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Advances in Diagnosis, Treatment, and Prognosis of Yolk Sac Tumors: A Comprehensive Review

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ABSTRACT

Yolk sac tumor, also known as endodermal sinus tumor, is a rare and malignant germ cell tumor that typically arises in the gonads (testes and ovaries) but can also occur in extragonadal sites, such as the sacrococcygeal area or mediastinum. Yolk sac tumors arise from germ cells, which are the precursors of eggs in females and sperm cells in males. During normal embryonic development, germ cells migrate to the gonads (testes or ovaries) and differentiate into mature reproductive cells. Clinical mass-effect signs are the typical presentation of yolk sac tumours. These signs include rapid belly expansion, ascites, early satiety, and abdominal pain, among others. Children with testicular yolk sac tumours frequently appear with large, painless testicular lumps. Yolk sac tumours can be deadly or very damaging if left untreated. Depending on the characteristics of the tumour and its stage, a combination of surgery, chemotherapy, and radiation therapy is usually employed to treat yolk sac tumours. Regular follow-up visits and imaging studies are typically conducted to monitor the patient's response to treatment, detect any recurrence, and manage potential late effects of therapy. Close collaboration between the healthcare team and the patient is essential to ensure the best possible outcomes. FDG PET/CT staging of YST in paediatric patients was only marginally better than traditional imaging.

Keywords: Yolk sac tumor, Alpha-fetoprotein, F-fluorodeoxyglucose

INTRODUCTION

Yolk sac tumor, also known as endodermal sinus tumor, is a rare and malignant germ cell tumor that typically arises in the gonads (testes and ovaries) but can also occur in extragonadal sites, such as the sacrococcygeal area or mediastinum. It is most commonly diagnosed in infants, children, and young adults. Yolk sac tumors are named after their resemblance to the yolk sac, a membranous structure that provides nourishment to the developing embryo during early pregnancy. These tumors are composed of germ cells, which are the precursors of eggs in females and sperm cells in males. The exact cause of yolk sac tumors is not fully understood, but it is believed to be related to abnormal development of germ cells. Certain risk factors have been identified, such as a history of undescended testes or certain genetic conditions, including Klinefelter

syndrome and Turner syndrome.

Clinically, patients with yolk sac tumors may present with a variety of symptoms depending on the location and extent of the tumor. In gonadal sites, males may experience testicular swelling or a painless mass, while females may have abdominal pain or a palpable mass. Extragonadal yolk sac tumors can cause symptoms related to the affected organ or site, such as back pain or respiratory distress.[1]

Diagnosis of yolk sac tumors involves a combination of imaging studies, such as ultrasound, computed tomography, or magnetic resonance imaging, and laboratory tests. Tumor markers, including alpha-fetoprotein, are often elevated in yolk sac tumors and can aid in the diagnosis and monitoring of the disease. The primary treatment for yolk sac tumors is surgical resection, which aims to remove the tumor completely. In cases where the tumor has spread or cannot be completely removed, a combination of chemotherapy and radiation therapy may be recommended. Chemotherapy regimens typically include drugs such as cisplatin, etoposide, and bleomycin. The prognosis for patients with yolk sac tumors varies depending on factors such as the stage of the tumor, the age of the patient, and the response to treatment. With early detection and appropriate management, the prognosis can be favorable, especially for localized tumors. However, advanced or metastatic yolk sac tumors carry a poorer prognosis.

It is thought that the endodermal sinuses of the primordial yolk sac are where yolk sac tumours get their start. In the United States, 500 new cases of NSGCT are reported annually. An extragonadal NSGC is an endodermal sinus or yolk sac tumour. In 1959, young patients' ovaries and testicles were found to have the tumour, and Telium classified it as a particular kind of malignant germ cell neoplasm. The reported median age for ovarian yolk sac tumours has ranged from 13 to 22 years, and in most recent series, it has been observed that the 5-year overall survival rate exceeds 85%. However, recorded results in postmenopausal women with ovarian yolk sac tumours have been noticeably worse. A phenomenon that is more frequently observed in postmenopausal patients may be a factor in the observed prognostic difference. This phenomenon has the potential for tumours with the phenotype of yolk sac tumours to be seen against a background of a traditional somatic epithelial malignancy, most frequently endome-trioid adenocarcinoma. Although both are incredibly rare, tumours in the uterus that have conventional carcinoma mixed in with a yolk sac tumour-like appearance seem to have a similar incidence to pure yolk sac tumours. It can be challenging to spot yolk sac tumours in locations other than the gonads. However, between 10 and 15% of YST is found in the mediastinum, retroperitoneum, and sacrococcygeal regions of the midline structures. The most typical testicular tumour in young children under the age of three is a condition known as infantile embryonal carcinoma, or yolk sac tumour. In this age bracket, yolk sac tumours have a favourable prognosis. Yolk sac tumours in adults are typically observed in conjunction with other types of germ cell tumours (such as teratoma and embryonal carcinoma), as opposed to the pure variety in newborns and young children. AFP and keratin are traditionally secreted by the yolk sac cells, and both premenopausal and postmenopausal patients frequently have elevated levels of these indicators.[2]

