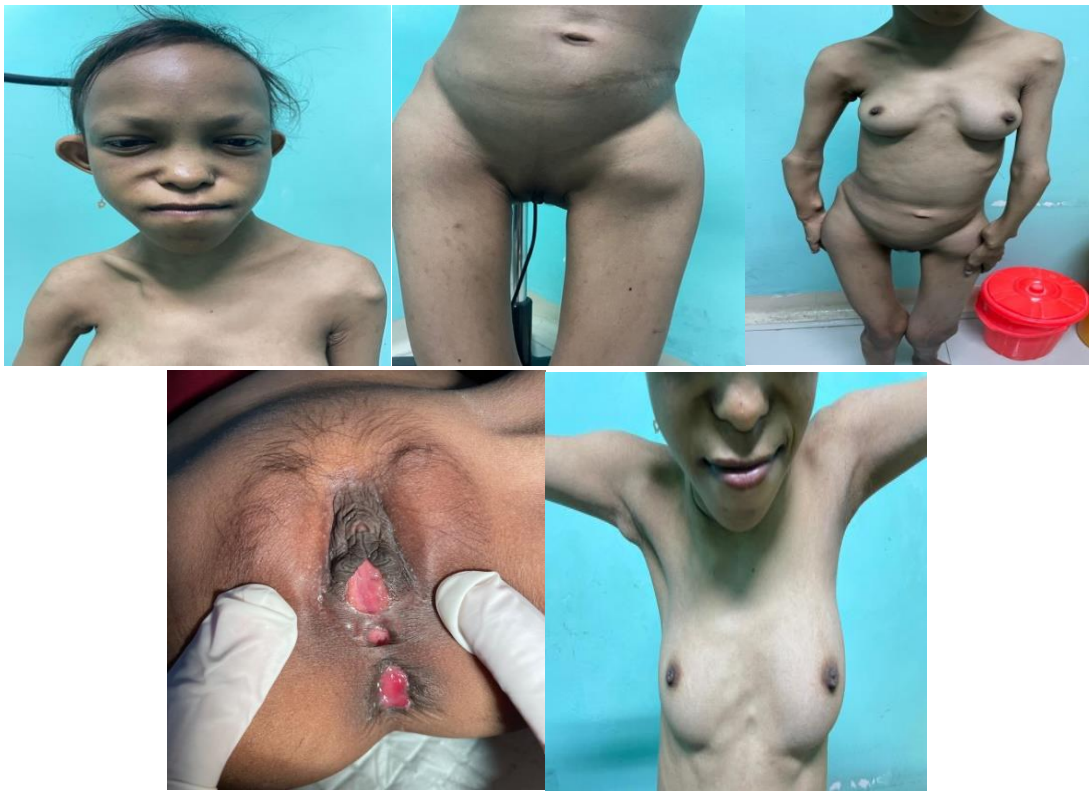

Figure 2.1 Examination Results on Patients

The findings on MRI were suggestive of Mullerian agenesis with proximal to distal vaginal agenesis. Bilateral endometriomas were also found. This patient was also suspected of scoliosis

