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Case Report

Immature Teratoma with Metastatic Gliosis

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Abstract

Immature teratomas represent three percent of all teratomas, one percent of all ovarian cancers and 20% of malignant ovarian germ cell tumors. They are made of immature components of germ cell origin. The incidence of immature teratomas is highest in young adults aged 18 to 39. The prognosis heavily depends on the FIGO stage and is influenced by factors such as cell type, tumor grade, capsular rupture, and metastatic risk factors. Initial treatment is complete surgical resection. When indicated, platinum-based adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP) is the treatment of choice. Next generation sequencing of the tumor can influence treatment in the recurrent setting. Temozolomide is an alkylating agent used to target high grades gliomas. Bevacizumab is a targeted therapy that interferes with the process of angiogenesis by inhibiting vascular endothelial growth factor (VEGF).

We report a 36-year-old female who presented with a 17.6cm x 10.5cm x 24.2cm intraabdominal mass and ascites. Upon tumor resection, she was found to have a stage IIIa, grade 2 immature teratoma of the left ovary, with glial tissue being the metastatic cell type. Disease progression continued despite treatment with BEP. She was then treated with 6 months of bevacizumab and temozolomide experimentally, given its rarity and targeted therapy for glial tissue. Despite therapy with monoclonal antibody, the tumor progressed again and was treated with docetaxel and gemcitabine. A repeat CT of the chest, abdomen and pelvis performed, demonstrated scattered peritoneal implants that were increasing in size. Chromosome analysis was performed and revealed somatic mutations of MLH1, MSH2, MSH6 and PD-L1. The patient has requested a break from chemotherapy but will be treated with direct immunotherapy when she restarts.

This case's importance lies in its rarity because there are fewer than 10 cases of immature teratomas with metastatic glial tissue noted in the world's literature. Furthermore, this is the first reported case of this cell type being treated with immunotherapy in the world literature.

Introduction

Teratoma originates from the Greek word "teras" which signifies monster. Immature teratomas are malignant tumors of the ovary and represent 1% to 3% of all germ cell tumors and 20% of malignant ovarian germ cell tumors. In comparison, mature teratomas are benign. The grading system depends on the proportion of mature and immature neuroepithelial tissues, mitotic activity, and degree of differentiation. Per Lavazzo et al., grade 0 tumors contain solely mature tissue whereas grades 1, 2 and 3 tumors are mitotically active and possess limited, moderate, and large amount of neuroepithelial tissue [1]. Following laparoscopic surgery, the pathological diagnosis of the excised tumor determines whether an ovarian tumor is mature or immature. Immature teratomas are composed of embryonic components, are 14 to 25 cm larger than mature cystic teratoma and possess solid components in the cystic elements.

Case Presentation

We report a 36-year-old female with medical history of Hashimoto's thyroiditis on Levothyroxine who presented with complaints of progressively worsening abdominal distention and clothes fitting tighter over the past two months. She also endorsed left lower quadrant abdominal and suprapubic pain. She reported her symptoms were associated with early satiety, constipation, and nausea without emesis. She also reported feeling tired. She stated that the probiotic prescribed by her primary care provider did not alleviate her pain. These symptoms prompted her to visit the emergency department. On physical examination, she had a distended abdomen with tenderness to palpation and a low-grade fever. Complete blood count was significant for anemia with a hemoglobin of 8.4 g/dL and hematocrit of 26.9%. Complete metabolic panel noted hypocalcemia of 7.5 mg/dL. Computed Tomography (CT) of the abdomen and pelvis was significant for a bulky mass arising in the anterior pelvis and extending cephalad above the level of the umbilicus. The mass measured 17.6 cm transversely, 10.5 cm in the antero-posterior dimension and 24.2 cm in the craniocaudal dimension. The lesion consisted of fluid and solid components with some calcifications and fat present. Furthermore, there was small to moderate free fluid in the posterior pelvis and lower abdomen bilaterally.

The patient agreed to exploratory laparotomy and underwent left salpingo-oophorectomy, appendectomy, omentectomy, left pelvic and aortic lymph nodes sampling and tumor debulking. Operative findings showed a large left-sided ovarian mass that was fleshy in nature. Frozen section noted possible teratoma with stromal components concerning for malignancy, therefore the patient was staged. Pathology results of specimens collected during the surgery showed grade 2 immature teratoma of the ovary, acute appendicitis, immature glial cells in the right pelvic peritoneum, peritoneal tumor and omentum, aortic and pelvic lymph nodes negative for metastatic tumor. Clinical stage shows FIGO Stage IIIA1(i) calculated as Stage IIIA2 (cT3a, cN0, cM0).

