Blood thicker than water: a case report on familial ovarian cancer*

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ABSTRACT

Reported is a case of a 43 year-old Gravida 3 Para 3 (3003) admitted due to progressive abdominal enlargement, weight loss and dyspnea. Admitting Impression was Ovarian New Growth, bilateral, malignant, with secondary Pleural Effusion. She underwent Total Abdominal Hysterectomy, with Bilateral Salpingooophorectomy, bilateral lymph node dissection, peritoneal fluid cytology, and infracolic omentectomy. Histopathology report showed a Malignant Mixed Mullerian Tumor of both ovaries with metastasis to the colorectal serosa. It is noteworthy that the patient has two siblings who succumbed to advanced stage ovarian cancer. This case report will discuss the possible hereditary genetic mutations involved in the development of familialovarian carcinoma.

Keywords: Ovarian cancer, malignant mixed mulleriantumor, hereditary breast ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome

INTRODUCTION

Ovarian cancer is extremely hard to diagnose in its early stages, and those afflicted at the time of diagnosis are typically asymptomatic and in the late stages of the disease, with metastasis to other organs. Fleming, et. al.,[1] reported that patients are usually diagnosed at the median age of 63 years and in more than 70% of cases, patients present with advanced disease. The National Cancer Database[2] also reports a 23-64% chance of having ovarian cancer in the 50-69 age group with only 13% occurring in the 40-49 age group.

Recent statistics from the Centers for Disease Control and Prevention[3] show that ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer deaths in the United States. It causes more deaths than any other cancer of the female reproductive system, but accounts for only about 3% of all cancers in women. In 2002, Redaniel, et.al.[4], reports the incidence rate of ovarian cancer among Filipino women in the United States to be 11.5 per 100,000 as compared to 10.3 for Caucasians and 8.9 for Asian and Pacific Islanders (API) with mortality rates highest among Filipino women at 6.3 per 100,000 and 6 and 3.3 per 100,000 for Caucasians and APIs respectively. In 2010, the Department of Health reported that ovarian cancer ranks as the 8th leading cause of cancer deaths in the Philippines, and the 5th most common cancer among Filipino women.[5]

A person's age at ovulation or the lifetime number of ovulatory cycles, is an index of a woman's ovarian cancer risk. Thus, nulliparity and refractory infertility increases risk, while multiparity is protective. Oral contraceptives, and tubal ligation or hysterectomy are likewise protective.[6]

Mutations in the BRCA1 and BRCA2 tumor suppressor genes have been found to be responsible for the majority of hereditary ovarian cancers. [7]

Malignant Mixed Mullerian Tumor (MMMT) is an aggressive type of ovarian neoplasm, accounting for only 1% of all ovarian cancers. MMMT usually occurs in postmenopausal women and responds poorly to treatment.[8] Histologically, carcinosarcoma tumors are composed of both carcinomatous and mesenchymal components, which may be either homologous (composed purely of ovarian tissues) or heterologous (containing tissues found in other organs). They have a poor overall survival rate.[9]

Reportedis a case of Ovarian MMMT managed in this institution and is of particular interest for the following reasons: 1.)MMMT comprises only 1% of all ovarian neoplasms; 2.) since patient has two sisters who succumbed to ovarian cancer, this case could involve a hereditary genetic mutation, which comprise only 5% of MMMT; 3.) patient has no other risk factors such as advanced age and prolonged exposure to ovulation; 4.) patient has two other sisters who are still asymptomatic and unscreened for ovarian cancer.

CASE REPORT

This is a case of a 43 year-old female, G3P3 (3003), who was admitted in this institution due to dyspnea. She had a 2-month history of difficulty of breathing and sudden weight loss described as loosening of clothes. One

