Case report

DOUBLE PRIMARY CANCER: BREAST CANCER AND GASTRIC CANCER

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ABSTRACT

Introduction: Breast carcinoma is the most prevalent malignancy and the second leading cause of cancer death in women, while multiple primaries are conditions where there is more than one synchronous or metachronous cancer in one individual. Double primary between breast carcinoma and colon cancer is a primary tumor with a high incidence, while breast carcinoma metastasis to the colon is a rare entity except for lobular histotype breast carcinoma. In this case report, a woman with double primary breast cancer is reported.

Case Report: A 50-year-old woman came with complaints pain of the entire abdomen since 2 days before go to hospital, worsening when starting to eat, accompanied by nausea. The patient had a history of modified radical mastectomy (MRM) for indications of right breast carcinoma cT3N0M0. In addition, a history of ovarian carcinoma that had undergone chemotherapy was also found. On esophagogastroduodenoscopy examination, a gastric mass was found with ulceration and necrosis and a biopsy showed high-grade neuroendocrine carcinoma and adenocarcinoma.

Conclusion: Breast malignancy can be invasive or non-invasive and can undergo metastasis. In addition to metastasis, cancer can also appear in two different places but histologically or morphologically different. This condition is called multiple primaries due to host, lifestyle, and environmental factors.

Keywords: breast cancer, gastric cancer, double primary

1. INTRODUCTION

Breast carcinoma is the most prevalent malignancy and is the second leading cause of cancer death in women. Breast carcinoma develops due to deoxyribonucleic acid (DNA) damage and genetic mutations that can be influenced by exposure to estrogen. Some genes are related to heredity, for example defects in pro-oncogene genes such as BRCA 1 and BRCA 2. Someone with a family history of breast carcinoma or ovarian carcinoma has a higher risk of developing breast carcinoma. [1] Breast carcinoma is related to hormone receptivity with the presence or absence of estrogen and progesterone receptor expression in malignant conditions. If the hormone receptor is still positive, then in theory it will be more responsive to hormonal therapy and most are not types of cancer that metastasize. [2]

Breast carcinoma often starts from ductal hyperproliferation that develops into benign tumors or metastases due to a number of carcinogenic factors. Tumor microenvironment such as stromal or macrophage influences play a role in the initiation and development of breast carcinoma. Macrophages can produce a mutagenic inflammatory microenvironment that can trigger angiogenesis and allow cancer cells to evade immune rejection. Different DNA methylation patterns are also observed between normal and tumor-associated microenvironments. This suggests that epigenetic modifications in the tumor microenvironment can trigger carcinogenesis. [3]

Multiple primaries are conditions when there is more than one synchronous or metachronous cancer in one individual. A tumor is considered a multiple primary malignancy if it arises in different places and/or from different histological or

morphological groups. Cancer is classified as an index cancer if there is no previous record of invasive cancer. According to the International Agency for Research on Cancer (IARC), tumors that arise in different places are classified to synchronous if they are diagnosed within an interval of less than 6 months or metachronous if they are diagnosed within a period of more than 6 months. The etiology of multiple primaries can be caused by host factors (genetic, hormonal, history of malignancy), lifestyle (smoking, alcohol), or environment (geographic or environmental exposure, pathogens in the context of infection, work). In addition, genetic disorders such as Li-Fumei syndrome due to abnormalities in the p53 gene as a tumor suppressor can also trigger a decrease in tumor suppressor function which then triggers the formation of several primary cancers in the digestive tract. [4,5]

