UNUSUAL HISTOPATHOLOGIC FINDING OF PAPILLOMATOUS HYPERPLASIA IN MATURE CYSTIC TERATOMA

Luzanta Caridad P. Pacis, MD; Nephtali M. Gorgonio, MD, FPOGS
'Amang' Rodriguez Memorial Medical Center
Philippines

INTRODUCTION

Teratomas are germ cell tumors of the ovary that are composed of well differentiated derivatives from the three germ cell layers the ectoderm, the mesoderm, and the endoderm. It can be represented by one or more of these layers and the tissues may be mature (benign) or immature (malignant) [1].

The most common germ cell tumor is a mature cystic teratoma (MCT). They are highly variable in form and histology and maybe solid, cystic, or a combination of both. Although they are benign, it can undergo malignant degeneration[1]. Malignant degeneration is extremely difficult to predict or to detect early[2].

The unique features of mature cystic teratoma have elicited considerable interest. Still, a number of clinical aspects of MCT remain enigmatic. A case of mature cystic teratoma with unusual histologic finding will be presented.

THE CASE

A 28 year old G1P1 (1001) was admitted with complaints of on and off abdominal pain for 1 month. She had history of hyperthyroidism during her pregnancy with no maintenance medication after giving birth. No other significant familial diseases.

The history of present illness started eleven years prior to admission when the patient had palpable, movable, nontender, approximately 6 cm in diameter hypogastric mass. At the same time she also noted palpitations, easy fatigability, and undocumented fever. She consulted a general practitioner and was given propranolol 5 mg tablet once a day which afforded relief of palpitations.

Seven years prior to admission, still with hypogastric mass, the patient had progressive weight loss. That same year she delivered to a live, full term, girl by normal spontaneous delivery in a lying-in, with blood pressure elevations occurring during labor. Upon workup, she was noted to have elevated Free Tri-iodothyronine (FT3) and free thyroxine (FT4) levels, thus was maintained on propylthiouracil (PTU) 5 mg daily for a year, which afforded relief of symptoms.

Six months prior to admission, the patient noticed enlargement of the hypogastric mass. On consultation, she was advised to undergo surgery but was lost to follow up.

One month prior to admission, still with palpable hypogastric mass, the patient now had on and off hypogastric pain. She sought consult with a general practitioner wherein initial pelvic ultrasound showed a complex mass. She was then referred to a tertiary institution where transvaginal ultrasound (TVS) and pelvic ultrasound showed a normal sized anteverted uterus with intact endometrium, and a pelvoabdominal mass, probably ovarian in origin. The pelvoabdominal mass was located at the superior portion of the corpus measuring 9.3 x 10 x 8.05 cm, thick walled (0.40 cm), with low level echoes, with a solid component measuring 5.50 x 4.63 x 6.06 cm. Another locule contained echogenic lines and dots, measuring 5. 17 x 5.03 x 5.14 cm. There was no flow on color mapping and International Ovarian Tumor Analysis (IOTA) LR2 was 29% risk for malignancy. There was no free fluid in the cul de sac. The laterality of the mass, which had malignant sonologic features, could not be determined, and the contralateral ovary was not visualized.

Further workup revealed an elevated CA-125, elevated HE-4, normal AFP and normal beta-HCG levels. FT4 and TSH were also normal. She was then advised operation hence admitted.

On examination, the patient was conscious, coherent, and ambulatory with the normal vital signs and normal body mass index of 24.7 mg/kg2. She had supple neck, no neck vein engorgement, no cervical lymphadenopathy. Abdomen is globular and distended, with a firm, fixed, cystic to nodular, non-tender, palpable mass at periumbilical area approximately 12 x 12 cm. Corpus and adnexa cannot be properly assessed on internal examination due to presence of pelvoabdominal mass. Rectovaginal examination revealed 6 x 5 cm cul-de-sac mass, more on the right.

The admitting diagnosis was G1P1 (1001) Ovarian new growth, probably malignant The patient underwent laparotomy with right salpingo-oophorectomy with frozen section. Intraoperatively there was no ascites. The right ovary was cystically enlarged to 23 x 8 x 15 cm, with a smooth glistening, grayish white capsule, containing creamy, yellowish sebaceous fluid with hair strands on cut section and no areas of necrotic and hemorrhagic tissues (Fig. 1). Frozen section revealed "mature cystic teratoma (Fig. 2)." The left ovary was also cystically enlarged to 5 x 4 x 4 cm with thin, smooth glistening grayish capsule, hence, left oophorocystectomy was done. The left ovarian cyst also contained thick creamy, yellowish sebaceous fluid with hair strands. The uterus was small, and the left fallopian tube and appendix were normal. The liver capsule was smooth, the gallbladder was normal, the spleen was smooth, and the bilateral kidneys were both palpated and noted to be smooth.