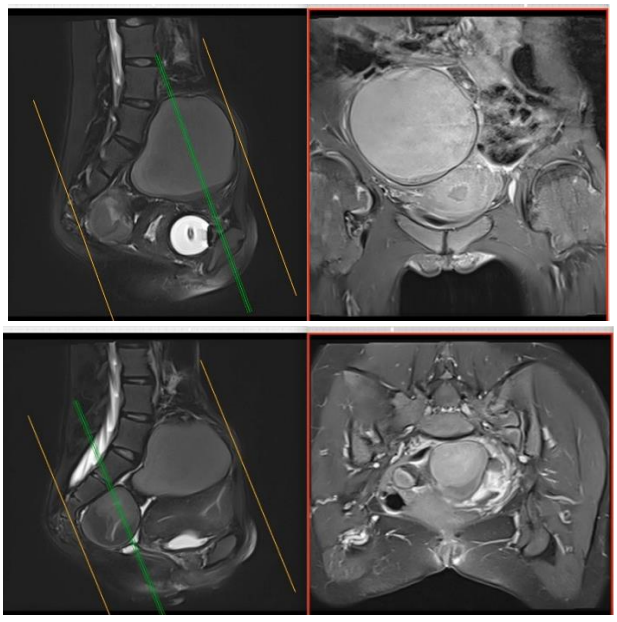

Image2 Abdominal Pelvic MRI Examination Results

Bilateral endometriomas (right size +/- 3.7 x 2.9 x 5.4 cm; left size +/- 8.7 x 6.9 x 6.4 cm) were also found. The patient was diagnosed with Kabuki Syndrome with cervicovaginal agenesis, primary amenorrhea, hematometra, endometrioma and bicornu uterus. The patient was proposed to be given pain management by giving continuous combined oral contraceptives (COC) to reduce cyclic pain, given 3 months and evaluation of the mass increasing in size / no improvement carried out hysterectomy. The results of the operation revealed the presence of pyometra and tubo ovarian abscess dextra sinistra so that TAH-BSO was performed.

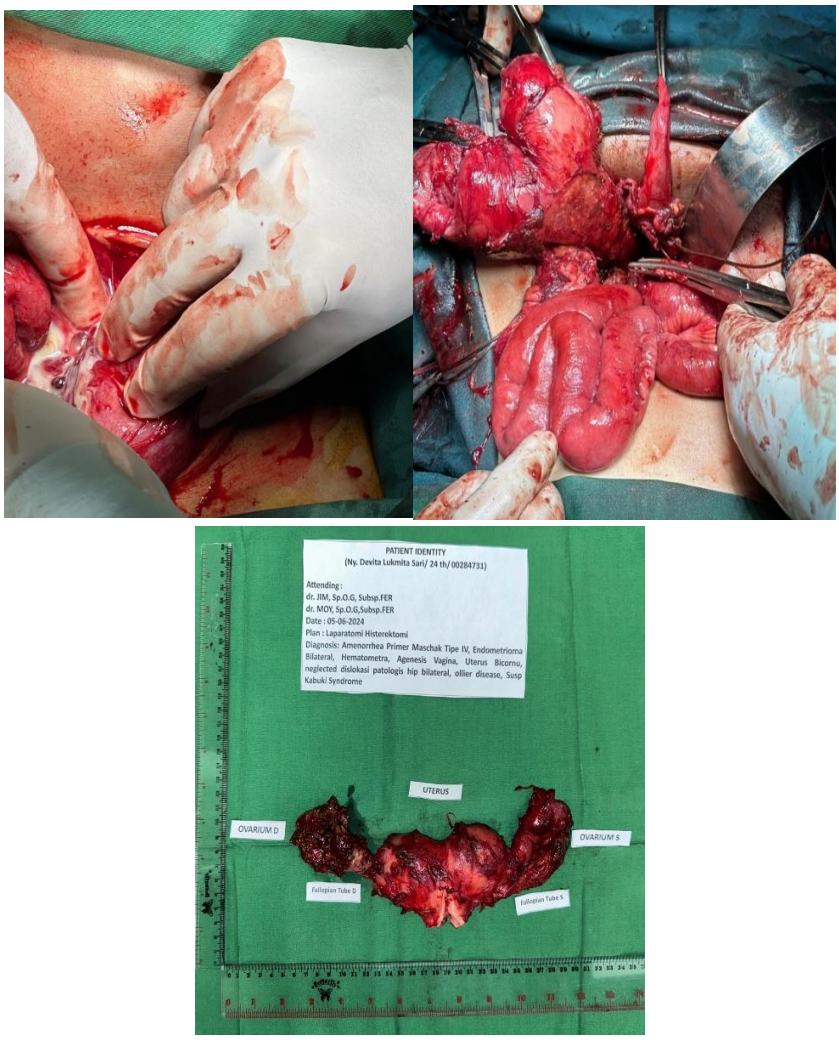

Figure 3 Pyometra, Durante Operation (Uterus Bicornu), PA Tissue

HRT was administered because the patient had iatrogenic POI. Periodic evaluation to adjust the dose and ensure adherence to therapy is essential to minimize risk and improve quality of life.

