A Rare Case Of Gliomatosis Peritonei Associated With A Mature Ovarian Teratoma*

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ABSTRACT

Gliomatosis peritonei is the deposition of benign glial implants, more commonly associated with an immature ovarian teratoma. This paper reports a case of a 24 year old gravida 1 para 1 (1001) who underwent unilateral salpingo-oophorectomy and complete surgical staging for a preoperative diagnosis of ovarian new growth, probably malignant. Intraoperatively, aside from the ovarian mass on the right, there was also note of an omental mass. Histopathology revealed a mature ovarian teratoma for the ovary and gliomatosis peritonei for the omental mass. Gliomatosis peritonei is a rare entity. There are currently no guidelines on how patients with this condition can be followed up. Transvaginal sonography and annual measurement of alpha-fetoprotein may play a role in the follow-up of patients in low resource settings.

CASE HISTORY

The patient is JP a 24-year old gravida 1 para 1 (1001), single, Roman Catholic, from Ilocos Norte who came in with a chief complaint of right lower quadrant pain.

The patient has no history of hypertension, diabetes, bronchial asthma, tuberculosis, cancer, or thyroid disease. She has no known allergies and did not undergo any surgery.

The family medical history is non-contributory, her father had hypertension and her mother had bronchial asthma. There was no history of diabetes, tuberculosis, goiter and cancer.

JP is a college undergraduate. She worked as a housekeeper in Cavite. She has a 0.3 pack year smoking history. Allegedly, she stopped smoking 2 years ago. She is an occasional alcohol beverage drinker and denies the use of illicit drugs.

She had her first coitus at 19 years old to 3 sexual partners. She had a history of oral contraceptive pill use for 5 months from 2009-2010.

The patient had her menarche at 13 years old, with subsequent menses occurring irregularly, every 2-3 months, lasting for 4-5 days, soaking 3-4 pads per day. Her last normal menstrual period was April 9, 2012.

She is a gravida 1 para 1 (1001), with the first pregnancy carried to term delivered by spontaneous vaginal delivery in a hospital in Ilocos. There were no fetomaternal complications noted and the child is alive and well today.

Her history of present illness started one month prior to admission when the patient noted an indiscrete right lower quadrant mass, cystic, movable and non-tender. The patient claimed that it was hard to qualify the size of the mass because of its cystic and movable character. There was no consult done at that time due to financial constraints.

Five days prior to admission, there was note of right lower quadrant pain, 5/10 on the visual analog score, intermittent, crampy in character, non-radiating. This was also associated with undocumented low-grade fever. However, the patient still did not seek any consult at this time and just opted to observe her symptoms.

One day prior to admission, there was persistence of the right lower quadrant pain, with associated loss of appetite. The patient then consulted a private doctor and a transvaginal/transabdominal scan was done which revealed the following result:

A thickened endometrium of 1.1 cm, and an ovarian new growth, right which measured 19.2 x 19.68 x 19.73 cm, thick walled, multiseptated, multiloculated with papillarities in its inner wall, with Sassone score of 12. She was then referred to our institution for further management.

On review of systems, pertinent was the absence of any constitutional signs and symptoms as well as symptoms related to bowel and urinary complaints. There was just around 10% weight loss over 1 year, which is insignificant.

On physical examination, there was a medium-built female, ambulatory and coherent, neither in distress nor in any pain. Vital signs were stable. The systemic physical examination was unremarkable. Centering on the abdomen, the abdomen was soft and flabby with

