Ovarian Cancer Clinical Aspects and at least Two Tumor Markers for Diagnosis Laboratory Examination

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ABSTRACT

Ovarian cancer is one of the gynecological malignancies with a bad outcome. Epidemiologically, it is the fifth cause of death in females worldwide. Patients have various complaints, and examinations available for early detection are inadequate, causing high mortality rates and late diagnosis. Prepare a more appropriate examination to establish an earlier diagnosis, especially in females with risk factors requiring screening. Laboratory examinations combined with other supporting examinations can provide better results to confirm the diagnosis of ovarian cancer and lower the morbidity rate. Knowing the updated examination to support the diagnosis, such as examination of ovarian cancer biological markers specific to HE4, CA-125, CEA, CA 19-9. A combination of examinations is needed for early detection of ovarian cancer.

Keywords: Ovarian cancer, HE4, CA-125, CEA, CA 19-9

INTRODUCTION

The ovaries have an essential function for reproduction and menstruation. Ovarian diseases can interfere with the egg’s growth, development, and maturation. The most common diseases are ovarian cancer, polycystic ovary syndrome, and ovarian cysts.¹

Ovarian cancer is a deadly gynecological malignancy estimated to be the first cause of death worldwide. Symptoms of ovarian cancer are not specific, so the diagnosis is often established when there are already metastasizes or the patient is already in the terminal phase.²

Ovarian tumor is one of the female reproductive systems neoplasm. These tumors originate from benign or malignant ovarian cells. Ovarian tumors comprise 30% of all cancers of the female reproduction system: more than 23,000 new cases yearly, and about 13,900 diagnosed die. The incidence of ovarian tumors is lower than uterine and cervical tumors. Ovarian cancer has the highest mortality rate among all gynecological malignancies. Ovarian tumors are malignant tumors with the highest mortality rate in the United States.³

Ovarian carcinoma is a common gynecological condition that occurs during pregnancy, ranging from 1:10,000 to 1:25,000. Compared to germ cell tumors, the histopathology of ovarian epithelial carcinoma occurs more frequently. Pregnancy does not affect the prognosis of ovarian carcinoma, but complications may include tumor torsion, rupture, and an increase in the likelihood of prematurity. This paper reports a female, 31 years old, primigravida, 34 weeks pregnant, with an enlarged abdomen and increased blood Carbohydrate Antigen (CA-125) levels with a left ovary solid mass accompanied by ascites on ultrasonography.¹

CAUSE

The cause of ovarian cancer is still unknown; a family history of cancer, an early first pregnancy, and hereditary specific transplants (BRCA1 and BRCA2) remain risk factors for cancer development. The early stages are usually asymptomatic. Signs and symptoms are found by chance on routine examinations, and 60% of patients are diagnosed at an advanced stage. Periodic medical check-ups with the gynecologist are recommended to detect malignancy in females.⁴ ⁵

The cause of ovarian carcinoma has not been definitively determined. It is thought that there are changes or mutations in the DNA of ovarian cells, resulting in abnormal and uncontrollable growth. The cause of the ovarian cell’s DNA genetic cells is still unknown, but tracing was carried out epidemiologically. Risk factors of ovarian carcinoma include the age of over 50 years, a smoking habit, a history of radiotherapy, undergoing hormone replacement therapy during menopause, a family history of ovarian or breast cancer, obesity, and endometriosis.⁶
There are both primary and secondary ovarian cancer, which is usually from metastasis of the malignancy of other organs. In some cases, females with Krukenberg tumors aged 45 years were associated with an increased frequency of signet-ring cell gaster carcinoma. Examinations show metastasis of the gastric tumor to the ovaries. In other cases, there is also metastasis from the breast to ovarian malignancy, which causes ovarian cancer; in terms of therapy, it turns out that ovarian removal has good results for breast malignancy.

The study of ovarian cancer patients' clinical and histopathological features at Hasan Sadikin Hospital, Bandung, from 2019 until 2020 using medical-record data, with patients diagnosed histopathologically selected using the total sampling method. The study included 140 patients aged 46-55 (31.4%) and multiparous (60.7%). Patients who had normal BMI were 57.1%. Most of the patients had symptoms of a lump in the abdomen (100%) that were cystic, lumpy (57.1%), solid (51.4%), immobile (35.0%), and unilateral (87.4%). The tumor marker mostly found was CA-125 (37.9%).

Peritoneal cytology is essential in the diagnosis and staging of gynecological neoplasms. However, this procedure to help diagnosis is necessary for localized tumors, not-too-severe diseases, or follow-up treatment. Peritoneal fluid-positive results for ovarian carcinoma will improve diagnosis.