DISCUSSION

Kabuki Syndrome (KS) was originally thought to occur only in Japanese people. Its prevalence was estimated at 1/32,000. However, the global incidence rate of KS is unknown (Cheon & Ko, 2015). The prevalence of KS in Australia and New Zealand is estimated to be around 1/86,000. However, this prevalence of KS is still considered inappropriate due to under-diagnosis (M. Adam & Hudgins, 2005). Kabuki Syndrome (KS) is caused by genetic factors

that are not fully understood, although most patients have normal chromosomes. Some cases show cytogenetic abnormalities, such as X or Y chromosome abnormalities, as well as other chromosomal anomalies such as heterozygous deletions in the KDM6A gene and mutations in the KMT2D gene that are often associated with KS. About 20% to 45% of patients still have no clear genetic basis, so further research is needed. Mutation analysis in KMT2D and KDM6A is an important step in the early diagnosis of KS. It is also recommended to perform Chromosomal Microarray Analysis (CMA) in prenatal diagnosis in fetuses with signs of growth delay and cardiovascular or musculoskeletal abnormalities.

Traditionally, Kabuki syndrome is diagnosed based on five main manifestations, namely characteristic facial features (lower lateral eyelid eversion, arched eyebrows with sparse lateral third, depressed nasal tip, and prominent ears), skeletal anomalies (spinal deformity, brachydactyly), dermatoglyphic abnormalities, mild to moderate mental retardation, and postnatal growth deficiency. Although these findings are helpful in diagnosis, Kabuki syndrome has a very diverse spectrum of symptoms. In 2019, an international consensus established diagnostic criteria to facilitate diagnosis, which includes a history of infantile hypotonia, developmental delay, as well as the presence of pathogenic variants in the KMT2D or KDM6A genes, or typical dysmorphic features such as lower eyelid eversion, arched eyebrows, depressed nose, large and prominent ears, and persistent fingertip pads. Supporting clinical manifestations in the diagnosis of Kabuki syndrome include short stature, microcephaly, cleft palate, hearing loss, congenital heart defects, feeding difficulties, and immunologic disorders. The diagnosis of Kabuki syndrome may be considered in patients with a history of infantile hypotonia and developmental delay if accompanied by at least three supporting clinical manifestations, or two supporting clinical manifestations with a possible diagnosis. Initially, the diagnostic criteria for Kabuki syndrome were based on five key features, but these criteria may need to be expanded in the future. Clinical manifestations in Kabuki Syndrome patients cover a wide range of body systems, including growth and endocrinology, infantile hypotonia, epilepsy, cardiac, gastrointestinal problems, external and internal ear abnormalities, orthodental manifestations, ophthalmologic, cancer, and nephrologic problems.

Kabuki disease can lead to different phenotypes of clinical manifestations and complications in each patient, depending on the mutated gene and the general condition of the patient. The proposed management depends on the phenotype and the affected organ as not all patients with the disease show the same symptoms. In addition, there is no universally effective cure for this disease. All available treatments aim to improve the patient's quality of life as there is currently no proven standard treatment for the disease. Genetic counseling is one of the most important recommendations for Kabuki patients and their families as it can help with more effective and better management of the disease. As these patients show almost all symptoms from birth, medical monitoring is necessary to prevent severe complications of the disease as, sometimes, some of the complexities of this condition can jeopardize one's life (Zhoulideh, 2023).

Since the cause is unknown, Kabuki syndrome can only be treated symptomatically. This means that the doctor mainly assesses the severity of the syndrome and then plans treatment accordingly. If there are restrictions in walking, standing or speaking, physical therapy is highly recommended. In contrast, if organ deformities have been diagnosed, doctors concentrate primarily on healing or treating the damaged organs. Life support and symptom

management are the most important issues for doctors. It can be concluded that in most of these cases, only the symptoms can be treated, but not the cause (Zhoulideh, 2023).