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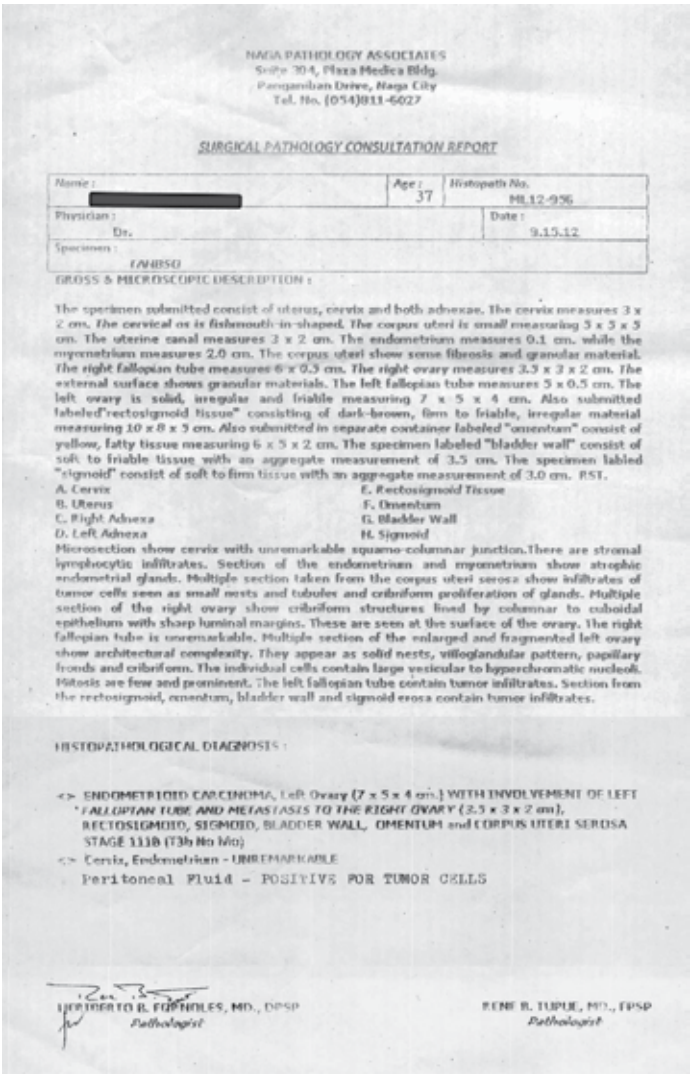
month prior to admission, there was observed progressive abdominal enlargement. No abdominal pain, changes in urinary and bowel habits were noted. Past medical, social and sexual history were unremarkable. She had 3 uncomplicated pregnancies carried to term and delivered via normal spontaneous delivery attended by a midwife. There was no history of oral contraceptive use. Family history revealed that two of the patient's siblings were both diagnosed with ovarian cancer. Her eldest sister had sudden abdominal enlargement in 2007, and surgical findings in another institution showedan ovarian malignancy. She died in the same year at age 49. Her younger sister, who also presented with abdominal enlargement for which an exploratory laparotomy with surgical staging was done, had a histopathology report of endometrioid carcinoma, left ovary, measuring 7x5x4cm, with involvement of left the fallopian tube and metastasis to the right ovary (which measured 3.5x3x2cm), rectosigmoid, sigmoid, bladder wall, omentum, and corpus uterine serosa (Figure 1). She succumbed in 2013 at the age of 36 in a provincial tertiary center. She still has two older sisters, both are currently asymptomatic.

Upon admission, BP was 120/80, with cardiac rate of 96 beats per minute, tachypneic at 32 cycles per minute, and febrile with a temperature of 38.7. Chest examination showed asymmetrical chest expansion, with lagging, dullness on percussion and decreased breath sounds from T7 and below on the right lung. Abdominal examination revealed a globular abdomen, with normoactive bowel sounds, soft, with a palpable solid, slightly tender, non-movable, regularly shaped pelvoabdominal mass with distinct borders measuring approximately 10x10cm; there was also noted shifting dullness and fluid wave. Internal examination revealed a firm, short, closed cervix, normal-sized uterus, and a solid, slightly tender, non-movable left adnexal mass, measuring approximately 10x10 x 8cm; there was also a right adnexal mass palpated measuring 3x2x2cm, which was described as solid, non-movable, non-tender with regular borders. No cervical motion tenderness was appreciated. Admitting Diagnosis was Ovarian New Growth, bilateral, Malignant; Pleural effusion secondary to malignancy, G3P3 (3003). Ultrasound showed that the uterus is retroverted with smooth contour and homogenous echopattern measuring 5.29x3.44x7.7cm; endometrium is isoechoic measuring 0.2cm with intact subendometrial halo; cervix measures 3.41x3.12x2.08cm; a left adnexal mass measuring 11.83x9.19x8.78cm, and a right adnexal mass measuring 3x2x2cm were also seen, which were assessed to be bilateral Ovarian New Growth, probably malignant. Masses were given a Sassone Score of 13 because the lesions were mostly solid, with the presence of papillary excerences, thick septa (4 mm), and mixed echogenicity.



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SURGICAL PATHOLOGY CONSULTATION REPORT

Name: [redacted] Age: 37 Histopath No. ML12-956
Physician: Dr. Date: 9.15.12
Specimen: EMBSO

GROSS & MICROSCOPIC DESCRIPTION:

The specimen submitted consist of uterus, cervix and both adnexae. The cervix measures 3 x 2 cm. The cervical os is fishmouth-in-shaped. The corpus uteri is small measuring 5 x 5 x 5 cm. The uterine canal measures 3 x 2 cm. The endometrium measures 0.1 cm. while the myometrium measures 2.0 cm. The corpus uteri show some fibrosis and granular material. The right fallopian tube measures 6 x 0.5 cm. The right ovary measures 3.5 x 3 x 2 cm. The external surface shows granular materials. The left fallopian tube measures 5 x 0.5 cm. The left ovary is solid, irregular and friable measuring 7 x 5 x 4 cm. Also submitted labeled"rectosigmoid tissue" consisting of dark-brown, firm to friable, irregular material measuring 10 x 8 x 5 cm. Also submitted in separate container labeled "omentum" consist of yellow, fatty tissue measuring 6 x 5 x 2 cm. The specimen labeled "bladder wall" consist of soft to friable tissue with an aggregate measurement of 3.5 cm. The specimen labled "sigmoid" consist of soft to firm tissue with an aggregate measurement of 3.0 cm. RST.