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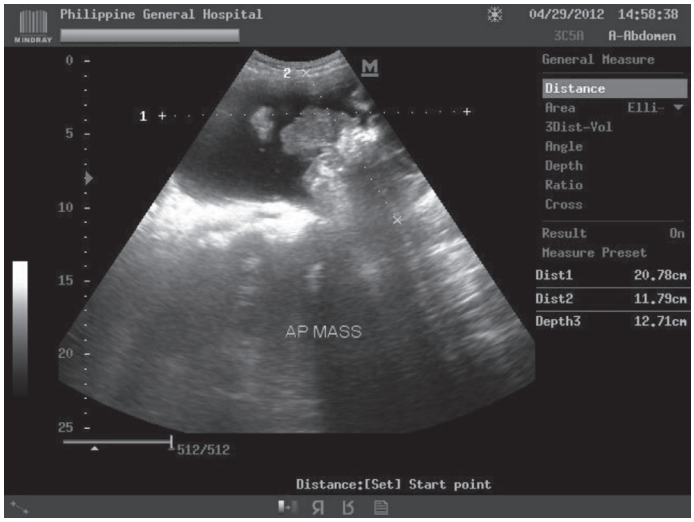

Figure 1. Transabdominal scan of the patient showing a multiloculated, multispetatedabdomino-pelvic mass with solid areas.

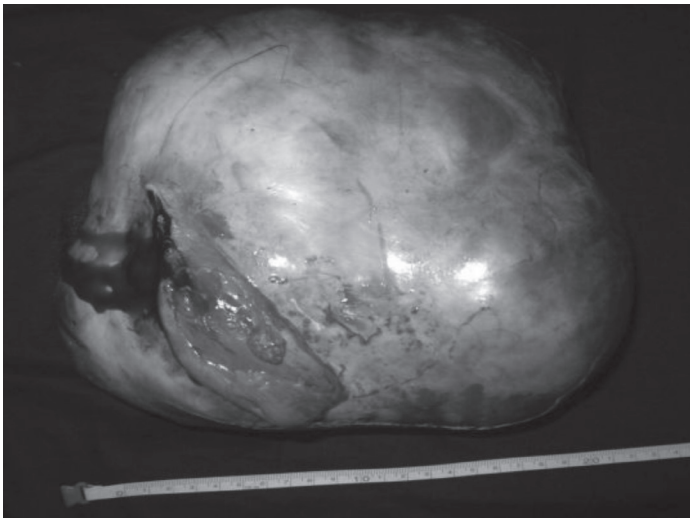

Figure 2. Gross picture of the right ovary after a salpingo-oophorectomy.

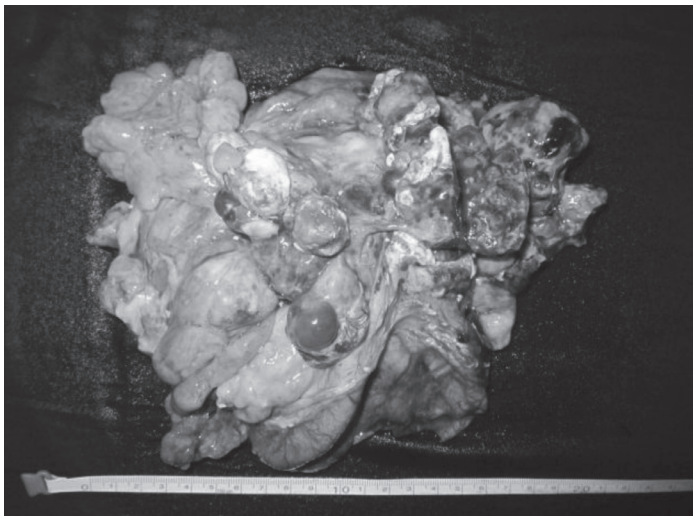

Figure 3. Gross specimen of the cut section of the right ovary.

