High grade ovarian serous carcinoma associated with chronic schistosomiasis*

By Shiara Marriz T. Marquez, MD; Jennifer T. Co, MD, FPOGS, FPIDSOG and Lylah D. Reyes, MD, MSc, FPOGS

Department of Obstetrics and Gynecology, Far Eastern University - Nicanor Reyes Medical Foundation Medical Center

ABSTRACT

Schistosomiasis has been established as a causative factor in urinary bladder, liver, colorectal and cervical cancer. However, its role in ovarian malignancy has not been described. With the premise that long-standing inflammation secondary to chronic infection predisposes to cancer by promoting an environment that cultivates genomic lesions and tumor initiation, we are left with an open question: Does chronic infection with schistosomiasis also predispose to ovarian cancer? In this paper, we presented a case of a 54-year-old diagnosed with high grade serous carcinoma of the ovary and fallopian tube with a history of chronic infection with Schistosomiasis. In this case, the infection caused neoplastic lesions in the right fallopian tube with subsequent seeding of malignant cells to the right ovary, indirectly causing the high grade serous ovarian carcinoma of the patient.

Keywords: fallopian tube, inflammation, ovarian neoplasms, schistosomiasis

INTRODUCTION

In 1858, Rudolph Virchow initially proposed his irritation theory for cancer. According to his observation, irritation of any type, including mechanical, chemical, or thermal, was the essential factor in neoplastic tissue proliferation.[1] Some years later, the vascular endothelial growth factor (VEGF) was discovered to induce chronic vascular permeability and reprogram the gene expression profile of endothelial cells. These leads to endothelial-cell activation, proliferation and survival, angiogenesis and arteriovenogenesis. Hence, the concept that tumors are wounds that do not heal. Non-healing wounds provide continuous inflammatory reaction that could be linked to tumor formation at the molecular level.[2]

Over twenty-percent (20%) of malignancies worldwide are caused by infectious agents.[3] For years, it has been established that viruses, bacteria and parasites are associated with human carcinogenicity. According to the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), there are more than 900 likely candidates with cancer-causing potential. These potential carcinogens were categorized into various groups. Schistosoma haematobium is listed under Group I. This means that S. haematobium has sufficient evidence of carcinogenicity both in humans and experimental animals.[4]

In this paper, we would like to present a case of a 54-year-old woman diagnosed with high-grade serous carcinoma of the right ovary and fallopian tube with evidence of schistosoma infection. Specifically, to discuss the ectopic migration of schistosomiasis, present the possible mechanisms on how it leads to ovarian malignancy and review the evidences regarding their association.

CASE REPORT

N.A.P., 54-years-old, Gravida 3 Para 3 (3003), post menopause for 11 years, married, Filipino, from Eastern Samar who was admitted due to progressive abdominal distention for the past three years. She also experienced intermittent right lower quadrant pain and weight loss. She was first diagnosed with Schistosomiasis in 1992, had reinfection and complication of compensated liver cirrhosis in 2010. She has no family history of any malignancy. Her obstetrical and gynecologic histories were both unremarkable.

Physical examination showed that the patient was conscious, coherent, not in cardiorespiratory distress, afebrile, with no signs of anemia nor jaundice. Abdomen was globularly enlarged, with abdominal girth of 103 cm, tense but not tender, with positive fluid wave. Pelvic examination showed a soft cervix and an unenlarged uterus. The adnexa cannot be fully assessed due to ascites.

Transvaginal ultrasound revealed an anteverted, unenlarged uterus, thin endometrium, and unremarkable cervix. The right ovary was converted into an irregular solid mass, measuring 3.14 x 2.48 x 2.36 cm, no intratumoral flow, with non-benign sonomorphologic features (Figure 1).

*Third Place, Philippine Obstetrical and Gynecological Society (Foundation), Inc. (POGS) Interesting Case Paper Contest, April 19, 2018, 7th Flr., Olive and Citron Function Rooms, Richmonde Hotel, Iloilo City

The left ovary, however was not visualized. There was free fluid in the cul-de-sac and ascites was noted (Figure 2). Cancer antigen (CA-125) and Human Epididymis Protein 4 (HE4) were elevated at 942.4 U/mL and 1165.1 pmol/L, respectively. Admitting diagnosis was Gravida 3 Para 3 (3003) Postmenopause for 11 years; Ovarian New Growth, Right probably Malignant; Liver Cirrhosis probably secondary to Chronic Schistosomiasis.