A. Cervix
B. Uterus
C. Right Adnexa
D. Left Adnexa
E. Rectosigmoid Tissue
F. Omentum
G. Bladder Wall
H. Sigmoid

Microsection show cervix with unremarkable squamo-columnar junction.There are stromal lymphocytic infiltrates. Section of the endometrium and myometrium show atrophic endometrial glands. Multiple section taken from the corpus uteri serosa show infiltrates of tumor cells seen as small nests and tubules and cribriform proliferation of glands. Multiple section of the right ovary show cribriform structures lined by columnar to cuboidal epithelium with sharp luminal margins. These are seen at the surface of the ovary. The right fallopian tube is unremarkable. Multiple section of the enlarged and fragmented left ovary show architectural complexity. They appear as solid nests, villoglandular pattern, papillary fronds and cribriform. The individual cells contain large vesicular to hyperchromatic nucleoli. Mitosis are few and prominent. The left fallopian tube contain tumor infiltrates. Section from the rectosigmoid, omentum, bladder wall and sigmoid erosa contain tumor infiltrates.

HISTOPATHOLOGICAL DIAGNOSIS:

<> ENDOMETRIOID CARCINOMA, Left Ovary (7 x 5 x 4 cm.) WITH INVOLVEMENT OF LEFT FALLOPIAN TUBE AND METASTASIS TO THE RIGHT OVARY (3.5 x 3 x 2 cm), RECTOSIGMOID, SIGMOID, BLADDER WALL, OMENTUM and CORPUS UTERI SEROSA STAGE IIIB (T3b No Mo)
<> Cervix, Endometrium - UNREMARKABLE
Peritoneal Fluid - POSITIVE FOR TUMOR CELLS

LEONARDO R. FERNANDES, MD., DPSP
Pathologist

RENE R. TUPUE, MD., FPSP
Pathologist

Figure 1. Histopathology Report of the patient's sister

Minimal ascites was also noted. Chest tube thoracostomy was immediately performed. Pleural fluid was sent for cytology and showed absence of malignancy. Once the patient was stabilized, total abdominal hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, peritoneal fluid cytology, and bilateral lymph node dissection were performed. Intraoperatively, a red, turbid peritoneal fluid amounting to approximately 500 ml was noted. The pelvic cavity was occupied by a firm, irregularly shaped left ovary measuring 13x10x5cm which on cut section had a soft to friable surface with yellow border; while the soft to rubbery right ovary measuring 3.5 x 2.5.x 2.0cm had a convoluted surface, which on further sectioning showed a well encapsulated tan-white surface. The uterus was smooth, firm, and symmetrical, measuring 6.0x5.5x4.0cm. Sectioning of uterus showed a tan-white, firm to rubbery myometrial wall. The anterior and posterior myometrial walls measured 2.2cm and 2.0cm respectively, while the endometrial thickness was 1.5 cm. There was a colorectal mass noted in the serosa which

was described as fixed and nodular measuring 13x12x6cm (Figure 2). The omentum was tan-yellow and described as soft to rubbery. Subdiaphragm was smooth; liver was firm, smooth with no palpable metastatic seedings; para aortic nodes were not enlarged.

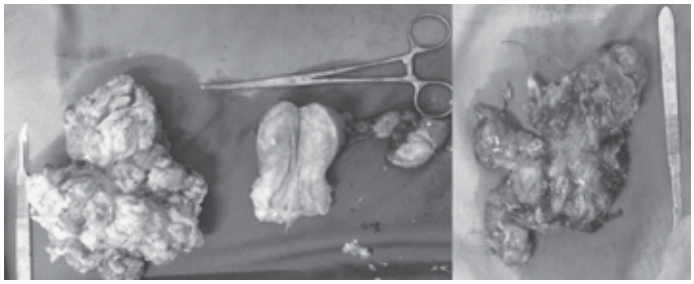


Figure 2. Cut section of left ovary, uterus with right ovary; Colorectal mass

Microscopic sections from the left fallopian tube, left ovary (Figure 3), right ovary (Figure 4 and 5), and colorectal mass (Figure 6) show a malignant mixed mulleriantumor characterized by admixture of malignant carcinomatous components composed of pleomorphic tumor cells lined by cuboidal to columnar epithelium exhibiting glandular complexity, some with branching papillary architecture, and some with clearing of cells, displaying nuclear atypia, increased nuclear-cytoplasmic ratio, vesicular nuclei, and prominent nucleoli which are infiltrating the stroma. Sections from colorectal mass (Figure 6) also show areas with cartilaginous elements admixed with red blood cells and necrotic tissues. Microscopic sections from the omentum (Figure 7) show invasion of the malignant tumor. Microscopic sections from the endometrium show round endometrial glands lined by columnar cells with pencil-shaped nucleus, surrounded with densely