The same mutation can cause different types of tumors, for example c-RNA virus can cause lymphoma, leukemia and liver cancer, H. pylori infection can cause mucus□associated gastric cancer and gastric lymphoma. In addition, patients with multiple primary cancers tend to be susceptible and sensitive to carcinogenic factors. If carcinogenic factors are not ruled out, they can cause cancer in other parts of the body. The use of chemicals and irregular chemotherapy applications can also play an important role in the development of some primary cancers. [5]
The diagnosis of multiple primary cancers still refers to the international standards developed by Warren and Gates in 1932 in Ouyang et al. [5]: 1) Each malignant tumor must be confirmed pathologically by histological examination; 2) each tumor must have its own specific pathological morphology; 3) tumor metastasis occurring from different sites or organs of the patient must be excluded. The incidence of multiple primary cancers reported nationally and internationally varies. The incidence of multiple primary cancers ranges from 0.73 to 11.7%, with a higher prevalence in older people. [6] In women with breast carcinoma, the incidence of multiple primary tumors is reported to occur in 4.1-16.4% of cases. The second malignancy occurs on average 5-8 years after the diagnosis of breast carcinoma due to endocrine factors or obesity. BRCA1 and BRCA 2 genes in breast carcinoma are closely related to the emergence of second tumors in the breast or ovary, while hormonal therapy, especially tamoxifen, increases the risk of subsequent primary cancers in the endometrium, stomach, colon, and ovary. The toxic effects of radiotherapy and chemotherapy also contribute to the increased risk of secondary primary tumors after the diagnosis of breast carcinoma. The effects of radiotherapy also have the potential to cause tumors in the contralateral breast, thyroid, bone, connective tissue, and lung. [4] Kim and Song conducted a study of 2,657 patients with breast cancer. Of all patients who had double primary after breast cancer, a fairly high rate of radiotherapy was only found in patients with lung cancer (82%) and hematopoietic system cancer (95%). Basically, the types of cancer related to radiotherapy affect organs close to the breast, such as: esophagus, lung, thyroid gland, stomach, thoracic and upper extremity soft tissue sarcoma and leukemia. Thyroid cancer is considered a radiation-induced cancer, because most thyroid cancers are not induced by treatment.[7]

The association between breast cancer and gastrointestinal cancers can be considered as a sporadic or germinal association. In the case of colorectal cancer, several studies emphasize the coexistence of common extrinsic and genetic predisposing factors. Double primary between breast carcinoma and colon cancer is a primary tumor with a high incidence, while breast carcinoma metastasis to the colon is a rare entity except for lobular histotype breast carcinoma.[8] The coexistence of breast and gastric cancer has also been reported. Cell adhesion molecules (CAMs) play an important role in the process of tissue morphogenesis during development and maintain tissue differentiation in adult organisms. Cellular adhesion factors and motility are mechanisms responsible for tumor initiation and development. In both, deregulation of the E-cadherin protein was found.

E-cadherin is the most important intercellular adhesion molecule in the adherens junction that keeps epithelial cells attached to each other. Loss of E-cadherin function as a tumor suppressor is associated with increased tumor invasiveness and metastasis.[9] E-cadherin is a protein that plays an important role in forming and maintaining epithelial polarization and differentiation through intracellular adhesion complexes. The expression of the E-cadherin protein is regulated by the E-cadherin gene (CDH1). [9]

There is a relationship between mutations in the CDH1 gene that expresses E-Cadhrine and Hereditary Diffuse Gastric Cancer (HDGC) Syndrome. HDGC Syndrome is a rare genetic disorder. It means that the risk of cancer and clinical conditions associated with HDGC may not occur from generation to generation in a family. The gene most associated with this syndrome is CDH1. Mutations in the CDH1 gene can increase the risk of gastric cancer, breast cancer and other related cancers.

2. CASE REPORT

A 50-year-old woman came with a lump in her breast since 1 month ago, the lump was initially the size of a quail egg then enlarged, the patient also complained of pain in the upper left abdomen since 2 days before go to hospital, worsening when starting to eat, accompanied by nausea. The patient did not experience difficulty defecating.