Etiology:

Yolk sac tumors arise from germ cells, which are the precursors of eggs in females and sperm cells in males. During normal embryonic development, germ cells migrate to the gonads (testes or ovaries) and differentiate into mature reproductive cells. However, in the case of yolk sac tumors, there is an abnormal development or differentiation of germ cells, leading to the formation of tumors.

Certain risk factors have been identified that may increase the likelihood of developing yolk sac tumors:

1. Genetic Factors: Certain genetic conditions are associated with an increased risk of yolk sac tumors. For example, individuals with Klinefelter syndrome (an extra X chromosome in males) or Turner syndrome (a missing or partially missing X chromosome in females) have a higher risk of developing these tumours.
2. Cryptorchidism: Cryptorchidism refers to the condition where one or both testes fail to descend into the scrotum. It is a known risk factor for testicular yolk sac tumors. The undescended testes are thought to be more susceptible to malignant transformation, including the development of yolk sac tumours.
3. Environmental Factors: While the exact environmental factors contributing to yolk sac tumors are not well established, exposure to certain chemicals and toxins during pregnancy or early childhood has been suggested as a potential risk factor. However, more research is needed to establish a definitive link.

It's important to note that most cases of yolk sac tumors occur sporadically without any identifiable risk factors. Additionally, the majority of yolk sac tumors are found in infants, children, and young adults, suggesting that there may be a developmental component to their etiology.

Tumours of the yolk sac are virtually without known cause. According to several studies, the aetiology of yolk sac tumours may be influenced by GATA-4 overexpression and RUNX3 gene hypermethylation. Although the pathophysiology of yolk sac tumours that appear after menopause is unclear, it is thought to be distinct from premenopausal malignancies. Neoplasia in the premenopausal stage is primarily caused by an unobliterated endodermal sinus. The following pathogenic theories are put forward for the postmenopausal period: (1) halted migration of germ cells during embryogenesis; (2) disoriented migration of germ cells; (3) abnormal differentiation of Although the pathophysiology of yolk sac tumours that appear after menopause is unclear, it is thought to be distinct from premenopausal malignancies. Neoplasia in the premenopausal stage is primarily caused by an unobliterated endodermal sinus.[3]

Clinical presentation and Imaging :

Clinical mass-effect signs are the typical presentation of yolk sac tumours. These signs include rapid belly expansion, ascites, early satiety, and abdominal pain, among others. Children with testicular yolk sac tumours frequently appear with large, painless testicular lumps. Less than 10% of cases at presentation have metastatic disease. When present in adulthood, yolk sac tumours are a part of mixed germ cell tumours that also include embryonal carcinoma, choriocarcinoma, teratoma, and seminoma. There are no noticeable signs other than a tumour in the testicles. Alpha fetoprotein levels in the serum are markedly raised in almost all individuals with yolk sac tumours, whether they are pure or mixed forms. Although uncommon, intratumoral calcification and fatty tissue may be signs of a mixed YST with a teratoma component. Ovarian yolk sac tumours swiftly form metastatic lesions that infect the ovaries' surrounding structures. The lymph nodes can also be a site of metastasis.[4]

Pathophysiology

The pathophysiology of yolk sac tumors involves uncontrolled cell growth and the formation of a mass or tumor. YSTs can invade surrounding tissues and may spread (metastasize) to distant sites, such as the lymph nodes, liver, lungs, or other organs. The spread of yolk sac tumors can occur through the lymphatic system or bloodstream. Some of the important pathologic hallmarks of Yolk sac tumour include a reticular pattern, a solid pattern, a hepatoid pattern with hyaline globules, a festoon pattern, enteric differentiation,

Schiller-Duval bodies, the presence of a granulomatous tissue reaction, and a polyvesicular vitelline pattern.[5]

Diagnosis

The diagnosis of yolk sac tumor involves a combination of clinical evaluation, imaging studies, laboratory tests, and histopathological examination. The following are the key steps in diagnosing yolk sac tumors:

1. Medical History and Physical Examination: The doctor will begin by taking a detailed medical history, including any symptoms the patient is experiencing, the duration of symptoms, and any relevant risk factors. A thorough physical examination will be conducted to assess for any palpable masses, enlarged lymph nodes, or other signs suggestive of a tumour.
2. Imaging Studies: Various imaging modalities are used to visualize the tumor and assess its location, size, and extent. These may include:
   Ultrasound: This non-invasive imaging technique uses sound waves to create images of the affected area. Ultrasound can help identify the presence of a mass, its size, and its characteristics.
   Computed Tomography (CT) Scan: CT scans use X-rays and computer technology to create detailed cross-sectional images of the body. A CT scan can provide information about the location and extent of the tumor, as well as any involvement of nearby structures or organs.
   Magnetic Resonance Imaging (MRI): MRI uses powerful magnets and radio waves to generate detailed images of the body's soft tissues. It can provide information about the tumor's location, size, and involvement of adjacent structures.
3. Laboratory Tests: Yolk sac tumors often produce specific tumor markers that can be detected in the blood. The most important tumor marker for yolk sac tumors is alpha-fetoprotein. Elevated AFP levels can be suggestive of a yolk sac tumor. Blood tests for AFP levels are often used for diagnosis, monitoring treatment response, and detecting potential recurrence of the tumor.
4. Biopsy and Histopathological Examination: To confirm the diagnosis of yolk sac tumor, a biopsy is typically performed. During a biopsy, a sample of the tumor tissue is removed for microscopic examination. A pathologist analyzes the tissue under a microscope to identify the characteristic features of a yolk sac tumor, such as the presence of yolk sac-like structures or other specific cellular components.

Using immunohistochemical staining, the diagnosis can be made. The most helpful stain is for -fetoprotein since AFP positivity is a sign of a yolk sac tumour. Fetoprotein staining varies and is frequently patchy; diffuse strong staining is not always visible in tumours. The AFP and anti-hepatocyte antibody cytoplasmic staining of hepatoid yolk sac tumours are both positive. Although positive staining can aid in the diagnosis of this uncommon variety of yolk sac tumour, it does not distinguish hepatoid yolk sac tumour from hepatoid carcinoma of the ovary or from metastatic hepatocellular carcinoma, as both of these also exhibit positive staining.

More than 95% of yolk sac tumours exhibit strong positive cytoplasmic staining with glipican-3, which has become a second positive confirmatory stain for the diagnosis.

On CT and MR scans, yolk sac tumours appeared as an enhancing, big, solid cystic mass with intertumoral haemorrhage. Our results are in line with data from Li et al., who found that SALL4 expression was present in 47.7% of endometrial cancer samples and was linked to higher metastases and poorer patient survival in endometrial malignancies.

Treatment

Yolk sac tumours can be deadly or very damaging if left untreated. Depending on

the characteristics of the tumour and its stage, a combination of surgery, chemotherapy, and radiation therapy is usually employed to treat yolk sac tumours. The main form of treatment for yolk sac tumours is surgery, which entails the removal of the tumour and any surrounding tissue that has been affected. In cases where the cancer is localised and hasn't spread, surgery alone may be curative. More therapy, however, might be required if the cancer has spread beyond its original location or if there is a risk of residual disease.

Chemotherapy is a vital component of the management of yolk sac tumours. It is typically administered both before and after surgery.[6]

Different chemotherapy drugs and treatment regimens may be used, depending on the disease's stage and severity, the patient's age, and their overall health. The most commonly used chemotherapy agents include cisplatin, etoposide, and bleomycin.

Only a few of the severe late toxicities that the bleomycin, etopside, and cisplating combination can produce include ototoxicity, neuropathy, early-onset cardiovascular disease, and secondary malignant neoplasms.

Paclitaxel, ifosfamide, and cisplantin can be used to control patients with increased neoplastic symptoms after the primary therapy is finished.

In some cases, radiation therapy may also be recommended, particularly if the patient is still sick following surgery or the tumour has spread to difficult-to-treat areas.[7]

In radiation therapy, cancer cells are targeted and killed using high-energy radiation, including X-rays and other forms.

Pharmacological treatment: The pharmacologic treatment of yolk sac tumors (endodermal sinus tumors) typically involves chemotherapy as the primary approach. The specific chemotherapy regimens used for yolk sac tumors may vary depending on factors such as the stage of the tumor, the patient's age, and individualized treatment plans. The following are some of the commonly used chemotherapy drugs:

1. Platinum-based Chemotherapy: Cisplatin is the most frequently used drug in the treatment of yolk sac tumors. It is highly effective against germ cell tumors and is often combined with other chemotherapy agents. Platinum-based chemotherapy drugs work by damaging the DNA in cancer cells, leading to their death.
2. Etoposide: Etoposide is another important chemotherapy drug used in the treatment of yolk sac tumors. It works by inhibiting the enzyme topoisomerase II, which is involved in DNA replication. Etoposide is commonly combined with cisplatin in chemotherapy regimens for yolk sac tumors.
3. Bleomycin: Bleomycin is a chemotherapy drug that works by causing DNA damage in cancer cells. It is often used in combination with cisplatin and etoposide. Bleomycin is particularly effective in the treatment of mediastinal yolk sac tumors.
4. Vinblastine: Vinblastine is occasionally used in combination chemotherapy regimens for yolk sac tumors. It works by disrupting the assembly of microtubules, which are essential for cell division.