Histopathology of the right ovary showed a " focus (1mm) of closely packed papillae lined by atypical columnar cells having ovoid to irregular nuclei with fine chromatin, occasional longitudinal grooves, and small nucleoli (Figure 3) The initial report was Mature cystic teratoma with a focus of Atypical Papillary Formation (1mm in widest dimension).

Immunohistochemistry with human bone marrow endothelial cell marker-1 (HBME-1) and Cytokeratin 19 (CK19) was requested to rule out papillary thyroid microcarcinoma. There was negative expression of both HBME-1 and CK19 (Figure 5, 6). Immunomorphologic features was most compatible with mature cystic teratoma but with a focus of papillomatous hyperplasia. The final histopathological report was Mature Cystic Teratoma with Papillomatous Hyperplasia, Right ovary; Mature Cystic Teratoma, Left ovary.

DISCUSSION

The clinical features of MCT remain enigmatic. Unusual clinical manifestations of mature cystic teratoma have been described in literature. Autoamputation of dermoid cyst and subsequent reimplantation in parasitic dermoid cyst[1] and a "floating ball" pathognomonic sign of ovarian cystic teratoma [2] are just some of these atypical clinical presentations. The unexpected event in the course of treating our patient will be presented.

1. A preoperative malignancy was entertained on the right ovarian mass based on an enlarging pelvoabdominal mass, a solid component seen on ultrasound examination with an IOTALR2 of 29% risk of malignancy, and elevated CA-125 and HE-4.

Mature cystic teratomas are asymptomatic in 50% to 60% of cases and are discovered only during a routine pelvic examination when a semisolid mass is palpated anterior to the broad ligament. The most frequent symptom is lower abdominal pain attributed to pelvic pressure, ovarian torsion or rupture which occurs in less than 3% of all cases. It occurs unilaterally in 88% of cases and bilaterally in 10% to 15% [3].

Our patient clinically presented with on and off abdominal pain with an enlarging pelvoabdominal mass. On exploration, bilateral mature cystic teratomas were seen.

The sonographic signs associated with ovarian MCT have been well-described. Malignant degeneration has a characteristic imaging features which is an underlying mature cystic teratoma: a sebaceous lipid component as well as a heterogeneous solid component protruding into the cavity or extending transmurally into adjacent organs [4]. Ultrasound has a more than 95% positive predictive value and a less than 5% false-positive rate[3].

The IOTALR2 risk model can be used by clinicians to preoperatively diagnose ovarian cancer in women and estimate the probability that an adnexal tumor is malignant. It uses six predictors: one clinical (the age) and five sonologic, which are the maximal diameter of the largest solid component, irregular internal cyst walls, presence of papillary projections with detectable flow, acoustic shadows, and ascites[5].

The LR2 findings in the index case includes the age of the patient (28 years old) and the solid component on ultrasound. With these, the estimated risk of malignancy is 29%.

Tumor markers were requested to possibly rule out malignancy. The CA-125 and HE-4 were elevated while AFP and BHCG were within normal limits. In a study done by Kawai M. et al., (1992) positive rate for malignancy of CA-125 was over 50% in all types of germ cell tumors except mature cystic teratoma, which showed a positive rate of 23.7% [6]. The human epididymis protein 4 (HE4), a serum biomarker, that is used together with CA-125 in the Risk of Malignancy Algorithm (ROMA), has been found to be more sensitive in premenopausal women in evaluating ovarian cancer. This is according to the study done by Wei, S., LI, H, i, and Zhang, B. (2016) which revealed specificity of 98.36% and a positive predictive value of 95%[7]. The clinical features observed in the index case thus led the surgeons to entertain malignancy.

2. The intraoperative frozen section revealed benign cystic teratoma. The initial histopathology report showed a focus of atypical papillary formation (1mm in widest diameter). To rule out papillary thyroid carcinoma, immunohistochemistry was requested.

Microscopically approximately 12 % of benign teratomas has thyroid tissue component. Malignant transformation of thyroid tissue in mature cystic teratoma can be classified histopathologically into three types; Papillary, follicular, and follicular variant of a papillary carcinoma[8]. Only a few papillary thyroid carcinoma have been reported in the literature.