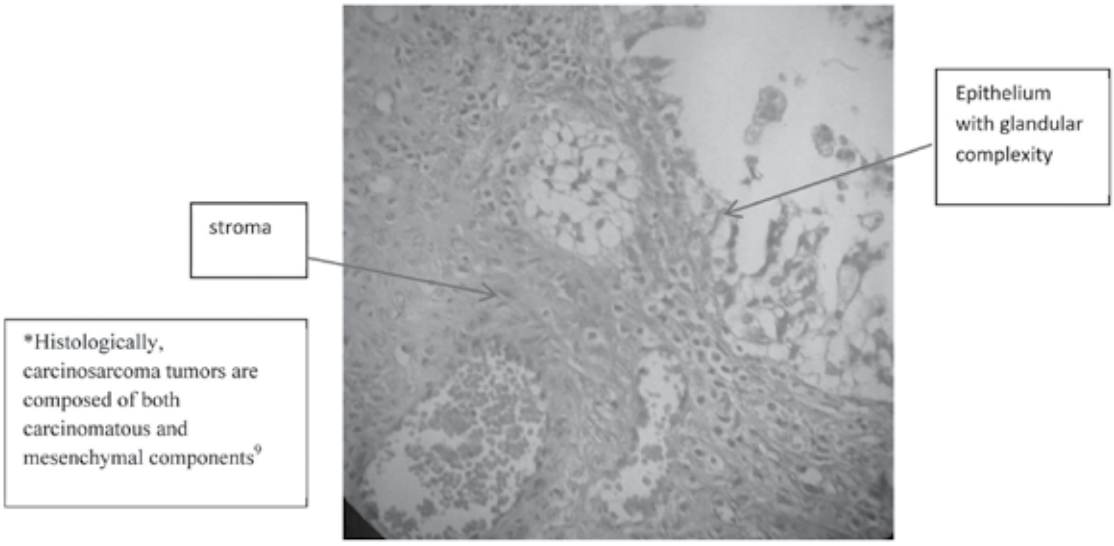


Figure 3. Left ovary (high power field)

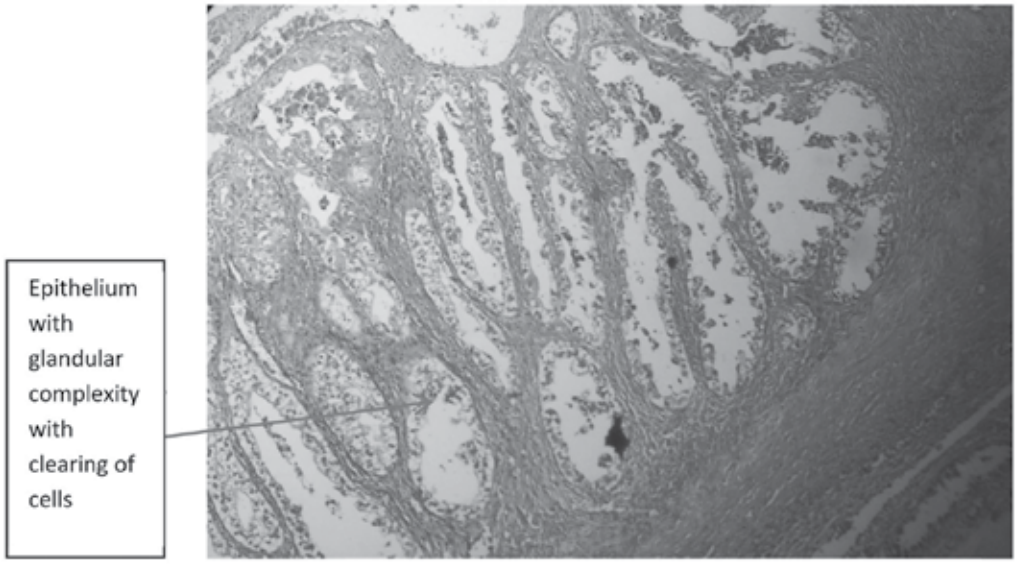


Figure 4. Right ovary (low power field)

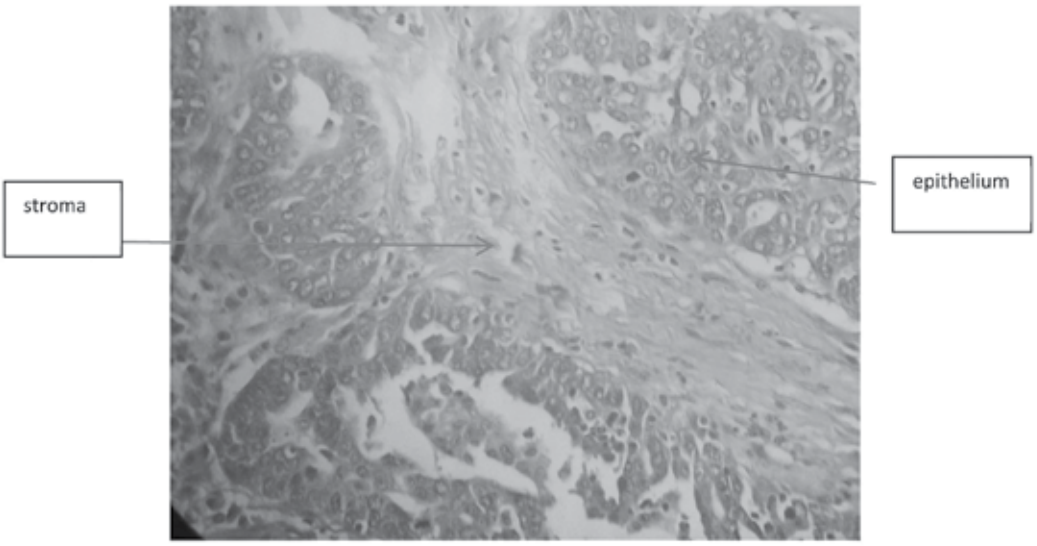


Figure 5. Right ovary (High power field)