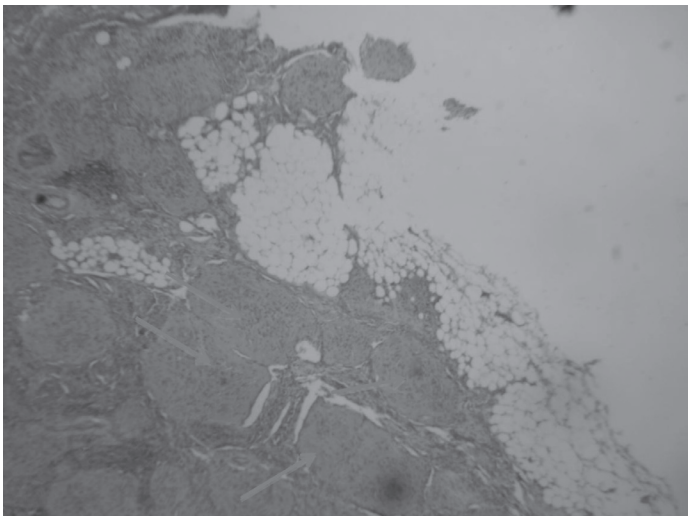

Figure 4. Histologic picture of the omentum showing infiltration of mature glial elements (arrows).

normoactive bowel sounds, abdominal girth was 86 cm and there was a palpable abdominal mass measuring 20 x 18 cm from the hypogastric area up to 2 cm above the umbilicus, cystic, slightly movable, tender on very deep palpation. On speculum exam, she had smooth, parous vagina, no masses seen, no discharge; the cervix was likewise smooth with no masses nor discharge. On rectovaginal exam, she had good sphincter tone, intact rectal vault, the inferior pole of the mass was palpable at the cul de sac, bilateralparametria were smooth and pliable.

The patient was sent to the ultrasound section where a transvaginal and transabdominal ultrasound was performed. The result revealed:

The uterus was anteverted with smooth contour and homogenous echopattern measuring 7.6 x 3.9 x 3.3 cm. The cervix measured 2.9 x 2.3 x 2.8 cm. The endometrium is hyperechoic measuring 0.6 cm with intact subendometrial halo. The left ovary measured 2.6 x 3.4 x 1.6 cm. Occupying the abdomino-pelvic cavity is a multiseptated, multiloculated cystic mass measuring 20.8 x 19.1 x 11.8 cm. The capsule measured 0.4 cm while the septum measured 0.4 cm. It has multiple solid areas measuring 3.9 x 1.3 cm. It has several papillary excrescences. There is minimal free fluid in the cul-de-sac.

The sonologic impression was:

Abdomino-pelvic mass consider ovarian new growth probably malignant (S=12, L=8);

Normal uterus with proliferative phase endometrium;

Normal left ovary

The patient was then admitted with the following impression: ovarian new growth, probably malignant.

The operative plan was discussed with patient and

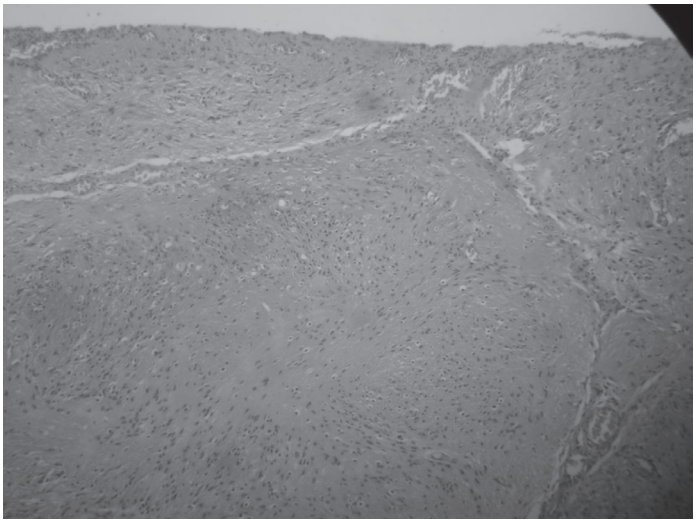

Figure 5. Histologic picture of the cul-de-sac implant showing the same mature glial elements that were seen in the ovarian mass itself and on the omentum.

she decided to have a conservative procedure done because she was still desirous of pregnancy. Hence, our plan for the patient was an exploratory laparotomy, peritoneal fluid cytology, unilateral salpingo-oophorectomy, frozen section with or without infracolicomentectomy, random peritoneal biopsy, bilateral lymph node dissection, paraaortic lymph node sampling and appendectomy.