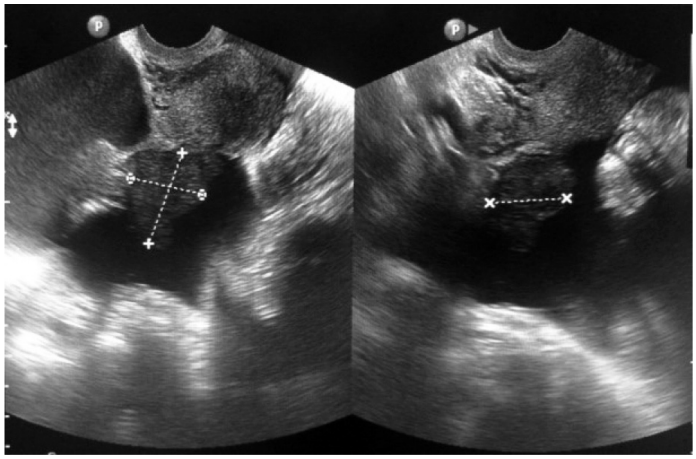

Figure 1. Transvaginal sonography shows that the right ovary is converted to an irregular solid mass, measuring 3.14 x 2.48 x 2.36 c with no intratumoral flow, International Ovarian Tumor Analysis (IOTA) simple rules: Unclassifiable; IOTA subgroup scoring for solid: 7; IOTA LR2: 78.2%.

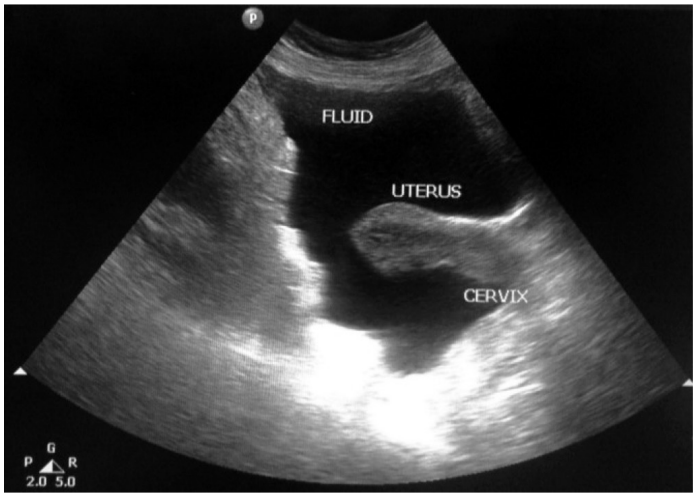

Figure 2. Transvaginal ultrasonography also demonstrates free fluid in the cul de sac secondary to ascites.

Total Abdominal Hysterectomy with Bilateral Salpingooophorectomy, with Frozen Section of the Right Ovary and Fallopian Tube were done. Intraoperatively, ascites was noted and amounted to 9 liters. The liver, spleen, subdiaphragmatic and bowel surfaces were smooth. The uterus, cervix, left ovary and left fallopian tube were grossly normal. The right ovary (Figure 3) however, was converted to an irregularly shaped, tan-brown solid multinodular mass, measuring 4.5 x 2.5 x 3 cm while the right fallopian tube (Figure 4) is brown-red and cystically enlarged measuring 8 x 4 x 2 cm with noted adhesion to the omentum.

Figure 3. The right ovary consists of a brown-red, irregularly-shaped, firm, multinodular piece of tissue measuring 4.7 x 2.5 x 3 cm. The external surface is smooth with prominent vascular markings. Section shows nodular, solid cut surfaces ranging from 0.7 to 2.8 cm in diameter.