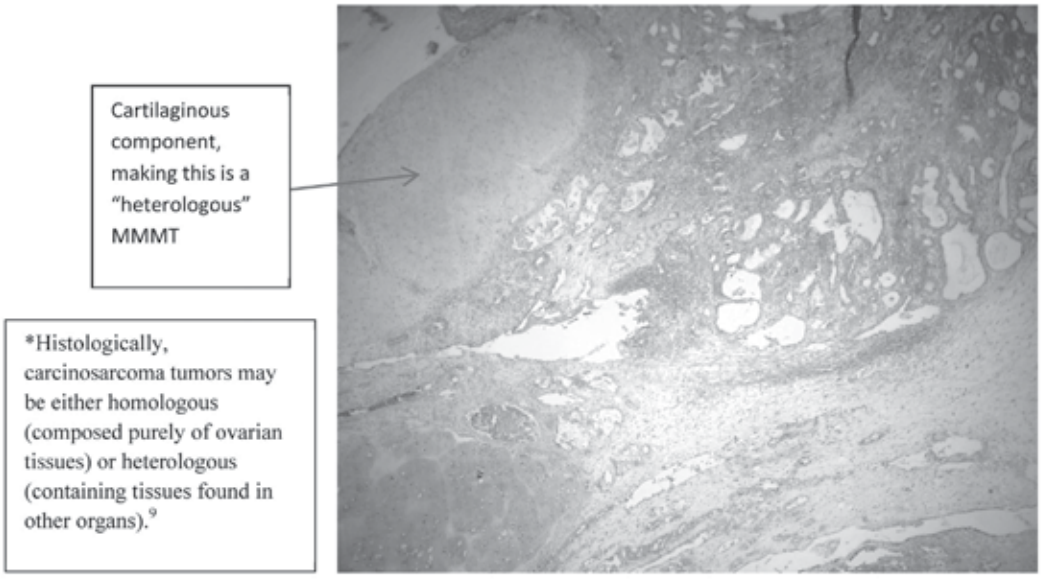


Figure 6. Colorectal mass. (low power field)