Kabuki Syndrome has also been associated with anomalies in the mullerian duct (Mama, 2012). If there is an active endometrium at the agenesis of the mullerian duct, the patient may experience cyclic or chronic abdominal pain. MRI should be performed to assess for remnant Mullerian. Although laparoscopy is not necessary to diagnose mullerian agenesis, it may be useful in the evaluation and management of patients reporting pelvic pain. Patients may have pain due to ovulation or endometriosis, which may improve with hormonal suppression. Patients may also have endometriosis due to retrograde menstruation resulting from obstruction of the uterine horn. When the uterine horn is occluded in the presence of active endometrium with no identified proximal cervix and vagina, laparoscopic removal of the occluded uterine structures should be performed. Evaluation of associated congenital anomalies is essential as up to 53% of patients with müllerian agenesis also have congenital malformations, especially of the urinary and skeletal tract. Skeletal abnormalities (e.g. scoliosis, spinal curvature disorders, wrist hypoplasia) have been reported in approximately 8-32% of patients; therefore, spinal radiographs (X-rays) may show skeletal anomalies even in asymptomatic patients. Various uterine anomalies, which include mullerian agenesis, may be associated with vertebral anomalous relationships, anorectal malformations, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal anomalies, defects in the extremities). The karyotype evaluation of patients with mullerian agenesis is 46, XX in most individuals (Committee on Adolescent Health Care, 2018).

Underdevelopment of the Müllerian duct leads to agenesis and atresia of the vagina, cervix, or uterus, which can cause hematometra and hematocolpos (Kallini et al., 2021). Hematometra is the collection or filling of the uterus with menstrual blood. Hematometra can occur and is a congenital or acquired disease. Hematometra most commonly presents with symptoms of amenorrhea, pelvic pain with or without urinary tract symptoms. A good pelvic examination and ultrasound are very useful to aid diagnosis (N Fobellah et al., 2021). Imaging on MRI and ultrasound shows a dilated uterine cavity corresponding to the size of the hematometra with an example as shown below (Kallini et al., 2021).

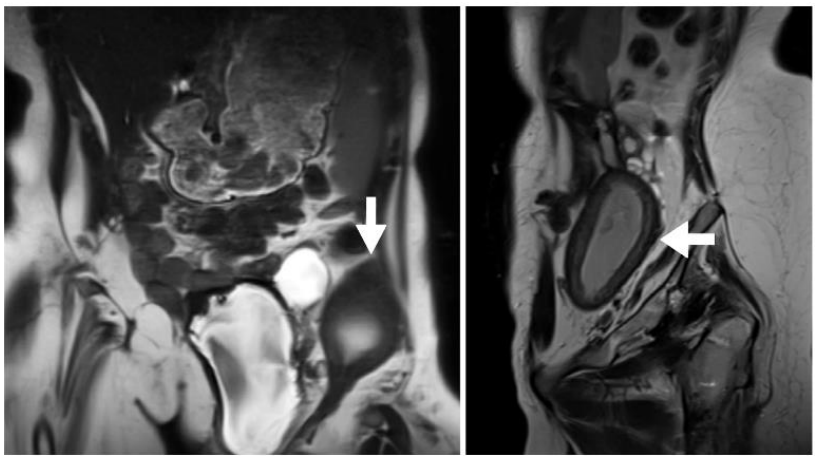

Image 1 Coronary and Sagittal T2 MRI Imaging in a Patient with Unicornuate Uterus and Cervico-Vaginal Agenesis. Dilated and Fluid-Filled Uterus (Arrow), Consistent with Hematometra (Kallini et al., 2021).

Cervical or cervico-vaginal agenesis usually presents around the age of menarche with complaints of primary amenorrhea and/or cyclical abdominal pain. Cervicovaginal agenesis is a rare congenital disorder of the female genital tract. Only a few cases and case series have been reported in the literature. The most common presenting complaint is primary amenorrhea with recurrent abdominal pain and/or chronic pelvic pain, palpable abdominal mass, and urinary complaints. Although clinical history and examination are very important in such cases, pelvic imaging should be considered for the exact anatomical abnormality. MRI is considered the gold standard for diagnosis as well as to look for causative anomalies, in this case such as cervicovaginal agenesis (Khoiwal et al., 2021).