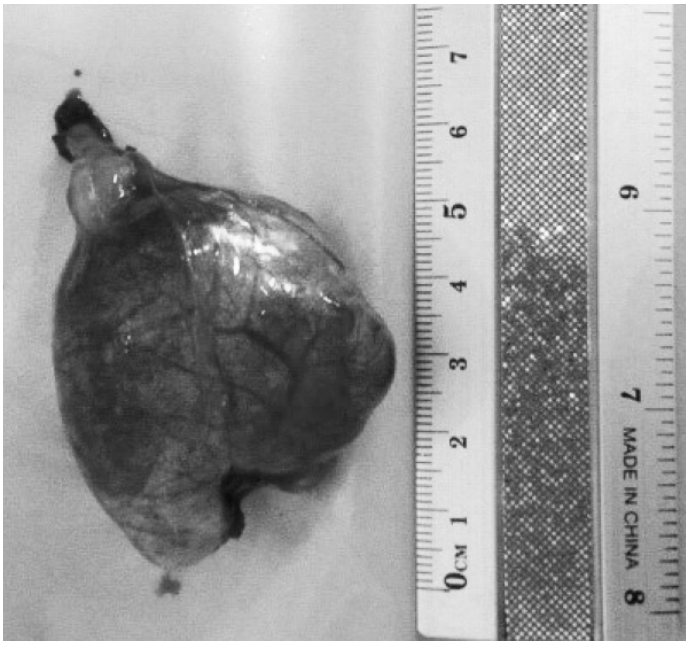

Figure 4. The right fallopian tube consists of an irregularly-shaped, brown-red, cystic piece of tissue measuring 6 x 4.5 x 3 cm. Section shows a cavity filled with yellowish-brown serous fluid. The inner lining is tan-white with an irregularly-shaped, tan-gray, fungating mass measuring 1.5 x 1.5 x 1 cm.

Frozen section revealed "Malignant", Histomorphologic Features Consistent with Poorly Differentiated Adenocarcinoma, favors Serous Carcinoma, High Grade, Right Ovary and Fallopian Tube; Schistosomiasis, Right Fallopian Tube; and "Benign", Left Ovary with Schistosomiasis. Hence, bilateral lymph node dissection and infracolic omentectomy were done for complete surgical staging.

Final Histopathologic report revealed a Serous Carcinoma, Poorly Differentiated, Right Ovary; Positive for Tumor: Right Fallopian Tube, Omentum, 2 out of 3 Right Internal Iliac Lymph Nodes, 2 out of 4 Right Obturator, 3 out of 5 Left Internal Iliac Lymph Nodes, 4 out of 5 Left Obturator; Negative for Tumor: Isthmus, Bilateral parametria, and Left Fallopian Tube, Peritoneal Fluid.

None of the clinical or complementary examinations to which the patient was subjected showed any signs of parasitic infection, except for the findings of schistosoma eggs in the surgical specimen.

She was referred to a specialized center for Schistosomiasis and underwent diagnostics such as Kato-Katz technique and Circumoval Precipitin Test (COPT) to which she tested negative. Hence, no antihelminthic was given in this case. The plan of the service team is to administer chemotherapy with Carboplatin and Paclitaxel. However, the patient decided to have her chemotherapy in Tacloban City.

CASE DISCUSSION

Schistosoma infestation usually involves the portal system. Infestation is referred to as ectopic when the eggs or the adult form of the parasite is found outside the portal system. In this case, the right fallopian tube and left ovary were infected. The patient was diagnosed with Schistosomiasis in the year 1992 and was treated with single dose Praziquantel. Living in Eastern Samar, an endemic area in the Philippines puts the patient at high risk of harboring the infection with subsequent ectopic migration.

Adult schistosomes inhabits the blood vessels for years and evades the immune system while excreting thousands of ova daily with subsequent deposition in adjacent tissues. In the patient, ectopic migration occurred in the right fallopian tube leading to an undetected chronic infection. Interestingly, the vascularization of the female pelvis has several anastomoses that drain the female genital organs to the mesenteric venous system and consequently to the portal vein. As the adult parasites migrate to the pelvic veins, they usually travel in an opposite direction to that of the blood flow, thus reaching the terminal portal venules and other tissue sites.[5] As the lesions form around the schistosome eggs that deposited in the tissues, granulomas develop. This results to a strong inflammatory response from the host and over time metaplasia sets in. Thus, eventually initiating malignant transformation on the particular tissue site.[6]

Schistosoma haematobium is the causative agent of urogenital schistosomiasis, and its association with squamous cell carcinoma (SCC) of the bladder is well known and established. The mechanisms accounting for its role in urinary bladder cancer include epithelium damage, chronic inflammatory processes and oxidative stress. Schistosoma eggs may also induce fibrosis with consequent proliferation, hyperplasia, and metaplasia of host cells ultimately leading to carcinogenesis. Nitrosamines and increased levels of urinary B-glucuronidase and cyclooxygenase-2 produced by adult schistosomes are also known bladder carcinogens.[7] It is also reported that Schistosoma species are linked with cancers such as cervical, colorectal, and liver cancer with low level of evidences.[6] However, it is not proven whether it is a predisposing factor in malignancies of other female reproductive organs.