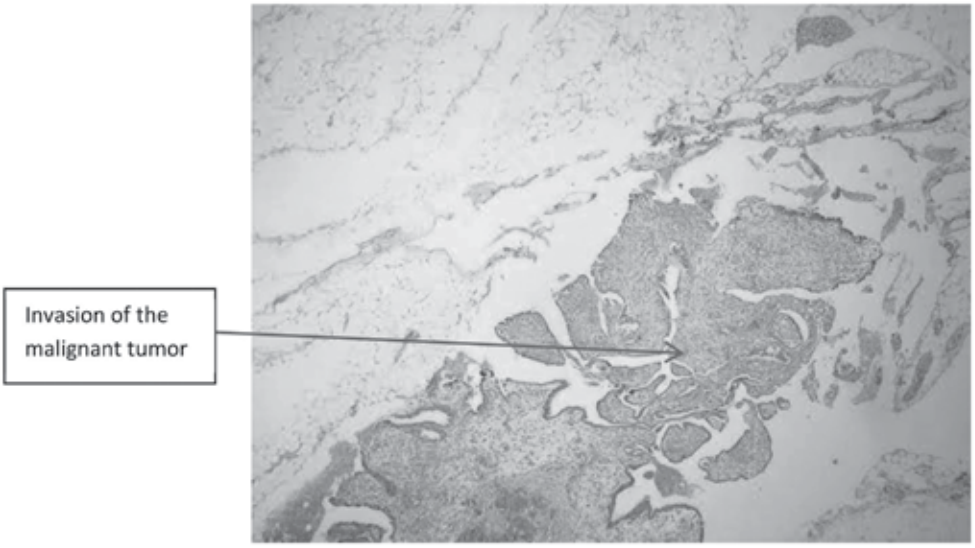


Figure 7. Omentum

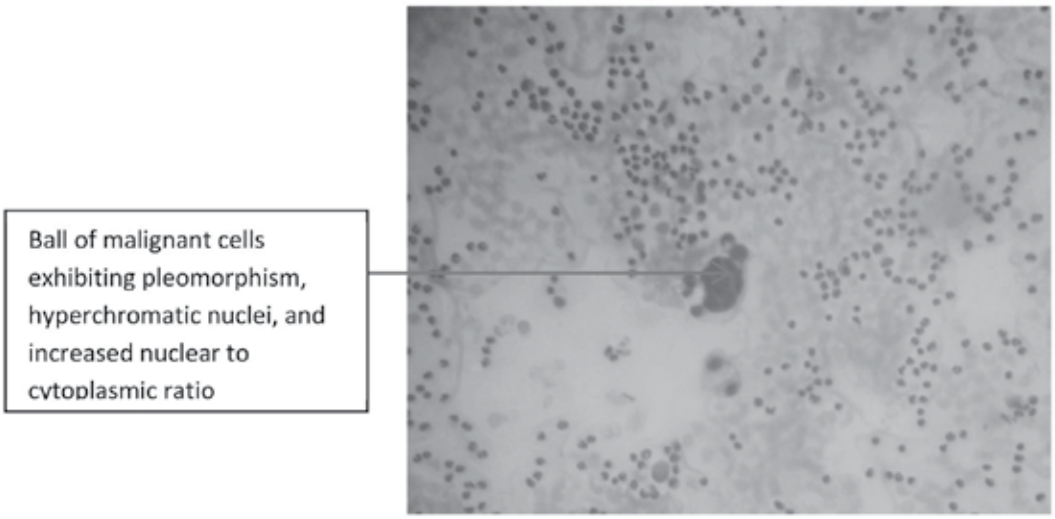


Figure 8. Peritoneal fluid

cellular stroma. The findings seen in the microscopic sections from left fallopian tube, left and right ovaries, as well as colorectal mass, were all consistent with the features of Malignant Mixed Mullerian Tumor, since MMMT is composed histologically of malignant epithelial and sarcomatous elements. Jinet. al.[10] reported that MMMT can be homologous, when the specimen contains malignant elements native to the ovary, or heterologous, when MMMT contains sarcomatous tissue not normally found in the ovary, such as bone or cartilage. The colorectal mass found in this case also showed areas of cartilaginous elements consistent with heterologous MMMT. Cytologic evaluation of the peritoneal fluid (Figure 8) showed hypercellular smears composed of abundantly scattered neutrophils, lymphocytes, and reactive mesothelial cells, admixed with enlarged crowded sheets and balls of malignant cells exhibiting pleomorphism, hyperchromatic nuclei, and increased nuclear to cytoplasmic ratio set in a background of red blood cells.

The patient was stable until 2 days post-operatively when she developed dyspnea, with absence of CTT output. Chest ultrasound revealed loculations, for which Video-assisted thoracostomy (VATS) was contemplated, so patient was transferred to another institution. During the patient's stay in the said institution, loculations resolved and VATS was no longer needed. Chemotherapy was offered but patient refused due to financial constraints.

DISCUSSION

Malignant Mixed Mullerian Tumor of the ovary, recently called Ovarian Carcinosarcoma, is a very rare tumor, comprising only 1% of all ovarian neoplasms.[11] It is not common to arise in the female genital tract, and when it does, it usually affects the uterine corpus, followed by the cervix, vagina, ovary, and fallopian tube. [12] Ovarian carcinosarcoma is an extremely aggressive subtype of epithelial ovarian cancer that is often advanced at diagnosis.[13]

In women with family histories of ovarian cancer, the risk of ovarian cancer is higher compared with the general population.[14] While approximately 90% of ovarian cancers occur sporadically, this patient falls under the 5-10% of women with ovarian cancer who have inherited genetic changes that predispose them to ovarian cancer, since she has two sisters who both died shortly after being diagnosed with ovarian cancer. Recent literature says that familial ovarian cancer confers a 4.6 relative risk (RR) of this disease in the proband's mother and a 1.6 RR in the proband's sister. This translates to a lifetime risk estimate of about 7.0% risk for the patient's mother, and 2.5% for the sister of an ovarian cancer patient, such as this patient.[15]

Two inheritable genetic mutations are known to predispose to ovarian cancer. Ninety percent of the ovarian cancers in the hereditary breast-ovarian cancer (HBOC) syndromes involves mutations mostly in the breast cancer-associated genes BRCA1 located on chromosome 17, and small proportions have mutations in BRCA2, located on chromosome 13; while mutations in at least four mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2) in the Lynch II syndrome (also known as hereditary nonpolyposis colorectal cancer syndrome) account for another 10–15% of hereditary ovarian carcinomas.[16]