She was started on Apixaban for Deep Venous Thrombosis (DVT) prophylaxis and Oxycodone as needed for pain.

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Additionally, she was started on Bleomycin, Etoposide and Cisplatin chemotherapy regimen every 21 days for 4 cycles. Repeat CT scan showed progression of disease with multiple soft tissue masses seen within the mesentery representing recurrence of the patient's disease at three months post exploratory laparotomy and start of chemotherapy. It also noted ill-defined density within the pelvis posterior to the uterus, also indicating disease recurrence. In the aim of obtaining a target, molecular testing was ordered. Chromosome analysis was subsequently done to direct treatment. Approval was obtained and patient was started on Temozolomide.

Results showed that immunohistochemistry of the mass was positive for MLH1, MSH2, MSH6 and PD-L1 and variation of undetermined significance of BRCA1 and AXIN2. The patient was started on immunotherapy with Bevacizumab through port-a-cath. At this point, she reported symptoms of shortness of breath accompanied by chest pain both at rest and with exertion as well as bilateral pedal swelling. She also developed chemotherapy induced hypertension. Following cardiology recommendations, the patient was started on Carvedilol, Amlodipine, and as needed Lasix for bilateral pedal edema. An echocardiogram was also ordered as Bevacizumab is known to cause hypertension and left ventricular dysfunction toxicity. The transthoracic echocardiogram showed mitral and tricuspid valve regurgitation. It also noted a normal left ventricular systolic function with an ejection fraction of 55%-60%. The patient's current chemotherapy regimen which included IV Bevacizumab and Temozolomide were stopped, and she was started on Gemcitabine and Docetaxel. The patient was also informed of the palliative nature of the treatment. Three months later, patient decided she would like to take a break from the chemotherapy and treatment was stopped.

Discussion

Immature teratomas are malignant tumors that occur in the first few decades of life. Tumor grading of immature teratomas is based on the amount of immature neural tissue present. The prognosis of immature teratomas depends mainly on the staging system provided by the International Federation of Gynecology and Obstetrics (FIGO) [2]. The other factors that influence prognosis are the tumor's grade, its growth pattern, the occurrence of capsular rupture and invasion of blood vessels. The yolk sac contained within the tumor has also been recognized as the source of alpha fetoprotein and a predictor of stage, grade, and rate of recurrence [3]. Javadi et al. report the revised 2014 FIGO staging system for ovarian cancers [4]. This information has been collected and summarized in table 1. Our patient was found to have a FIGO Stage IIIA1(i) calculated as Stage IIIA2 (cT3a, cN0, cM0). This signifies she had microscopic extra pelvic peritoneal involvement. Javadi et al. further report that patients who present with an exclusively retroperitoneal lymph node involvement have a better prognosis than patients with abdominal peritoneal involvement as it is the case in this patient [4].

The pathology results of the left ovary were notable for grade 2 immature teratoma of ovary. The right pelvic peritoneum, omentum, abdominal fluid, and peritoneal tumor were remarkable for the presence of immature glial tissue. The left fallopian tube, appendix, left pelvic and aortic lymph nodes were negative for tumor. Immunohistochemical stains were positive for Glial Fibrillary Acidic Protein, which is consistent with immature teratoma. In addition, mesothelial cells were positive for pankeratin, calretinin and vimentin. As seen in figure 1, pathological imaging for the tumor was notable for cartilage, glandular and immature neural tissue.

According to Lavazzo et al., fertility sparing management is the suggested as the standard of care of immature teratomas in young female patients [1]. Young female patients with immature teratomas should be educated about onco-fertility and guided throughout the decision-making process. Per Lavazzo et al., the proposed algorithm for the management of immature teratoma is to first check the desire for fertility of the patient. Once this step is completed, the grade of the tumor should be clarified, and radiologic imaging and tumor markers should be taken into consideration. If fertility is not desired, complete surgical resection may be performed. If fertility is desired, the next step in management depends on the grade of the tumor. For grade 1 tumors that have positive imaging and tumor markers, fertility sparing surgery and comprehensive staging is completed. Grade 1 tumors with negative imaging and positive or negative tumor markers benefit from a conservative approach with observation, physical examination, and measurement of tumor markers every 2 to 4 months for the first two years along with imaging as clinically indicated. For grade 2 to 3 tumors with positive imaging and tumor markers, fertility sparing surgery with comprehensive staging or chemotherapy is the plan of care. For grade 2 to 3 tumors with negative imaging or positive or negative tumor markers, the patient should receive chemotherapy. If there is response to treatment, the patient may be observed; if there is no response to treatment, tumor resection or observation should be considered. If there is further progression, platinum-based chemotherapy can be performed. In this case, our patient had a grade 2 moderately differentiated tumor with positive imaging and tumor markers. She agreed for and underwent exploratory laparotomy with left salpingo-oophorectomy, appendectomy, omentectomy, left pelvic and aortic lymph nodes sampling and tumor debulking.