CLINICAL ASPECTS OF OVARIAN CARCINOMA

Anamnesis

In the early stages, ovarian malignancies often do not have significant symptoms; patients are sometimes without complaints, so they usually do not see a doctor for their ovarian problems. If the tumor gets bigger, patients often complain of discomfort in the lower part of the abdomen, accompanied by increasing pain. It feels heavier while the cancer grows.

In slow-growing types of tumors, especially epithelial ovarian tumors, often they do not give significant complaints. This condition often causes severe pain and can be urgent if the tumor gets bigger, causing an enlarged abdomen, constipation, anorexia, quickly feeling full, and nausea.

Physical examination

Physical examination of the patient can be in the form of palpation of the abdominal region, usually finding a palpable mass in the lower abdomen. To distinguish whether it is malignant or not, palpation of malignant ovarian tumors can be initiated based on the bilateral nature of the tumor mass, solid consistency, limited movement, the surface of the cancer is not slippery, ascites can occur in the Douglas cavum, and a noticeable lump on the Douglas cavum.

Ultrasound support examination

Ultrasound examination (ultrasound) can see the size of the tumor adhesions with surrounding tissue and assess whether the ovarian tumor can be removed surgically or requires follow-up therapy. The ultrasound can be used intraoperatively using laparoscopy.

LABORATORY EXAMINATION

Hematology examination

Variations of the examination results from the hematological examination can be found based on the patient's condition. Hemoglobin examination can show normal levels, but anemia can also occur if food intake is disturbed or the patient has anorexia, resulting in anemia. From several case reports, there could be an increase in leukocyte levels due to an infection; there could be an increase in platelet levels due to the activation of platelets by endothelial dysfunction of blood vessels in tumor tissues.

Clinical chemistry examination

The clinical chemical examination assesses organic functions such as kidneys and liver and monitors prognosis. The clinical chemical analysis includes the urea, creatinine, uric acid, and liver enzymes such as serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and gamma-glutamyl transferase.

Urinalysis examination

Urinalysis examination in ovarian cancer mainly examines the type of ovarian cancer, including products produced by malignant tumors, such as angiogenesis inhibitors such as endostatin (ES), angiostatin (AS), and thrombospondin. To be known, endotactins and angiostatins of epithelial ovarian cancer patients are found in urine to be used as a marker for epithelial ovarian cancer.

SEROLOGICAL EXAMINATION OF MARKER TUMORS

CA-125

Diagnosis of ovarian cancer uses the HE4, CA-125, RMI, and ROMA algorithms. The CA-125 test in serum has low sensitivity in the early stages and is
affected by conditions such as menstruation and endometriosis.\textsuperscript{6}

CA-125 was first studied in the 1980s. Its levels are increased in high-grade serous ovarian carcinoma (HGSC) and are the leading cause of death in ovarian cancer. The complexity of HGSC is increased by tumor heterogeneity. It is divided into inter-tumor and intra-tumor heterogeneity, which has important implications for assessing metastasis, treatment, and therapeutic resistance. In contrast, between-tumor heterogeneity for assessing prognosis can lead to variations in survival rates.\textsuperscript{6,15}

A case of metastatic tumor from elsewhere, such as Krukenberg's primary tumor in an unmarried 15-year-old girl. She had flatulence and was pregnant. The CA-125 examination gave high results. During intraoperative operations, solid masses in the left and right ovaries were removed, and the operation was carried out in conjunction with the Department of Surgery. It was found that the tumor had infiltrated the sigmoid colon, and a transversal ostomy was performed.\textsuperscript{7}

Less than 20% of patients with advanced ovarian cancer survive more than ten years. Surgery and chemotherapy were the mainstays of therapy for some time. Primary debulking surgery is the preferred initial surgical option for patients with advanced ovarian cancer, where complete resection of the tumor is performed so that no residual tumor is visible. It is necessary to examine tumor markers and monitor the success of therapy. CA-125 plays a role in monitoring therapy.\textsuperscript{15}

The COVID-19 crisis has a severe impact on ovarian cancer patients. Many deaths occur in ovarian cancer patients who were infected with COVID-19. As a result, adequate treatment is needed to treat this case. CA-125 examination requires fast, accurate, and precise results. During the COVID-19 pandemic, the CA-125 examination used a 5-(2-phenylbenzo[b]thiophen-3-yl) thiophene-2-carbaldehyde (PTTC) based sensor. This examination is the newest method for CA-125 assessment to treat COVID-19 patients with ovarian cancer using electrochemical impedance spectroscopy measurements.\textsuperscript{13}