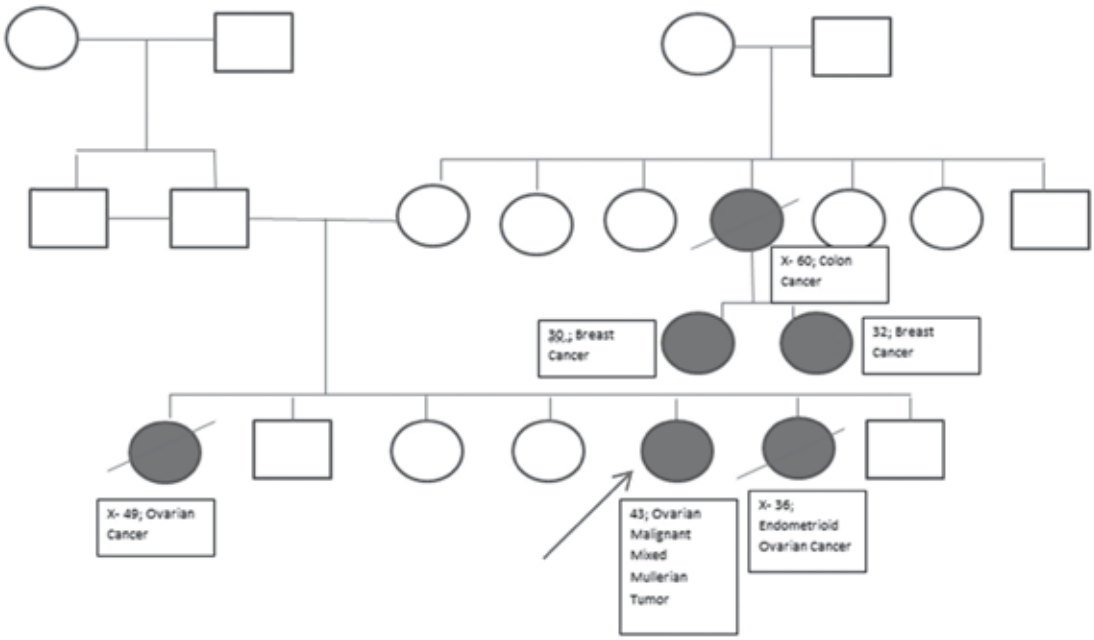
Autosomal dominant inheritance has been established in these syndromes. The lifetime risk of ovarian cancer in those with BRCA1 gene mutation may be as high as 28 to 44%, while for those with BRCA2 mutation, the risk is 27%.[17]

It is also important to note that hereditary ovarian cancers, in general, occur in women approximately 10 years younger than those with nonhereditary tumors.[14] As stated in the National Cancer Database[2] report, in the

general population, those who are 50-69 years of age are 23-64% more likely to have ovarian cancer, while only 13% of the general population with age 40-49 is predisposed to develop ovarian cancer. In this case, the patient was diagnosed with ovarian cancer at the age of 43 years. The same can be said about her sister, who was diagnosed and died at the age of 37 due to endometrioid ovarian carcinoma.

Pedigree analysis is also necessary in determining the risk for hereditary ovarian cancer. The risk of carrying a mutation that predisposes to ovarian cancer depends on the number of first and second degree relatives with a history of epithelial ovarian carcinoma or breast cancer, and on the number of malignancies that occur at an earlier age. [14]

Below is the pedigree analysis of the patient:



Since our patient has two sisters who both died because of ovarian cancer, this patient has a 35 to 40% risk. The same goes for their two remaining sisters who are still asymptomatic and unscreened.

CA125, a monoclonal antibody, is used to diagnose ovarian cancer, even though the sensitivity is only 50%.[14]. It has a 96% positive predictive value in identifying malignancy in postmenopausal patients presenting with an adnexal mass and an elevated serum CA125 of more than 200U/mL. Its specificity in premenopausal patients is low because it tends to be elevated in common benign conditions.[14] The addition of transvaginalsonography has enhanced its specificity. In current practice, CA125 is still requested, not for diagnostic purposes, but for monitoring tumor response.[17] In this patient, the test was requested but not performed due to financial constraints.

The American Cancer Society states that no screening test has proven to be effective and sufficiently accurate for early detection of ovarian cancer. However, for women who are at high risk, the combination of a thorough pelvic examination, transvaginal ultrasonography,and a blood test for the tumor marker CA-125 may be offered.[18] Since these recommendations were not done for this patient earlier, these can be offered to her 2 sisters who are still unscreened.

Combining CA125 with other markers in tumor marker panels has been shown to increase sensitivity by 5-10%; however, specificity is decreased.[19] Initial analysis of a tumor marker panel that included CA125, leptin, prolactin, osteopontin, insulin-like growth factor II, and macrophage inhibitory factor was reported to significantly improve sensitivity and specificity.

Surface-enhanced laser desorption ionization time-of-flight (SELDI-TOF) technology is a new approach in identifying ovarian cancer by using proteomic patterns. Although this study is still in the early phase, this seems to be promising as it has the sensitivity of 100% and specificity of 95%.[20]

The measurement of plasma DNA levels and allelic imbalance by digital single nucleotide polymorphism analysis is another new approach, which is 87% correlated with stage I and II patients and 95% correlated with stages III and IV patients.[21]

Like an advanced epithelial ovarian neoplasm, ovarian MMMT patients usually present with a pelvic mass, abdominal distention, and belching.[11] This patient

consulted due to dyspnea and an enlarging abdomen. Dyspnea was secondary to the malignant pleural effusion. This is expected as 75% of ovarian MMMT is diagnosed in stage III or IV, where in 90% of cases, have already metastasized to extragonadal sites.[22]

It has also been suggested that expression of CD10 should be examined - it may be one of the characteristics of MMMT[23]. However, the significance of CD10 expression needs to be elucidated by further studies.