The patient was first started on Bleomycin, Etoposide and Cisplatin chemotherapeutic regimen. Etoposide inhibits DNA synthesis by interfering with the activity of topoisomerase II. It is predominantly active against cells in the late S- and G-2 phases of the cell cycle. Cisplatin is an alkylating agent that acts in a cell-cycle nonspecific manner. Bleomycin is an antineoplastic antibiotic that binds to DNA and causes scissions of DNA strands [5]. Tumor progression continued and the patient was started on Temozolomide. Per Zhang et al., Temozolomide is a DNA alkylating agent that induces cell cycle arrest at the G2/M phase, hence causing apoptosis [6]. The patient's tumor continued to progress, and she was subsequently started on Bevacizumab.

Unlike the previous treatment, Bevacizumab is an immunotherapy aimed to prevent pathologic angiogenesis. According to Wilson et al., pathologic angiogenesis enhances

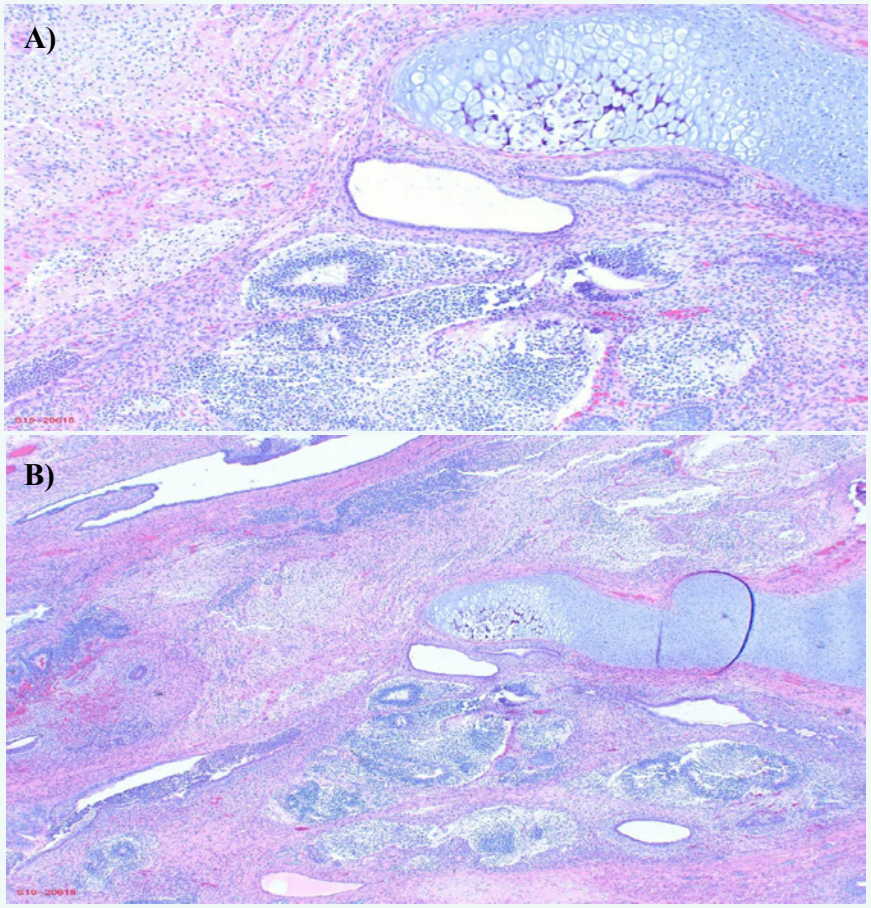

Figure 1 Histologic imaging showing glandular, cartilage and immature neural tissue.

the growth of solid tumors and causes chronic inflammation, cartilage damage, atherosclerotic plaque formation, and scarring of the eye [7]. This journal also postulates that abnormal angiogenesis starts with an angiogenic switch, a poorly understood mechanism, that upregulates the production of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, interleukin-8, platelet-derived endothelial growth factor; and downregulates anti-angiogenic proteins such as thrombospondin, endostatin and angiostatin. Bevacizumab is a monoclonal antibody that binds circulation VEGF, hence preventing binding of VEGF to its cell surface receptor and curtailing pathologic angiogenesis. Cancer angiogenesis research has shown that early angiogenesis therapy is more successful than late treatment. This is explained mainly by the fact that tumor blood vessels produce more varied growth factors later in disease than they do earlier, meaning patients need drugs against multiple growth factors. It is however known that antiangiogenic drugs typically only target just 1 or 2 growth factors. Combining angiogenic therapy with other interventions such as chemotherapy, radiation therapy or vaccine therapy may be most effective overall.