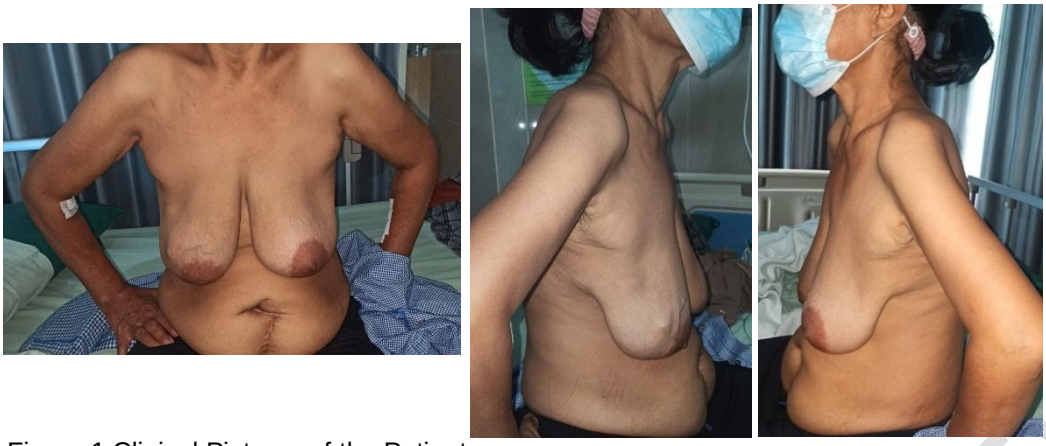
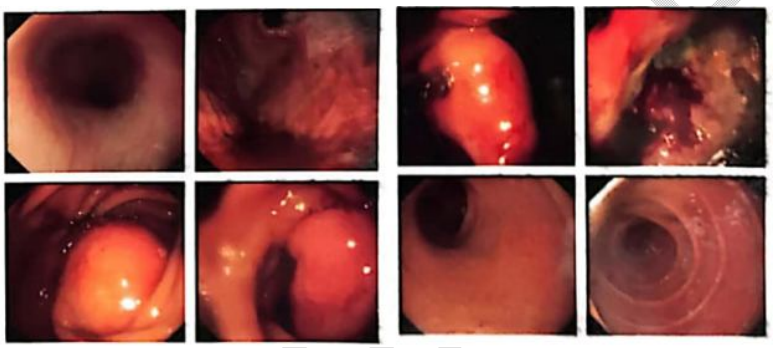


Figure.1 Clinical Pictures of the Patient

From the physical examination, there was one lump in the right breast that was felt to be hard and fixed with a bumpy surface accompanied by tenderness, the lump was 8x7x4cm in size. On physical examination of the abdomen, a flat surface was found without distension, an intraumbilical lump measuring 8x8x4 with a post-op wound, bowel sounds (+), tympanic percussion, tenderness in the left upper quadrant, a mass measuring 8x8x4 cm was felt with clear boundaries, hard consistency, fixed. The patient then underwent esophagogastroduodenaloscopy (EGD), a gastric mass was found with ulceration and necrosis. Further examination in the form of a biopsy on the distal corpus to the gastric antrum showed high-grade neuroendocrine carcinoma and adenocarcinoma.
Figure.2 The Patient's EGD result showed a gastric mass with ulceration and necrosis.



Thoracic X-ray and abdominal USG showed no metastasis in the lungs and intra abdomen. From the results of the breast USG, there was a picture of high suspicious malignancy of the right breast - BIRADS 4c (need tissue diagnosis) and multiple lymphadenopathy of the right breast. No abnormalities were found in the left breast and there was no bilateral axillary or bilateral infraclavicular lymphadenopathy. FNAB examination of the right breast lump found carcinoma. The patient was diagnosed with Ca Mamma (D) cT3N1M0 and Neuroendocrine Carcinoma Gaster cT2N1M0 which was suspected to be a double primary tumor based on clinical findings.

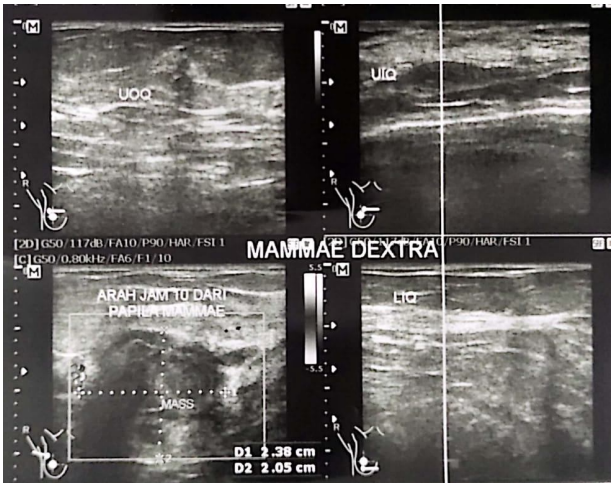


Figure 3 The results of the right breast ultrasound found a highly suspicious malignancy image of the breast – BIRADS 4c