Ultrasound is also an indispensable inexpensive diagnostic tool, as it can image a complex ovarian mass, with both solid and cystic components, internal echoes and/or septations, and ascites or evidence of peritoneal metastases in the presence of an ovarian mass, are highly suggestive of ovarian malignancy.[24] One must also take note of the size and laterality of the lesion, as cystic masses more than 8cm in diameter are more likely to be neoplastic. In this patient, a predominantly solid mass measuring 9.02 x8.78 x 7.72cm was seen on the left adnexa, and 3x2x2cm solid mass on the right adnexa, with Sassone score of 13. Minimal ascites was also noted. Other procedures like CT scan and MRI may be requested to help in staging and planning the surgery.[17]

Microscopically, specimens from left ovary and fallopian tube, right ovary, and colorectal mass all exhibited an admixture of malignant carcinomatous component composed of pleomorphic tumor cells lined by cuboidal to columnar epithelium exhibiting glandular complexity, some with branching papillary architecture, and some with clearing of cells, displaying nuclear atypia, increased nuclear-cytoplasmic ratio, vesicular nuclei, and prominent nucleoli which are infiltrating the stroma. This is consistent with the histologic criteria of MMMT, which must show a biphasic differentiation with malignant epithelial components and malignant sarcomatous components.[17] Sections from colorectal mass (Figure 6) also showed areas with cartilaginous elements admixed with red blood cells and necrotic tissues.

A study done by Reed[17] shows that the diagnosis of a metastatic ovarian carcinosarcoma can be problematic, as when MMMT metastasizes, the sarcomatous component is either absent or is present in very minimal amount. This has not been the case in this patient, as both the epithelial and sarcomatous components were seen in the colorectal mass. There is no statistical difference in survival rates between homologous and heterologous MMMT.

Because this tumor is rare and there are very limited reports in literature to date that define the prognostic factors and optimal treatment strategies associated with survival in women with ovarian carcinosarcoma, treatment has still not been well established.

The goal of surgery in ovarian MMMT is not to leave any residual disease. Once ovarian cancer is suspected, total abdominal hysterectomy, bilateral salpingooophorectomy, omentectomy, and peritoneal washings should be done. Lymphadenectomy and blind biopsies from diaphragmatic surface can be included.[22] These were all performed in this patient. Excision of the colorectal mass was also done. The patient was assessed to have Ovarian Malignant Mixed Mullerian Tumor Stage III-C since the patient had a colorectal metastasis involving the serosa, and pleural fluid cytology was negative for malignant cells. The FIGO 5-year survival rate for this patient is 23% for stage IIIC. But since this patient's histopathology revealed MMMT, it is decreased to 18%.

A study by Jarnigan, et. al.,[25] supports the concept that no gross residual disease is associated with improved survival outcomes over traditional "optimal" cytoreduction to ≤1 centimeter. In their analysis, even when controlling for age and stage, the association between cytoreduction to no gross residual disease and survival remains.

Chemotherapy, which the patient refused, should have been in the form of Platinum-based regimens used in epithelial ovarian tumors. It has been hypothesized that the sarcomatous and carcinomatous components both arise from a single malignant epithelial precursor which has undergone metaplastic change to a sarcomatous form, which contributed to the presence of both histological types.[9] Recent literatureshow a 68% overall response rate compared with 23% response rate in the non-platinum containing regimens[26].

The prognostic factors of ovarian MMMT are reported to be the age at presentation, insufficient surgical removal, and the stage. The recurrence rate is 50% in stage I and up to 90% to 100% in stage II or greater.

By understanding the hereditary ovarian cancer syndromes and its relation to this patient, it cannot be overemphasized that a comprehensive family history is really fundamental for early diagnosis. It is a useful tool to arrive at a sound clinical judgement to prevent disease progression in genetically susceptible individuals, like the patient's two remaining sisters. They should also be tested for BRCA1 and BRCA2.

SUMMARY

In summary, the clinicopathologic features of a patient with a primary ovarian Malignant Mixed Mullerian Tumor (MMMT) is discussed. Ovarian MMMT is a rare malignancy comprising only 1% of ovarian neoplasms. The familial association of the disease, given that the patient has two sisters who were diagnosed with an advanced stage of ovarian cancer and succumbed to the disease at a much earlier age than what is reported in the general population, points to a possible hereditary syndrome which occurs in only 5% of ovarian neoplasms.

The following recommendations put forward by Berek, et. al.[14] for the management of women at high risk for ovarian cancer will be useful in clinical practice: 1.) Patients who are high risk should undergo genetic counselling and may be offered genetic testing for BRCA1 and BRCA2; 2.) Those who want a conservative management to preserve their reproductive organs can have a transvaginal sonography every 6 months; 3.) Young women should be offered oral contraceptives before they attempt to have a family; 4.) Prophylactic bilateral salpingooophorectomy should be offered to those with completed family or pregnancy; 5.) Annual mammographic screening should be offered to those with strong family history of breast and ovarian cancer from age 30 and beyond; 6.) Periodic screening mammography, colonoscopy, and endometrial biopsy should be offered to those with Hereditary Non Polyposis Colorectal Cancer syndrome.

However, in a low-resource setting, the following will be recommended for monitoring and/or screening women who are at high risk for developing ovarian cancer:

1. Physical examination focusing on the breast, abdomen, and rectal area every 6 months
2. Transvaginalsonography every 6 months
3. Mammography annually
4. CA125 for postmenopausal women

Genetic testing for BRCA1 and BRCA2 will be reserved for those who are financially capable.

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