Her baseline laboratory examinations revealed anemia (hemoglobin: 99 mg/dL) and a slightly elevated platelet count which is probably just reactive thrombocytosis. Ca-125 was elevated at 165 U/mL.

A holoabdominal ultrasound was done which showed a huge abdomino-pelvic mass, probably ovarian new growth; minimal caliectasia, right; unremarkable ultrasound of the rest of the abdominal organs.

Intraoperatively, there was around 150 cc of ascitic fluid. The subdiaphragmatic surface, liver, gallbladder, spleen, kidneys, small and large intestines were smooth and grossly normal. The appendix was grossly normal. There was a suspicious area noted on the omentum which measured 2 x 2 cm. There were no lymph nodes palpable.

The right ovary was converted to 20 x 17 x 13 cm multiloculated, multiseptated cystic mass with smooth intact capsule. The right fallopian tube was stretched out measuring 9 x 2.5 x 5 cm and was grossly normal.

On cut section, there was hair, sebum, cartilage, and areas of necrosis and hemorrhages. There were multiple solid areas, the largest of which measured 6 x 4.5 x 3 cm. The capsule measured 0.1 cm and the septum measured 0.1 cm. The uterus, which was small, and the left adnexa were both grossly normal.

The rest of the abdominal and pelvic organs were grossly normal.

The omental mass and the ovary was sent for frozen section and the result revealed mature cystic teratoma for the ovary and gliomatosis peritonei for the omental implant. However, since grossly, the mass looked malignant and only four sections were taken for frozen section, the surgeons proceeded to do complete surgical staging. The patient was transfused packed red cells during the operation and she tolerated the procedure well.

The postoperative diagnosis is: mature cystic teratoma, right ovary by frozen section; cannot entirely rule out ovarian malignancy, right ovary, stage IA.

The patient had an unremarkable postoperative course, she was sent home on the 4th postoperative day. She was seen only once at the OPD a week after her discharge, and then she was lost to follow up.

The pathologist received fifteen specimens labeled right ovary, omentum, cul de sac, right obturator, left obturator, right external iliac, left external iliac, left paraaortic, right pelvic side wall, left pelvic side wall, right paracolic, left paracolic, bladder, and peritoneal fluid.

Scanning and high power views of the right ovary showed the presence of mature tissues derived from the three germ layers. These mature tissues are arranged in an orderly pattern throughout all slides from all the sections which differentiates it from an immature teratoma where the tissues are arranged haphazardly. Final histopathologic diagnosis revealed mature cystic teratoma in the right ovary and gliomatosisperitonei in the omental mass and cul de sac implant. All other specimen submitted were negative for tumor.

DISCUSSION

The term gliomatosisperitonei (GP) was first introduced in 1906 by Neuhauser. It was described as a condition wherein miliary implants of glial tissue are found on the peritoneum.[1] This is a rare association occurring almost exclusively with immature ovarian teratomas. Its association with mature ovarian teratomas is even more rare.[2]

Due to its rarity, the true incidence of gliomatosis peritonei is not known. According to a case report published in the Indian Journal of Cancer in 2005, only about 88 cases of gliomatosisperitonei are found in the literature.[3]

Macroscopically, the peritoneal implants are small in size and can be localized on the parietal or visceral peritoneum. Its appearance is indistinguishable from disseminated tuberculosis and carcinomatosis, making diagnosis difficult just by gross inspection alone.[4]

Microscopically, the peritoneal implants may contain mature or immature glial tissue and usually they are more differentiated than the primary tumor.[5] An implant containing immature glial tissues is graded similarly as an im-

Table 1. Immature Teratoma Grading (O'connor and Norris)