The choice and combination of chemotherapy drugs may depend on the stage of the tumor and the overall health of the patient. The treatment plan is typically determined by a multidisciplinary team of healthcare professionals, including oncologists and pediatric specialists.[8]

In addition to chemotherapy, other treatment modalities such as surgery and radiation therapy may be employed, depending on the specific characteristics and extent of the tumor. Surgical resection aims to remove the tumor completely, while radiation therapy uses high-energy beams to target and destroy cancer cells. It is important to note that the treatment approach for yolk sac

tumors is highly individualized, and the specific treatment plan will depend on factors such as tumor stage, location, and the patient's overall health. The prognosis for yolk sac tumors has improved significantly with the use of multi modal treatment approaches, resulting in high cure rates, particularly for localized or early-stage tumors.

Non Pharmacological treatment: The primary treatment for yolk sac tumors (endodermal sinus tumors) is typically based on a combination of non-pharmacological interventions, including surgical resection and radiation therapy. These non-pharmacological treatments play a crucial role in the management of yolk sac tumors. Here are the key non-pharmacological treatment options:

1. Surgical Resection: Surgery is the mainstay of treatment for yolk sac tumors. The goal of surgical intervention is to remove the tumor completely. The extent of surgery depends on the tumor's location and stage. In cases of gonadal tumors (testes or ovaries), the affected organ is typically removed (orchiectomy or oophorectomy). For extragonadal tumors, such as mediastinal or sacrococcygeal tumors, complete surgical resection is aimed at removing the tumor and any involved nearby structures.
2. Lymph Node Dissection: Yolk sac tumors have the potential to spread to nearby lymph nodes. Therefore, surgical removal of lymph nodes in the affected region may be performed as part of the treatment. Lymph node dissection helps to reduce the risk of recurrence and further metastasis.
3. Radiation Therapy: Radiation therapy uses high-energy beams to target and destroy cancer cells. It is often employed as an adjunct to surgery or in cases where complete surgical resection is not possible. Radiation therapy may be used to treat residual tumor cells, reduce the risk of local recurrence, or target metastatic sites. The specific radiation therapy technique and dosage are determined based on the tumor location and stages.
4. Combination Therapy: In some cases, a combination of surgery and radiation therapy may be utilized to maximize treatment effectiveness. The decision to combine these treatments depends on factors such as tumor size, location, and the presence of metastasis.
5. Chemotherapy: While we have discussed pharmacological treatment in a previous response, it is worth mentioning that chemotherapy, which involves the use of medications, is an integral part of the overall treatment approach for yolk sac tumors. Chemotherapy is used in combination with surgery and radiation therapy to target cancer cells throughout the body, including potential metastases.[9]

It is important to note that the treatment plan for yolk sac tumors is highly individualized and depends on various factors, including the tumor stage, location, and the patient's overall health. The treatment approach is determined by a multidisciplinary team of healthcare professionals, including surgeons, radiation oncologists, and pediatric oncologists.

Regular follow-up visits and imaging studies are typically conducted to monitor the patient's response to treatment, detect any recurrence, and manage potential late effects of therapy. Close collaboration between the healthcare team and the patient is essential to ensure the best possible outcomes.[10]

CONCLUSION

Yolk sac tumor is a rare and malignant germ cell tumor that primarily affects infants, children, and young adults. It can arise in the gonads or extra gonadal sites and is characterized by the presence of germ cells resembling the yolk sac. Diagnosis involves imaging studies and laboratory tests, while treatment usually consists of surgical resection followed by chemotherapy and/or

radiation therapy. The prognosis varies depending on several factors, and early detection and treatment are key to improving outcomes for patients with yolk sac tumors.

FDG PET/CT staging of YST in paediatric patients was only marginally better than traditional imaging. However, post-therapy patients with YST who underwent PET/CT demonstrated good diagnostic specificity and had a significant impact on therapeutic management.

LIST OF ABBREVIATION:

1. FDG- F-fluorodeoxyglucose
2. PET/CT- Positron emission tomography–computed tomography
3. YST- Yolk sac tumour
4. SALL4- Sal-like protein 4
5. CT-Computed tomography, or
6. MRI- Magnetic resonance imaging
7. AFP- Alpha-fetoprotein
8. NSGCT- Non-seminomatous germ cell tumors

Declaration by Authors

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