There is a wide range of literature indicating that genital schistosomiasis is a significant factor for ectopic pregnancy and infertility in schistosomiasis-endemic areas.[8] But can it lead to malignancy? Two cases of ovarian carcinoma have been published containing viable eggs of Schistosoma mansoni. However, the association described was that the neoplasm probably became a migratory route for the adult parasites and the embolization of eggs.[5]

As depicted in Figure 5, Hoang, Brindley, Meyer and Velavan (2016) proposed a mechanism by which infection

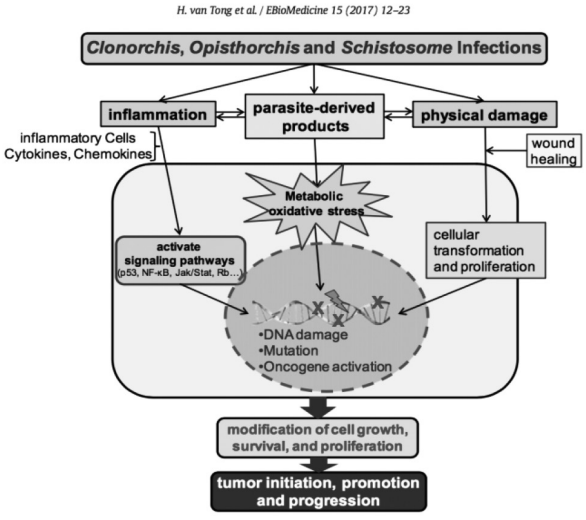

Figure 5. Proposed mechanisms of carcinogenicity induced by parasitic infections. Chronic inflammation, parasite-derived products, and physical damage initiate events that damage the chromosomal deoxyribonucleic aid (DNA) with consequent modification of the cell growth, proliferation and survival ultimately initiating and promote malignancy.[7]
Image from Hoang, VT, Brindley, PJ, Meyer, CG, Velavan, TP. Parasite Infection, Carcinogenesis and Human Malignancy. EBioMedicine. 2016; 15:12-23.

like schistosomiasis induces carcinogenesis. First, the chronic inflammatory response during infection leads to the activation of signaling pathways including p53, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), janus/kinase (Jak/Stat) and retinoblastoma protein (Rb) that could produce somatic mutations and/or activate oncogenes. The production of fluke-derived products and metabolites also causes oxidative stress. Lastly, physical damage of host tissues during the development of parasites concurrent with the active wound healing process leads to increased cell transformation and proliferation. All of these mechanisms can initiate damage to the chromosomal deoxyribonucleic acid (DNA) ultimately leading to tumor initiation, promotion and progression.[7] In this case, the right ovary and fallopian tubes were positive for tumor. However, infection was evident only in the right fallopian tube as documented by biopsy. What's more interesting is the finding of schistomiasis in the left ovary. If chronic inflammation can lead to malignant transformation, how come the left ovary with evident schistosomiasis did not develop carcinoma? On the same note, it was the right ovary that developed the cancer.

Traditionally, the origin of high-grade serous carcinoma has been assumed to be from the surface epithelium or epithelial inclusions in the ovary. Recently, it has been hypothesized that the fimbriated end of the fallopian tube, being in close proximity to the ovarian surface is the origin of high-grade serous carcinomas of the ovary. This is supported by the discovery of a lesion called Tubal Intraepithelial Carcinoma (TIC) detected at the fimbriated end of the fallopian tube which has the cytologic appearance of high-grade serous carcinoma of the ovary.[9] In this case, the primary lesion could have originated from the right fallopian tube, and through its fimbriated end, there was subsequent implantation to the right ovary.

It has also been proposed that when high-grade serous carcinoma in the fallopian and ovary are coexistent, the fimbriated end of the fallopian tube is the primary site of origin for the ovarian tumor. Hence, it has been hypothesized that the invasive high-grade serous carcinoma in the fallopian tube which developed from TIC subsequently implanted on the ovary. This then developed into a high-grade serous carcinoma that clinically and grossly appears to be an ovarian primary tumor.[9] This theory is further strengthened with the fact that although the left ovary has evident infection, it did not undergo malignant transformation since the fimbriated end of the fallopian tube was free from any lesion unlike its contralateral counterpart.