Grade 1	Amount of immature neuroectoderm occupies < 1 low-power (4x objective) magnification field
Grade 2	Amount of immature neuroectoderm occupies >1 but > 3 low-power (4x objective) magnification field
Grade 3	Amount of immature neuroectoderm occupies >3 low-power (4x objective) magnification field

mature ovarian teratoma. Currently, we follow the grading proposed by O'Connor and Norris (Table 1). [6]

There are two schools of thought with regards to the pathogenesis of gliomatosisperitonei. Some authors believe that the glial implants arose from the teratoma itself, either by tumor rupture or through lymphogenous metastasis. On the other hand, some authors believe that the glial implants did not come from the teratoma itself; instead the implants arose from pluripotent stem cells in the peritoneum. [7]

To support the theory that gliomatosis peritonei arose from an associated ovarian teratoma, some authors observed that there were capsular defects seen during surgery for a teratoma with an associated GP. Moreover, GP detected during second look laparotomy had capsular rupture at the time of primary surgery. [7]

Some authors also argue that GP arose from lymphogenous metastasis because mature glial tissues were sometimes found in lymph nodes associated with immature teratomas. [7]

A more interesting theory on the pathogenesis of GP was proven by Ferguson et. al., that the glial implants in GP arose from normal tissue, not from associated teratoma. They were able to prove their theory through DNA extraction and genetic analysis which showed difference in the zygosity at the same loci when a glial implant was compared to a sample taken from the teratoma. They speculated that this phenomenon could have happened when pluripotent Mullerian stem cells in the peritoneum underwent glial metaplasia in response to favorable environmental conditions, the so-called "field effect". They further cited a case report whereby a case of GP was described in a child without a teratoma who underwent VP shunting during early infancy. [8]

A diagnosis of gliomatosis peritonei is made histologically. Tumorous implants may be seen on CT scan and MRI but the exact nature of these implants can only be confirmed microscopically. Such implants mimic the appearance of peritoneal carcinomatosis and peritoneal tuberculosis. (4) Immunohistochemical markers of the implants are positive for neural markers such as GFAP, S100 and NSE. MIB1 is a gene involved in regulating apoptosis and the absence of MIB1 indicates the neuroprolifertaive nature of the tissue. Normal AFP may rule out the possibility of metastasis from an immature ovarian teratoma. [9]

Gliomatosis peritonei by itself has low malignant potential. The prognosis of ovarian teratoma is closely associated with tumor grade as proposed by Thurlback and Scully. In the series by Norris et al. of 58 patients, 5-year survival rate for patients with Grades 1–3 were 82, 63, and 30%, respectively. [6]

Interestingly, patients who have immature ovarian teratomas in association with mature glial implants appear to have a much-improved prognosis. This statement holds true only if stringent criteria for diagnosis of GP is adhered to, as proposed by Thurlback and Scully: (a) peritoneal surface, omentum, and diaphragmatic surfaces must be extensively sampled histologically and (b) each of the sampled implants should be composed exclusively, or almost exclusively, of Grade 0 glial tissue. If these two conditions are met, the prognosis of the disease is excellent. [10]

Progression of the peritoneal implants may be as follows: [1]

1. Transformation to fibroblasts and eventual disappearance
2. Persistence without morphologic changes
3. Transformation to malignant tissue

Surgery is the primary treatment for both mature and immature teratomas as well as for peritoneal gliomatosis associated with these tumors.