Examining CA-125 can be from body fluids, usually from venous blood. Patients are usually asked to fast while an approximately 3 mL blood sample is taken and separated by serum immediately. Blood was centrifuged at 3000 rpm for 5 minutes. Supernatants were collected to check the value of tumor markers. Serum levels of CA-125 were detected using immuno-assay chemiluminescence devices.\textsuperscript{7}

Research conducted on patients with ovarian cancer showed high levels in people with ovarian cancer. Furthermore, serum pretreatment and post-treatment therapy were carried out by assessing CA-25 levels. It was found that a decrease in CA-125 levels in post-exosomes was carried out in treatment.\textsuperscript{9}

The CA-125 tumor marker is a biomarker commonly used to evaluate females with pelvic mass. A value of 35 u/mL is considered a standard limit. Combined CA-125 and ultrasound testing improved specificity and positive approximation. A histological diagnosis is made during surgery with a frozen section examination. A meta-analysis of Frozen cuts shows a sensitivity of 96% to 99% and a specificity of 66% to 93%.\textsuperscript{11}

CA 19-9

The CA 19-9 examination aims to study the characteristics of ovarian cystic teratoma in conjunction with an increase in CA 19-9. This marker is valuable in discriminating cysts. Study results show that CA 19-9 can be an essential instrument in diagnosing adult cystic teratoma of the ovaries. CA 19-9, in combination with CA-125, may be a helpful marker in cystic teratoma discrimination from cancer. CA-125 and CA 19-9 are antigenic determinants of human epithelial ovarian carcinoma. When combined, the study determined whether elevated levels of CA-125, CA 19-9 and carcinoembryonic antigen will result in a more consistent correlation with tumor growth or recurrence compared to what can be achieved with long-term treatment. Serum CA-125 was increased above 35 U/mL in 83% of patients, CA 19-9 levels above 37 U/mL in 17%, and carcinoembryonic antigen levels above 2.5 ng/mL in 37% of 105 patients. Individually, there was no correlation between scores for the fourth marker and patients with increasing values.\textsuperscript{16}

CEA examination

To predict patient prognosis before treatment, reliable and inexpensive monitoring of epithelial ovarian cancer is to evaluate serum carcinoembryonic antigen (CEA) and Carbohydrate Antigen-125 (CA-125) in primary epithelial ovarian cancer. This combined examination was performed in 2008 and 2016 on 326 patients with primary ovarian and epithelial cancer diagnosed retrospectively. The combination of CEA and CA-125 examinations gives better life expectancy results.\textsuperscript{2}

Multivariate Cox regression and univariate analyses are used to evaluate predictively. The CEA concentration was above 2.6 ng/mL, and the increase in levels of CA-125 and CEA predicted significant
growth. One of the examinations was the CEA examination to find the primary tumor. From the immunohistochemistry panel of tumor tissues and masses, it turned out that Ovarian cancer was a metastasis of a cervical tumor. However, the immunohistochemistry examination did not stand alone.

Examination of human epididymis protein 4 (He4)

Human epididymis protein 4 (HE4) is a tumor marker for diagnosing malignant ovarian tumors. HE4 is a glycoprotein of the four-disulfide core protein of whey acid, under the name WFDC2, and a more prominent protein called "WAP" for whey acid protein. The primary gene encodes the WAP protein on chromosome 20q12-13. HE4, consisting of 2 WAP domains, was first isolated in the epididymis and plays a role in sperm maturation. This biomarker is expressed in small amounts by the epithelial tissue of the respiratory organs and reproductive organs. It is expressed in larger amounts in ovarian tumors, especially in endometrioid ovarian cancer. In other cases, HE4 is expressed in clear cell ovarian carcinoma as in other epithelial ovaries with a less intense expression.

Osteopontin

Osteopontin as a tumor marker, combined with CA-125 examination, can be used to predict malignancy in patients with ovarian tumors. Forty-seven patients with negative and 43 with positive histopathological results obtained a median CA value of 125 higher. This study found that the combination of CA-125 and osteopontin had a higher sensitivity for detecting ovarian malignancy compared to CA-125 only. Combining CA-125 and osteopontin will improve specificity, positive predictive value, and accuracy.

CONCLUSION

Early detection of ovarian cancer was needed to reduce the mortality rate caused by ovarian cancer. The ability to carry out early detection requires the combination of appropriate examinations to determine whether the ovarian cancer is primary or secondary. Efforts are aimed at finding the disease at an early stage when the presence of an ovarian tumor is not yet clear.

REFERENCES

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