Malignant transformation arising from MCT is diagnosed with difficulty in the preoperative period owing to the lack of any specific signs and symptoms. The preoperative ultrasound findings also in these patients with malignant transformation may not differ much from those seen in uncomplicated MCT. Tumor markers maybe non-specific [9]. Therefore, to rule out thyroid papillary carcinoma, immunohistochemistry was used.

A study was done by Casey, Lohse and Lloyd (2003) on Formalin- fixed paraffin-embedded tissues from 30 randomly selected patients with papillary thyroid hyperplasia and an equal number from patients with papillary thyroid carcinoma. The results indicate that HBME-1 may be useful in helping to distinguish papillary thyroid carcinoma from hyperplasia in diagnostically difficult cases [10].
Human bone marrow endothelial cell marker-1 (HBME-1) is a marker of mesothelial cells whereas Cytokeratin 19 (CK19) has been shown to be a marker for diffuse cytoplasmic positivity. Several literatures would demonstrate the use of HBME-1 and CK 19 as marker of malignant thyroid carcinoma [11,12,13]. Malignancy is suggested with positive HBME-1 while CK19 verifies papillary differentiation [13]. Fortunately, both markers had negative expression in our patient.

3. The final histopathology report is "Mature cystic teratoma with a focus of papillomatous hyperplasia" of the right ovary.

It is difficult to distinguish papillary thyroid hyperplasia from papillary thyroid carcinoma as both lesions may present as papillary fronds with fibrovascular cores, nuclear crowding, and nuclear anisocytosis[10]. Hyperplasia, in which there is an increase in the number of cells in an organ or tissue that appear normal under a microscope, may or may not become cancer.

Eighty percent of MCT occurs during the reproductive age. Malignant degeneration is rare and occur in only 1-2 % [14]. Though the reason for malignant degeneration is not clear, it is postulated by some authors that the long-term presence and non-removal of mature cystic teratoma may be followed by such malignant degeneration [15]. In the index case, although it took eleven years before the mass was removed, the early surgical procedures done could have prevented the progression of the lesion from hyperplasia to carcinoma.

4. The operation consists of right salpingooophorectomy and left oophorocystectomy for bilateral MCT in a 28 year old woman.

The consensus among investigators is that operative laparoscopy is the method of choice for removing ovarian mature cystic teratoma. Some investigators, however recommended laparotomy for mature cystic teratoma >10 cm[15]. In the index case, the cyst size was 23 x 8 x 15 cm.
Preoperatively, the patient should be informed of the possibility of removing the ovary. In younger women, ovarian cystectomy is the standard operation unless the patient chooses oophorectomy. Oophorectomy should be the technique of choice in postmenopausal women and in perimenopausal women with multiple cysts in the same ovary or with large ovarian mature cystic teratoma where there is not much ovarian tissue to conserve [15]. In the index case, left cystectomy was done to preserve the reproductive function of the patient while right oophorectomy was done since the size of the cyst is large and malignancy was entertained.

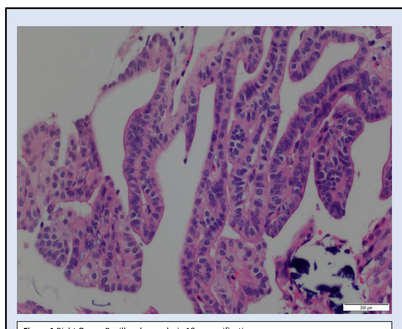

Figure 1 Right Ovary, Papillary hyperplasia 10x magnification.
Atypical columnar cells having ovoid to irregular nuclei with fine chromatin, occasional longitudinal grooves, and small nucleoli.

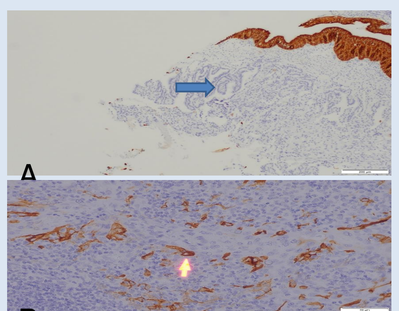

FIGURE 2 Right ovary, CK19 histochemical staining (A) Blue arrow. Negative (B) Yellow arrow. Positive control