In this case, the patient is proposed to be given pain management, pro laparoscopic cyst puncture + evacuation of hematometra, neovagina, administration of dienogest 1x2 mg, suggestion of continuous combined oral contraceptives (COC) to reduce cyclic pain, given 3 months and evaluate the mass increases in size / no and if it fails IEC hysterectomy.

Kabuki disease may present different phenotypes of clinical manifestations and complications in each patient, depending on the mutated gene and the general condition of the patient. The proposed management depends on the phenotype and the organs affected as not all patients with the disease show the same symptoms. All available treatments aim to improve the patient's quality of life as there is currently no proven standard treatment for the disease (Zhoulideh, 2023).

Surgical management of hematometra due to imperforate hymen and transverse vaginal septum is straightforward and has minimal complications. However, neovagina and neocervix creation surgery is more complex and associated with high morbidity and limited success; many of these patients eventually require hysterectomy. In the literature, many have concluded that the treatment of choice should be hysterectomy, and psychological support as reconstructive surgery has serious complications such as sepsis, endometriosis, and the need for multiple surgeries due to restenosis (Khoiwal et al., 2021).

On the contrary, as surgical skills and assisted reproductive techniques develop over time, conservative surgery can be considered as the first-line treatment. Cervico-vaginal agenesis should be suspected if a young girl has primary amenorrhea and cyclic abdominal pain, as in this case. Early diagnosis and management are critical for a successful outcome (Khoiwal et al., 2021).

The occurrence of a bicornu uterus as well as complete cervico-vaginal agenesis are rare findings. These cases can have symptoms of cyclic pain. Thus, cervico-vaginoplasty and metroplasty options are not realistic in these cases. In the literature review, there are very few cases of bicornu uterus with cervico-vaginal agenesis. Generally, the approach taken in these cases is hysterectomy followed by neovagina creation at a later date (Meena et al., 2019). The neovaginal creation methods used in the management of cervico-vaginal agenesis can be divided into two groups: non-surgical and surgical techniques. While non-surgical techniques are based on mechanical dilatation procedures, surgical methods involve intra-abdominal traction or the use of allogeneic or autogenic transplants. To date, no randomized controlled trial has been conducted to evaluate and compare the long-term outcomes of different methods of neovaginal construction (Kölle et al., 2019).

Endometriomas are cystic lesions that are a severe type of endometriosis disease. Endometriomas are most commonly found in the ovaries. Endometriomas contain dark brown

endometrial fluid and are sometimes referred to as "brown cysts". The presence of endometriomas indicates a more severe stage of endometriosis. Endometriomas can cause chronic pelvic pain and infertility and often require surgery as a treatment (Hoyle & Puckett, 2023). To make a diagnosis, anamnesis, physical examination, and supporting examination are carried out. In the anamnesis, it can be found that there is pain in the pelvic area that lasts long enough and interferes with daily activities. Another symptom that the patient complains of is infertility. Moderate or severe endometriosis affecting the ovaries will interfere with ovum motility in the uterine tube which ultimately causes infertility (Iskandar, 2021).

This examination has low sensitivity, because CA 125 levels are also elevated in infectious conditions pelvic inflammation, myoma, and the early trimester of pregnancy. Therefore, CA-125 is usually only used as a prognostic monitor for postoperative endometriosis. CA-125 > 65 IU/ml preoperatively indicates the severity of endometriosis. This is appropriate, where in this patient the CA-125 examination result was 107 U/mL. On ultrasound, it can be seen that there is a diffusely enlarged uterus and a picture of uterine wall thickening, especially in the posterior part with echogenic foci, eccentric endometriosis cavity, thickening with a hyperechoic picture, 5-7 mm cystic pockets that spread to resemble a honeycomb picture. Magnetic resonance imaging (MRI) images may show diffuse myometrial wall thickening. Laparoscopy is the gold standard diagnostic tool for diagnosing endometriosis. When endometriosis grows in the ovaries, cysts called endometriomas may form. Usually the contents are blackish brown in color so it is also called a chocolate cyst (Iskandar, 2021)