Table 1. Patient's Laboratory Results

Hemoglobin **7.9 mg/dl**	Golongan Darah B
Hematocrit **24%**	Hemostasis
Leucocytes **18.500/ul**	PT 14.1 s
Thrombocyte: **489.000/ul**	APTT 33.3 s
Erythrocyte: **2.96 million/ul**	INR 1.100
Erythrocyte Index:	Clinical Chemistry
MCV 81.2/um	GDS 86 mg/dl
MCH 26.6 pg	SGOT **39 u/l**
MCHC 32.8 g/dl	SGPT 14 u/l
RDW 17.8%	Albumin **3.1 g/dl**
MPV 9.4 fl	Creatinine **1.5 mg/dl**
PDW 16%	Ureum 103 mg/dl
Diff Count :	Electrolyte
Eosinophils 0.20%	Blood Na **129 mmol/L**
Basophils 0.10%	Blood K **5.6 mmol/L**
Neutrophils 93.10%	Blood Cl **97 mmol/L**
Lymphocyte 3.50%	Serology
Monocyte 3.10%	HBsAg non-reactive

After the FNAB results were known on the right breast, the management was continued with surgery to remove the right breast or Modified Radical Mastectomy (MRM) and the PA results showed Invasive Ductal Carcinoma Grade 3.

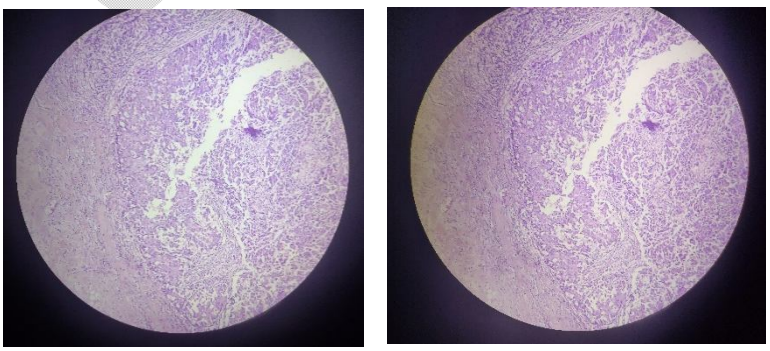
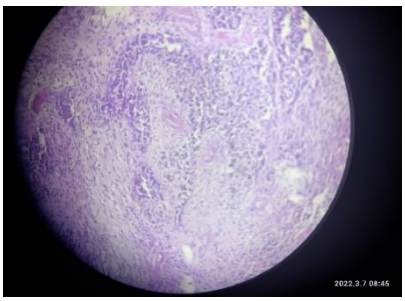


Figure.4 The histopathological picture of right breast tissue



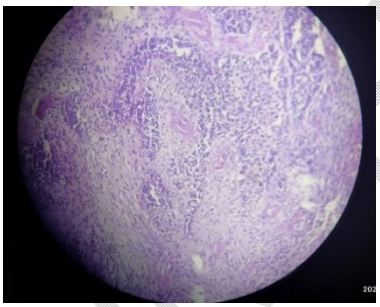


Figure.5 The histopathological picture of gastric tissue

3. DISCUSSION

The results of anamnesis and physical examination showed that the patient experienced disorders due to gastric tumor symptoms. Gastric tumors are the fifth most common cancer and the third most common cause of cancer death globally because the diagnosis is only found at an advanced stage. It is estimated that there are more than 1 million new cases of gastric tumors each year with 784,000 deaths globally in 2018. Risk factors for this disorder include Helicobacter pylori infection, age, high salt intake, and a diet low in fruits and vegetables. [10] Patients came with the main complaint of pain throughout the abdomen that worsens when start to eat accompanied by nausea. The most common symptoms of gastric tumors are dyspepsia, anorexia, easily get full, weight loss, and abdominal pain. Dysphagia or regurgitation can occur in

proximal gastric tumors or cancers located in the gastroesophageal area. These symptoms are often not dominant, not specific, and may remain asymptomatic as the disease progresses. If at the time of diagnosis clinical symptoms have arisen, often the tumor is already in an advanced stage so that it is difficult to cure.[11,12]

The patient also had a history of modified radical mastectomy (MRM) for right breast carcinoma. Breast malignancy can be invasive or non-invasive. In advanced stages, cancer cells can spread to other organs in the body. Metastasis from breast cancer can be found in the axillary lymph nodes, and/or in distant sites such as the lungs, liver, bones and brain. After the primary tumor is removed, microscopic tumor cells or micro-metastases can remain in the body, allowing the cancer to return and spread. In this patient, multiple right breast lymphadenopathy was found without metastasis in the left breast. [1,13]