For gliomatosis peritonei associated with a mature cystic teratoma, simple surgical excision of the primary tumor is all that is necessary. [11]

For GP associated with an immature teratoma, complete surgical staging and extensive sampling of all implants is necessary because further management and prognosis will be affected by whether immature glial elements are seen on the implants or not. If there are no immature glial elements seen, treat based on the stage and grade of the primary ovarian teratoma. On the other hand, if immature glial elements are present, treat as in metastatic carcinoma, which includes complete surgical staging and chemotherapy. Chemotherapy options include the bleomycin, etoposide and cisplatinregimen (BEP), or the vincristine, adriamycin, cyclophosphamide regimen (VAC), which is usually reserved for recurrent carcinoma. [3,12]

Many more cases of mature gliomatosis peritonei need to be followed for several years before the true natural history of the condition and an accurate rate of malignant evolution can be ascertained. However, despite the low malignant potential, peritoneal gliomatosis cases of malig-

nant progression have been identified. Currently, there are three cases of such in the literature. The first was reported by Shefren, et.al: A case of a 16 year old girl with Grade 3 Immature ovarian teratoma who developed malignant glial implants and died 5.5 years after initial surgery. [13] Another similar case was reported by Dadmanesh, et. Al: A 13 year old girl who developed a tumor resembling a glioblastoma 7 years after initial surgery for grade 1 teratoma and low grade gliomatosis peritonei. [14] Finally, a report by Trabelsiet. Al on a 37 year old woman who presented 7 years after removal of an immature ovarian teratoma with a malignant tumor resembling glioblastoma.[15] All these patients received complete surgical staging, extensive sampling of the implants and underwent chemotherapy for the immature teratoma.

In the review of literature done, it was noted that the cases wherein malignant transformation of gliomatosis peritonei occurred were all associated with an immature teratoma. There is no literature related to malignant transformation of GP associated with a mature cystic teratoma.

Due to the rarity of this condition, there is no widely accepted guidance as to how long and by which means these patients should be followed up. As with most gynecologic conditions, imaging plays a central role in the follow up of patients with gliomatosis peritonei. CT scan would readily detect peritoneal deposits, however, a disadvantage of this procedure is the accumulated radiation dose exposure throughout the long-term follow up period. [16]

Transvaginal ultrasound is an alternative radiation-free imaging technique for assessment of the pelvic structures. However, the peritoneal deposits are usually very small (<3 mm) and an inexperienced operator may miss out on these small lesions. Moreover, the small lesions may become more inconspicuous when obscured by bowel gas, or when they lie within the abdomen and are out of the field of view of the transvaginal probe. [16]

Monitoring alpha-fetoprotein during follow up is usually done, but may provide false reassurance. Levels frequently stay within normal limits in cases of gliomatosis peritonei even when previously elevated in association with the original teratoma, and likewise may also remain normal in tumor recurrences containing immature elements. [16]

A good imaging modality for follow up is MRI. It is free from radiation dose and is usually well tolerated. It can also demonstrate macronodules of glial tissue readily. The best contrast resolution is provided by T2 weighted images. Deposits of glial tissue are of moderately high signal with this resolution.[16] MRI may miss very small implants, making PET-CT scan another option for monitoring. Other disadvantages of MRI include its limited availability and its higher cost.

In the review of literature than by England et.al, cases of malignant evolution have been described up to 7 years from original surgical clearance of a teratoma. Hence, they recommend that imaging follow up should occur annually for at least 5–7 years. Furthermore, they concluded that MRI might be the best option for monitoring because it is safe, reproducible and accurate for the imaging of patients with a history of immature ovarian teratoma and mature gliomatosis peritonei.

CONCLUSION

Going back to our index case, we were presented with a 24 year old G1P1 (1001) who underwent right salpingo-oophorectomy and complete surgical staging for a mature cystic teratoma and gliomatosis peritonei on the omentum and cul-de-sac, the question now is, what is the recommended follow up for her? Although gliomatosis-peritonei associated with mature cystic teratoma imparts an overall good prognosis on the patient, data is still lacking with regards to the possible progression of this disease entity; hence it is more prudent to monitor this patient for the possibility of a malignant degeneration. And based on literature, annual determination of AFP may be helpful combined with imaging such as MRI, or for financially constrained patients, transvaginal and holoabdominal ultrasound may still play a role.

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