The treatments that can be given to endometriosis patients are medication, hormonal, surgical, and a combination of medication and surgery. The choice of treatment depends on the individual circumstances of the patient, which include (1) the symptoms that appear and their severity, (2) the location and severity of endometriosis, and (3) the desire to have further children. Treatment by giving painkillers such as paracetamol 500 mg 3 times a day, Non-Steroidal Anti Inflammatory Drugs (NSAIDs) such as ibuprofen 400 mg three times a day, or mefenamic acid 500 mg three times a day can be given. Tramadol, paracetamol with codeine, Gamma Amino Butyric Acid (GABA) inhibitors such as gabapentin can also be given. Progestin administration allows antiendometriosis effect by causing early decidualization of endometrial tissue followed by atrophy. Administration of depot progesterone injections such as birth control injections can help reduce symptoms of pain and bleeding. treatment of endometriosis by administration of low-dose contraceptive pills. Monophasic combined oral contraceptives (once daily for 6-12 months) are a frequent first choice to induce a false pregnancy condition with onset of amenorrhoea and decidualization of endometrial tissue. Any combination of contraceptive pills in low doses containing 30-35 μg of ethinylestradiol used continuously can be effective against endometriosis treatment (Iskandar, 2021).

Conservative surgery can also be performed, where the aim of the surgery is to remove all the endometriosis nests and release the adhesions and restore the reproductive anatomical structure. Endometriosis nests are removed by excision, cautery ablation, or laser. While endometriosis cysts < 3 cm are drained and the cyst wall cauterized, cysts > 3 cm are cystectomized leaving healthy ovarian tissue. Surgical treatment can be done by laparotomy or laparoscopy. Radical surgical treatment can also be performed with hysterectomy and bilateral salfingo-oophorectomy, and is performed on women who have failed conservative medical or surgical treatment and do not need reproductive function (Iskandar, 2021).

In this case, because TAH-BSO has been performed, the patient is in a state of premature ovarian failure caused by medical intervention or referred to as Iatrogenic POI (Premature Ovarian Insufficiency). POI is a condition where ovarian function diminishes or stops before the age of 40, causing infertility and other hormonal problems. In the iatrogenic context, POI is usually induced by medication or medical procedures such as chemotherapy, radiation for cancer, or surgery involving the ovaries or reproductive system. Certain medications used to treat cancer, autoimmune or other conditions can damage the ovaries, causing a decrease in hormone or egg production.

As KS is not usually associated with severe medical complications, it is thought that the prognosis of survival to adulthood is good, especially if congenital abnormalities, such as congenital heart disease, and infections are well managed in childhood (M. Adam & Hudgins, 2005).

CONCLUSION

Kabuki syndrome is a rare disorder that occurs in approximately 1 in 32,000 people worldwide, including in Indonesia, known for its highly variable symptoms and different clinical manifestations in each individual, making diagnosis challenging. Diagnosis of the syndrome is usually based on five main manifestations, namely a distinctive face, skeletal anomalies, dermatoglyphic abnormalities, mental retardation, and postnatal growth deficiency. The syndrome can also cause anomalies of the mullerian duct, such as cervico-vaginal agenesis. Various supporting examinations such as karyotyping, MRI, and X-ray, are used to aid diagnosis. The management of Kabuki syndrome is tailored to the phenotype and affected organs, with a multidisciplinary approach, although a standardized treatment that proves effective is not yet available. The focus of treatment is to improve the patient's quality of life, and the prognosis for survival to adulthood is generally good, especially if diagnosis and management are early. Regular hormone therapy (HRT) is important for adolescents with POI to prevent serious complications, with dose adjustment and adherence to therapy indispensable.

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