The occurrence of two malignancies simultaneously can be caused by the process of metastasis or the presence of multiple primary conditions. Tumors are considered multiple primary malignancies if they arise in different places and/or from different histological or morphological groups. According to the International Agency for Research on Cancer (IARC), tumors that arise in different places are said to be synchronous if they are diagnosed within an interval of less than 6 months or metachronous if more than 6 months.[4,5] In women with breast carcinoma, the incidence of multiple primary cancers is reported to occur in 4.1-16.4% of cases. The second malignancy occurs on average 5-8 years after the diagnosis of breast carcinoma due to endocrine factors or obesity. The BRCA1 and BRCA 2 genes in breast carcinoma are closely related to the emergence of a second tumor in the breast or ovary. While hormonal therapy, especially tamoxifen, increases the risk of subsequent primary cancers in the endometrium, stomach, colon, and ovary due to the toxic effects of radiotherapy and chemotherapy.[4] This patient developed breast cancer after a history of ovarian cancer. In the double primary between breast carcinoma and ovarian cancer, the relationship between the two is associated with the BRCA1 and BRCA2 genes.[14]

Endoscopy results before mastectomy showed the possibility of the patient having a double primary between breast carcinoma and gastric tumor. The relationship between breast cancer and gastrointestinal cancer can be considered as a sporadic or germinal association.[8] Gastric cancer and breast cancer can occur in the same patient, especially in women with CDH1 and BRCA2 mutations. There is a report of synchronous occurrence of gastric adenocarcinoma and gastric metastasis from mammary carcinoma in the same patient. The results showed that the two types of adenocarcinoma in gastric biopsies had different immunohistochemical features. Pyloric biopsies were positive for cytokeratin 20, CDX2, and MUC5AC while corpus biopsies were similar to breast biopsies, positive for ER, PgR, gross cystic disease fluid protein-15 (GCFDF15), GATA binding protein 3 (GATA3), and mammoglobin. Briefly, breast cancer can include invasive and non-invasive histologies. Invasive breast cancers include invasive ductal carcinoma, invasive lobular carcinoma and other rare histologic forms, such as breast sarcoma or breast lymphoma. Non-invasive breast carcinomas include ductal carcinoma in situ and lobular carcinoma in situ. Statistically, gastric metastases are usually caused by invasive lobular carcinoma. Gastric malignancy is characterized by upper gastrointestinal bleeding while gastric metastases are generally asymptomatic.[15]

Gastric tumors are diagnosed macroscopically by endoscopic examination and then histologically confirmed by mass biopsy. The clinical stage determines the curative or palliative treatment approach. To support the need for treatment, CT scan of the abdomen and thorax is needed to determine the presence or absence of liver, lung, or peritoneal metastasis. Endoscopic ultrasonography can help to identify superficial mass invasion that does not penetrate further than the submucosa (T1) or muscularis propria (T2) with a sensitivity and specificity of 0.85 (95% CI 0.78-0.91) for T1 and 0.90 (0.85-0.93) for T2.[16] In the early T stage, considering the tumor size, differentiation, and presence of ulceration, endoscopic resection is possible. While laparoscopic exploration to detect peritoneal metastasis is recommended for patients with gastric tumors at stage 1B or higher who are planned for surgical resection.[11]

Based on the examination, the patient was diagnosed with T2N1M0 suspected gastric tumor based on clinical findings. Laparoscopic gastrectomy has emerged as an option for conventional gastrectomy. Trials from East Asia for early gastric cancer with risk factors for lymph node metastasis have shown that laparoscopic distal gastrectomy is not superior and has fewer wound complications than open distal gastrectomy.[17,18] In locally advanced (T2-T4a) gastric cancer, published short-term results from the KLASS-02 trial showed less morbidity, less postoperative pain, and shorter length of stay after laparoscopic compared with open distal gastrectomy.[19] Regarding survival, early reports from KLASS-02 and the STOMACH and LOGICA trials showed non-inferiority in survival for laparoscopic surgery. However, there are fewer data regarding total gastrectomy. [20,21]