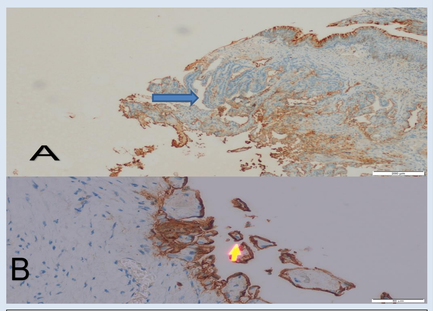

FIGURE 3 Right Ovary, HBME-1 histochemical staining. (A) Blue arrow. Negative on atypical papillary formation (B) Yellow arrow. Positive control for HBMEI

CONCLUSION

Mature cystic teratoma can present histologically with papillomatous hyperplasia. Whether hyperplasia in this case could lead to carcinoma remains unknown.

In cases where there is a need to distinguish MCT with papillary thyroid carcinoma from hyperplasia, immunohistochemistry can be done using HBME-1 and CK-19.

In patients with bilateral MCT, ovarian cystectomy and oophorectomy can be done depending on the age, size of the cyst and risk of malignancy.

REFERENCE

1. Lee, K. H., Song, M. J., Jung, I. C., Lee, Y. S., & Park, E. K. Autoamputation of an ovarian mature cystic teratoma: a case report and a review of the literature. World J Surg Oncol. 2016; 14: 217.
2 . Hsiang, C.-W. Liu, , W.-C, Huang, G.-S, Hsu, H.-H, Chang, , W.-C. A floating ball: a pathognomonic sign of ovarian cystic teratoma, QJM. 2014, Volume 107, Issue 4, Pages 319–320.
3. Dolan, MS, Hill, Cherie, Valea, FA. Benign Gynecologic Lesion: Vulva, Vagina, Cervix, Uterus, Oviduct, Ovary, Ultrasound Imaging of Pelvic Structures; In: Lobo R, Gerhenson D, Lentz G ; Comprehensive Gynecology, 7th ed. Philadelphia: Elsevier,Inc., 2017: 18
4. Outwater, Ek, Siegelman, ES, Hunt, JL. Ovarian teratomas: tumor types and imaging characteristics. Radiographics. 2001 Mar-Apr;21(2):475-90.
5. International Ovarian Tumour Analysis. LR2 risk model to diagnose ovarian cancer. 1999. https://www.iotagroup.org/iota-models-
6. Kawai, M, Kano T, Kikkawa F, et al., Seven tumor markers in benign and malignant germ cell tumors of the ovary. Gynecol Oncol. 1992 Jun;45(3):248-53.
7. Wei, S., LI, H, i, and Zhang, B. The diagnostic value of serum HE4 and CA-125 and ROMA index in ovarian cancer; Biomed Rep. 2016 Jul;5(1):41-44.
8. Dane, C. Ekmez, M, Karaca, A. Ak A, Banu D, Follicular variant of papillary thyroid carcinoma arising from a dermoid cyst: A rare malignancy in young women and review of the literature. Taiwan J Obstet Gynecol. 2012 Sep;51(3):421-5.
9. Jitsumori, M., Munakata, S., Yamamoto, T (2017). Malignant transformation of mature cystic teratoma diagnosed after a 10-Year interval. Case Rep Obstet Gynecol. 2017.
10. Casey, Mb, Lohse, CM, Lloyd, RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. Endocr Pathol. 2003 Spring;14(1): 55-60.
11. Cheung, C., Ezzat, S., Freeman, J. Rose, IB, Asa, SL. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001. 14, 338–342.
12. Palo, S, Bilig Ds. (2017). Differential diagnostic significance of HBME-1, CK19 and S100 in various thyroid lesions. Malays J Pathol. 2017 Apr;39(1):55-67.
13. Rathore R, Sharma S, Agarwa S. Malignant transformation in mature cystic teratoma of the ovary: a retrospective study of eight cases and review of literature. Prz Menopauzalny. 2018 Jun;17(2):63-68.
14. Coleman RL, Ramirez PT, Geherson DM. Neoplastic Diseases of the Ovary: Screening, Benign and Malignant Epithelial and Germ Cell Neoplasms, Sex-Cord Stromal Tumors; In: Lobo R, Gerhenson D, Lentz G: Comprehensive Gynecology, 7th ed. Philadelphia: Elsevier,Inc., 2017: 33
15. Sinha A., Ewies A. Ovarian Mature Cystic Teratoma: Challenges of Surgical Mnagement Obstet Gynecol Int. 2016;2016:2390178.