The staging of ovarian cancer is based on the criteria provided by the International Federation of Gynecology and Obstetrics (FIGO). Given the final histopathologic report mentioned above, the patient is diagnosed with Ovarian Serous Carcinoma, Right; Stage III A-1; Poorly Differentiated. Regardless of the presence of infection with Schistosomiasis, the management for the patient in this case would not differ. Conventionally, six to eight cycles of combination platinum and taxane-based therapy are now recommended as adjuvant therapy for most patients with advanced disease like in this case.[10] Hence, the patient was scheduled for her first cycle chemotherapy with Carboplatin and Paclitaxel which she decided to receive in Tacloban.

With regards to the treatment of the patient's schistosomiasis, definitive diagnosis of active infection is essential. However, such diagnosis has been difficult to attain because demonstration of infection is dependent on detection of the parasite eggs in urine and/or stool. Other tests have been employed to diagnose the infection such as the Kato-Katz technique. This test measures the egg output in fecal specimen using methylene blue-stained cellophane soaked in glycerine or glass slides. Circumoval Precipitin Test (COPT) is another method which on the other hand detects antibodies and/or antigens in blood or urine samples. This is done if the eggs cannot be demonstrated in fecal or urine specimen. These tests were both done in our patient and were negative. Hence, no antihelminthic drug was initiated in this case.

SUMMARY

Chronic infection with schistosomiasis might be a potential cause of carcinoma by promoting general inflammation and subsequently affecting key cellular processes. This can result from combined parasite-host interaction events such as chronic inflammation, parasite-derived products, and physical damage and their effects on the chromosomes which lead to the modification of the cell growth and proliferation. However, in this case, the mechanism involved with inflammation may not be the only factor contributing in the malignant transformation of the right ovary. If it did, the left ovary found to harbor schistosoma eggs, should have developed the cancer as well. Based on the concept of the tubal intraepithelial carcinoma (TIC) detected at the fimbriated end of the fallopian tube, we can assume that the primary site is the right fallopian tube. As this was found to be infested with schistosoma and based on proximity could have seeded on the right ovary leading to neoplasia. ■

REFERENCE

1. Byun, JS, Gardner, K. Wounds That Will Not Heal: Pervasive Cellular Reprogramming in Cancer. *The American Journal of Pathology.* 2013; 182(4):1055-1064.

2. Dvorak, HF. Tumors: Wounds that do not heal—Redux. *Cancer Immunol Res.* 2015; 3(1):1-11.

3. Khaled, H. Schistosomiasis and Cancer in Egypt: Review. *Journal of Advanced Research.* 2013; 4:461-466.

4. A review of human carcinogens - Part B: Biological agents. (2009). Retrieved from http://monographs.iarc.fr/

5. Amorim, AG, Pagio, FAB, Ferreira RN, Filho, AC. Genital Schistosomiasis: A Report on Two Cases of Ovarian Carcinomas Containing Viable Eggs of Schistosoma mansoni. Hindawi Publishing Corporation Case Reports in Obstetrics and Gynecology Volume 2014, Article ID 508718.

6. Samaras,V, Rafailidis, P, Mourtzoukou, E, Peppas, G. Chronic bacterial and parasitic infections and cancer: a review. *J Infect Dev Ctries*. 2010; 4(5):267-281.

7. Hoang, VT, Brindley, PJ, Meyer, CG, Velavan, TP. Parasite Infection, Carcinogenesis and Human Malignancy. *EBioMedicine.* 2016; 15: 12-23.

8. Owusu-Bempah A, Odoi AT, Dassah ET. Genital Schistosomiasis Leading to Ectopic Pregnancy and Subfertility: A Case for Parasitic Evaluation of Gynaecologic Patients in Schistosomiasis Endemic Areas. Hindawi Publishing Corporation Case Reports in Obstetrics and Gynecology Volume 2013, Article ID 634264.

9. Vang, R, Le-Ming, S, Kurman, RJ. Ovarian Low-Grade and High-Grade Serous Carcinoma: Pathogenesis, Clinicopathologic and Molecular Biologic Features, and Diagnostic Problems. *Adv Anat Pathol*. 2009 September; 16(5):267-282.

10. Lobo, RA, Gershenson, DM, Lentz, GM, Valea, FA. Comprehensive Gynecology, 7th ed. USA: Elsevier, 2017.