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Growing Teratoma Syndrome of the Ovary with Neuroendocrine Tumor: A Rare Case Report

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Abstract: Growing teratoma syndrome (GTS) is a rare complication of the malignant ovarian germ cell tumors characterized by enlarging benign metastatic masses during or after chemotherapy with normalized tumor markers. Benign masses consist of mature teratomatous elements. Surgical excision of the masses remains the mainstay of the treatment. We present a rare case of GTS following an embryonal cell carcinoma of ovary with neuroendocrine tumor arising from the splenic deposit. The patient initially presented 15years ago as a recurrence following embryonal cell carcinoma of ovary operated elsewhere. After secondary cytoreductive surgery followed by chemotherapy, she presented with multiple masses after 11years. Histopathology of the excised masses revealed mature teratoma with neuroendocrine tumor. This case emphasizes the long term follow up needed for prompt recognition of GTS. Also, this case is unique in the finding of a secondary malignancy arising in a GTS of the ovary with only one case reported till date.

Keywords: Embryonal carcinoma, growing teratoma syndrome, mature teratoma, neuroendocrine tumors, ovarian germ cell cancer..

INTRODUCTION

Growing Teratoma Syndrome (GTS) of the ovary is defined as enlarging retroperitoneal or metastatic masses containing benign mature teratomatous elements during or after chemotherapy for Non Seminomatous Germ Cell Tumors (NSGCT) in the context of normal tumor markers levels. Growing teratoma syndrome has been reported in both males and females.

The reported incidence is 1.9 to 7.6% in case of testicular NSGCTS [1-3] and around 12% in ovarian malignant germ cell tumors [4]. In recent times, there have been an increasing number of reports on GTS owing to the increased awareness of such condition among oncologists and also availability of newer convenient diagnostic imaging tools. We present a rare case of growing teratoma syndrome following an embryonal cell carcinoma of ovary after a long disease free interval. Also, this case would be probably the second of its kind reported in the literature to the best of our knowledge where a neuroendocrine tumor is arising in the setting of growing teratoma syndrome.

CASE REPORT

A 30 years old unmarried lady had earlier presented to our institute 15 years back (January 2003) with complains of growing abdominal mass 12 months post-surgery. She had undergone an initial surgery (February 2002) consisting of hysterectomy with right salpingo-oophorectomy for embryonal cell carcinoma of ovary elsewhere. She had not received any adjuvant therapy and was advised follow up. Ultrasound examination revealed 30 x 20 cm complex abdominal mass arising from the pelvis. Tumor marker analysis revealed serum Alpha-Feto Protein (AFP) level of 345 IU/ml [Normal = 0 to 5 ng/ml]. She underwent laparotomy in view of recurrence with left salpingo-oophorectomy, omentectomy with pelvic lymphadenectomy with optimal tumor debulking (January 2003). Histopathology revealed embryonal cell carcinoma ovary, FIGO stage 3c. Post operatively four cycles of adjuvant chemotherapy consisting of Bleomycin, Etoposide and Cisplatin (BEP) were given. She was asymptomatic and was under follow up regularly.

After 12 years, she again presented in February 2015 with abdominal pain. Physical examination was normal. There were no signs of metastatic spread or lymph nodes enlargement or ascites. On evaluation, ultrasonography revealed multiple solid cystic lesions in liver surface, spleen, and pelvis. There was no ascites. Serum AFP level was 2.9ng/ml. Laparotomy was done with tumor debulking and resection of the peritoneal,

pelvic, bladder, sigmoid, liver and splenic deposits [Figure 1].