The occurrence of breast cancer and double primary gastric cancer is associated with the loss of E-cadherin protein expression. E-cadherin is part of the classic class I cadherin, a type of transmembrane glycoprotein on the cell surface that plays a role in influencing the function of adhesion between cells. E-cadherin consists of 3 domains, namely the extracellular domain, the transmembrane domain, and the intracellular domain. The extracellular domain consists of 5

cadherins and has 4 calcium binding sites mediated by the adhesion function of E-cadherin. The intracellular domain interacts with α and β-catenin to form a bond and is associated with the actin cytoskeleton to maintain the stability of cell structure, inhibit individual cell movement, and participate in cell signal transduction. [23]

The human E-cadherin protein is regulated by the CDH1 gene located on chromosome 16q22.1. Mutations in CDH1 are the only germline molecular mutations associated with hereditary diffuse gastric cancer and lobular breast cancer. Abnormal E-cadherin expression has a significant impact on cell-cell interactions that lead to the destruction of epithelial tissue balance. This causes cells to have higher mobility and be more invasive so that tumors are more likely to infiltrate and metastasize. [23] Loss of E-cadherin is associated with increased invasion, decreased proliferation and survival of cancer cells, the number of circulating tumor cells, cancer cells in distant organs, and metastatic growth. In this condition, there is an upregulation of the transforming growth factor β (TGF-β) gene, reactive oxygen species, and apoptotic signals. [22]

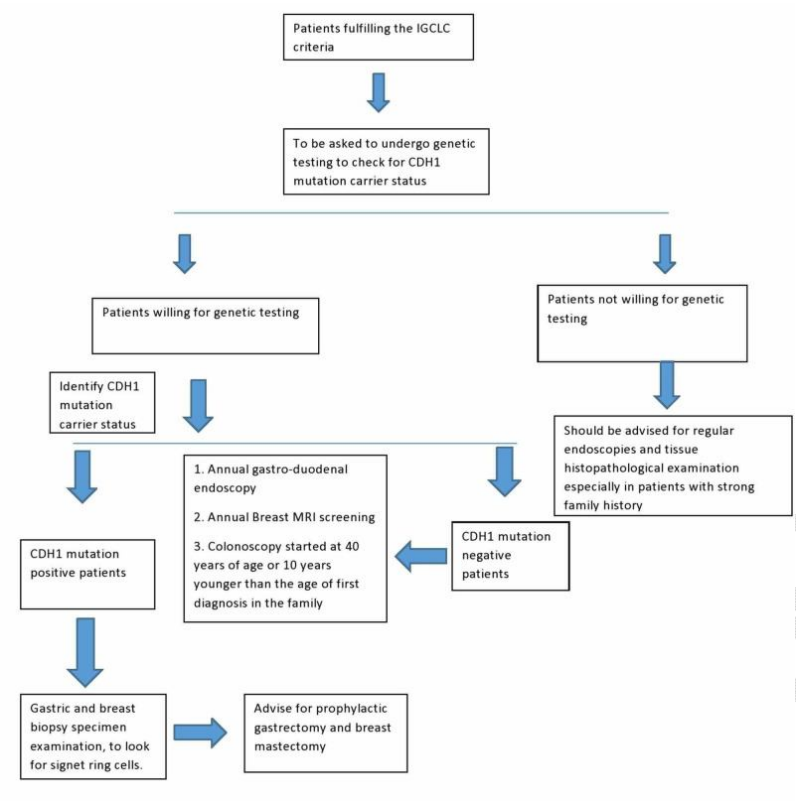
Genetic and environmental factors play a role in the occurrence of cancer. In one-third of gastric cancer cases, there is a genetic role called hereditary diffuse gastric cancer. Genetic factors in gastric cancer are influenced by the loss of E-cadherin expression. Abnormalities in the CDH1 gene are found in both sporadic and inherited gastric cancer. Mutations that occur are generally in the form of changes in gene expression levels, germline and somatic mutations, deletion of the 16q22.1 allele, promoter methylation and non-coding RNA that regulates epigenetic gene silencing so that abnormal expression of E-cadherin occurs .[23] Loss of E-cadherin expression is also found in breast cancer. Under normal circumstances, E-cadherin is expressed by breast epithelial tissue and plays an important role in epithelial cell adhesion, as well as epithelial to mesenchymal transition.[24] Padmanaban et al. research stated that E-cadherin plays a role as a survival factor in invasive ductal carcinoma during the process of systemic dissemination and spread during metastasis, by limiting reactive oxygen-mediated apoptosis.[22] Loss of E-cadherin expression is often used to confirm lobular histology, which occurs in about 10-15% of breast cancer cases. This condition is also associated with malignant progression, metastasis, and decreased survival rates in breast cancer patients.[24]