Tumor progression continued despite Bevacizumab and the patient was started on Gemcitabine and Docetaxel. As reported by Calvacante et al., the most common mechanism of action of Gemcitabine is by inhibiting DNA synthesis [8]. Per Farha et al., Docetaxel works by both inhibiting microtubular depolymerization and attenuating the effects of bcl-2 and bcl-xL gene expression [9]. Tumor progression continued despite this treatment, at which point, the patient requested to take a break. Per Marwah et al., surgery and chemotherapy can give longer survival even in recurrent disease [10]. Patients who decide to opt out of treatment may therefore be monitored and provide palliative care. Nishida et al. reports that the five-year survival rate for stage I immature teratoma is 90% to 95%, whereas this survival rate drops to 50% for grade 1 to 2 cancers and to 25% or less for grade 3 tumors [11].

Conclusion

Immature teratomas mainly affect young female patients in the first few decades of life. Its prognosis is good when diagnosed early and guarded when patient present at later stages of the disease. Fertility sparing approach is the standard of care and various treatment options should be thoroughly discussed with patients. These options commonly involve surgery and chemotherapy. Immunotherapy with drugs such as Bevacizumab are promising and most effective when initiated early. The five-year survival rate is excellent for stage I immature teratomas,

but this survival rate decreases drastically for grade 1, 2 and 3 tumors.

References

1. Lavazzo C, Vorgias G, Iavazzo PE, Gkegkes ID. Fertility sparing approach as the standard of care in young patients with immature teratomas. J Turk Ger Gynecol Assoc. 2017 Mar 15;18(1):43-47. doi: 10.4274/jtgga.2016.0090. PMID: 28506950; PMCID: PMC5450210.

2. Gheorghisan-Galateanu A, Terzea DC, Carsote M, Poiana C. Immature ovarian teratoma with unusual gliomatosis. J Ovarian Res. 2013;6(1):28. Published 2013 Apr 16. doi:10.1186/1757-2215-6-28

3. Outwater EK, Siegelman ES, Hunt JL. Ovarian teratomas: tumor types and imaging characteristics. Radiographics. 2001 Mar-Apr;21(2):475-90. doi: 10.1148/radiographics.21.2.g01mr09475. PMID: 11259710.

4. Javadi S, Ganeshan DM, Qayyum A, Iyer RB, Bhosale P. Ovarian Cancer, the Revised FIGO Staging System, and the Role of Imaging. AJR Am J Roentgenol. 2016 Jun;206(6):1351-60. doi: 10.2214/AJR.15.15199. Epub 2016 Apr 4. PMID: 27042752.

5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals. Lyon (FR): International Agency for Research on Cancer; 2012. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100A.) ETOPOSIDE IN COMBINATION WITH CISPLATIN AND BLEOMYCIN. Available from: https://www.ncbi.nlm.nih.gov/books/NBK304323/

6. Zhang J, Stevens MF, Bradshaw TD. Temozolomide: mechanisms of action, repair and resistance. Curr Mol Pharmacol. 2012 Jan;5(1):102-14. doi: 10.2174/1874467211205010102. PMID: 22122467.

7. Wilson J. Angiogenesis Therapy Moves beyond Cancer. Annals of Internal Medicine. 2004, 141:2. Doi: https://doi.org/10.7326/0003-4819-141-2-200407200-00027

8. Lucas de Sousa Cavalcante, Gisele Monteiro, Gemcitabine: Metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer, European Journal of Pharmacology, Volume 741, 2014, Pages 8-16, ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2014.07.041. (https://www.sciencedirect.com/science/article/pii/S0014299914005780)

9. Farha NG, Kasi A. Docetaxel. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537242/

10. Marwah N, Batra A, Gupta S, Singhal SR, Sen R. Gliomatosis Peritonei Arising in Setting of Immature Teratoma of Ovary: A Case Report and Review of Literature. J Obstet Gynaecol India. 2016;66(3):192-195. doi:10.1007/s13224-015-0708-7

11. Nishida M, Kawano Y, Yuge A, Nasu K, Matsumoto H, Narahara H. Three cases of immature teratoma diagnosed after laparoscopic operation. Clin Med Insights Case Rep. 2014;7:91-94. Published 2014 Sep 3. doi:10.4137/CCRep.S17455