The case report of Okamoto et al. described synchronous occurrence of gastric adenocarcinoma and gastric metastasis from mammary carcinoma showing two types of adenocarcinoma on gastric biopsy. Both showed small clusters of atypical cells with increased chromatin condensation consistent with poorly differentiated adenocarcinoma. On immunohistochemistry, only the pyloric biopsy was positive for cytokeratin 20, CDX2, and MUC5AC. The corpus biopsy was immunohistochemically similar to the breast biopsy, staining positive for ER, PgR, gross cystic disease fluid protein-15 (GCFDF15), GATA binding protein 3 (GATA3), and mammoglobin. In these patients, the breast cancer was invasive ductal carcinoma, whereas the gastric metastasis was usually caused by invasive lobular carcinoma. Gastric malignancy is characterized by bleeding, whereas gastric metastasis is usually asymptomatic.[15]

According to Harsit K Goud, et al., there is a relationship between CDH1 gene mutations that express E-Cadhrine with Hereditary Diffuse Gastric Cancer (HDGC) Syndrome. HDGC Syndrome is a rare genetic disorder. It means that the risk of cancer and clinical conditions associated with HDGC may not occur in generations in a family. The gene most associated with this syndrome is CDH1. Mutations in the CDH1 gene can increase the risk of gastric cancer, breast cancer and other related cancers.
The patient's breast cancer was stage T3N0M0. Six days before admission, the patient underwent a modified radical mastectomy on the right breast. Mastectomy is indicated in patients with multifocal or multicentric breast disease related to the volume and distribution of the disease, as well as patients who present with advanced locoregional disease, including large primary tumors (T2 lesions greater than 5 cm) and skin or chest wall involvement. In addition to systemic chemotherapy and radiation therapy, patients who present with inflammatory breast cancer are also indicated for mastectomy due to the tumor burden in the dermal lymphatic channels and more widespread involvement of the breast parenchyma. In most cases, primary treatment of breast cancer requires local surgical treatment and may be combined with neoadjuvant or adjuvant therapy, including radiation, chemotherapy, hormone antagonist drugs, or a combination of these. Tumor characteristics such as size and location and patient preference are important parts of the decision-making process because survival rates are almost the same between patients who undergo mastectomy or lumpectomy and adjuvant radiation therapy.[28]

Management of HDGC Syndrome according to the International Gastric Cancer Linkage Consortium (IGCLC) [9]. In patients with HDGC syndrome, supporting examinations are performed to ensure the involvement of the CDH1 or E-Cadhrine gene, if the E-Cadhrine result is negative, gastro-duodenal endoscopy examination is performed, breast MRI screening and colonoscopy are started at the age of 40 years or 10 years younger than the age of the family member who has the diagnosis. If the result is positive, a gastric and breast biopsy is performed to see signet ring cells and continued with prophylactic gastrectomy and mastectomy.

Figure 6 Screening and management of patients with CDH1 gene mutations



4. CONCLUSION

The patient was diagnosed with breast cancer with double primary gastric carcinoma. After modified radical mastectomy (MRM) on the right breast, the patient complained of symptoms of gastric ulcer and generalized peritonitis.

Breast malignancy can be invasive or non-invasive and can undergo metastasis. In addition to metastasis, cancer can also appear in two different places but histologically/morphologically different. This condition is called multiple primaries due to host, lifestyle, and environmental factors. Diagnosis of primary cancer refers to international standards, including: 1) each malignant tumor must be confirmed pathologically by histological examination; 2) each tumor must specifically have its own pathological morphology; 3) tumor metastasis that occurs from a different place or organ from the patient must be ruled out.

Breast cancer can be confirmed by history taking, physical examination, especially mammography, followed by optimal biopsy sampling. While gastric tumors can be confirmed by supporting examinations in the form of endoscopy and mass biopsy. In multiple malignancies that occur in different places, immunohistochemical confirmation is needed to determine the relationship between the two masses.

Complications, such as generalized peritonitis, may occur in gastric tumor perforation due to necrosis and ischemia of the gastric wall. In this case, if the gastric perforation cannot be resected, the patient will only be treated with palliative management. Both operative and adjuvant management such as administration of cytostatics require the patient's general condition and stable hemodynamics except in emergency conditions.

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