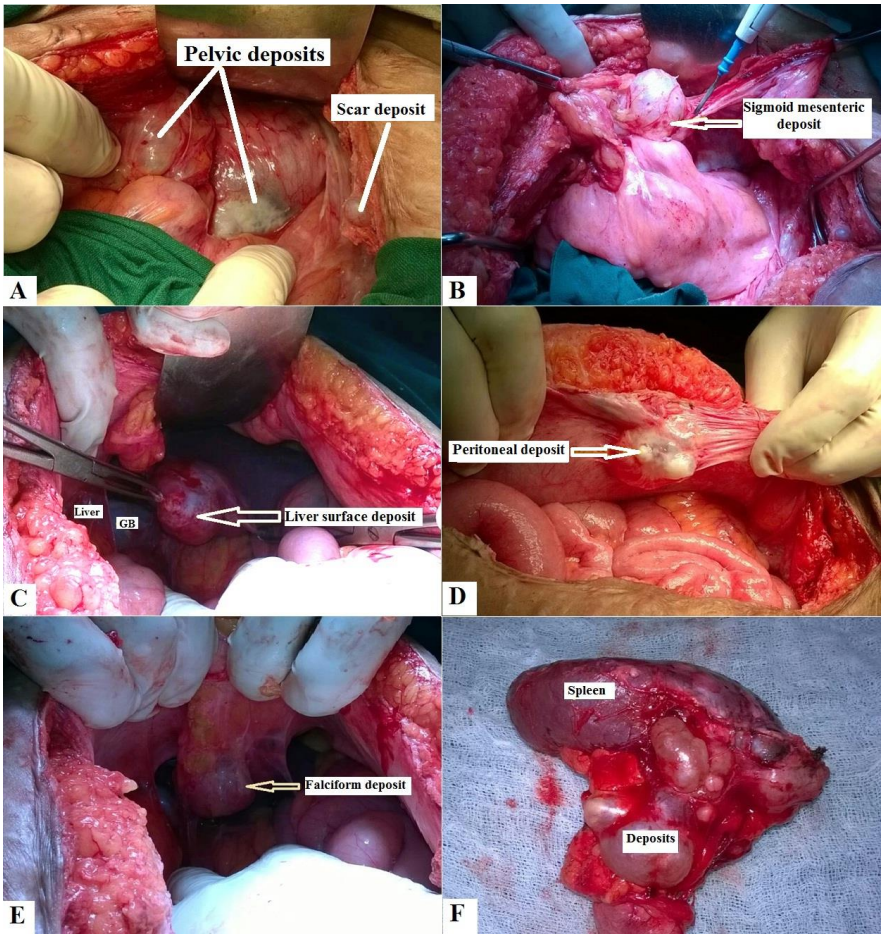

Fig-1: Intra operative pictures of the growing teratoma masses in pelvis [A] & sigmoid mesentery [B], over the liver surface & falciform ligament [D], [C], anterior abdominal wall peritoneal deposit [E] and splenectomy specimen with splenic hilar deposits [F]

Histopathological examination of the deposits revealed mature teratomatous elements in all the deposit [Figure 2]. However, splenic capsular deposit showed mature teratoma with neuroendocrine tumor grade 1.

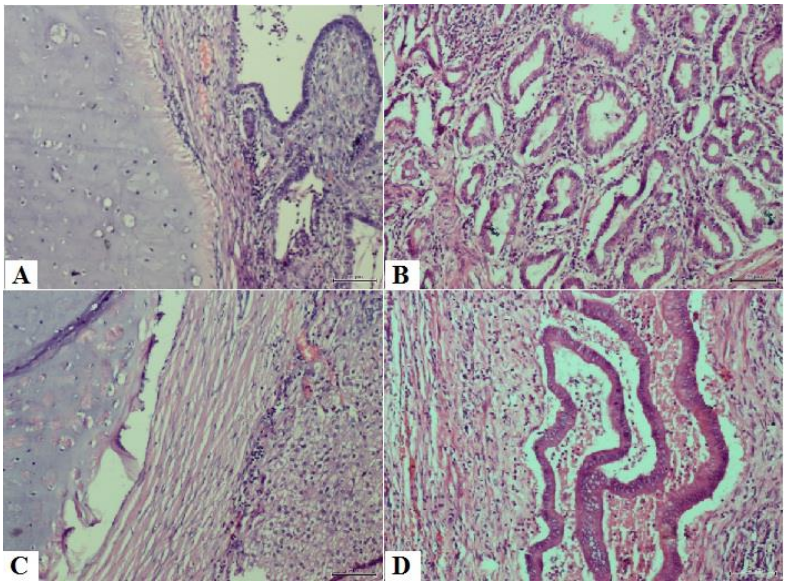

Fig-2: Histopathological sections from the pelvic deposit [A], Sigmoid mesenteric deposit [B], liver deposit [C], peritoneal deposit [D] showing mature teratomatous mesodermal & endodermal components like cartilage [A] [C] & Glands [B]

Immunohistochemical staining of this deposit was positive for synaptophysin, chromogrannin and cytokeratin with low Ki 67 index [Figure 3]. Her postoperative period was uneventful. She did not receive any adjuvant treatment and is presently asymptomatic throughout the last 40 months of follow up.

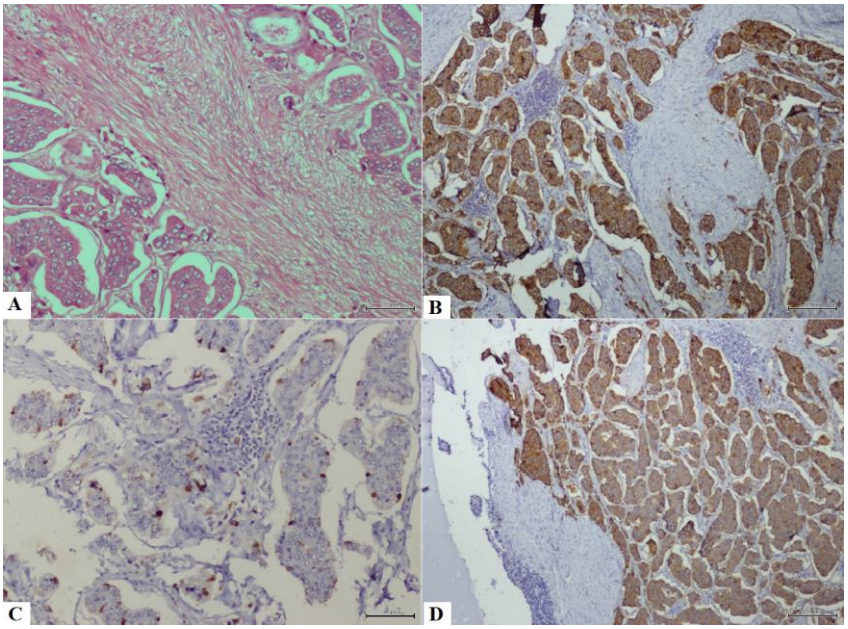

Fig-3: Neuroendocrine tumor arising from the mature teratomatous elements from the splenic hilar deposit [A] with tumor cells arranged in organoid pattern, relatively monomorphic with single central nuclei, salt & pepper chromatin, inconspicuous nucleoli and moderate amount of eosinophilic cytoplasm. The tumor cells stain positive for synaptophysin [B] & cytokeratin [D] and diffusely positive staining for chromogranin [C] with low Ki 67 index

DISCUSSION

The term growing teratoma syndrome (GTS) was first coined by Logothetis *et al*. in 1982 when he described six patients with enlarging metastases during systemic chemotherapy for primary mixed metastatic NSGCTs of testes [1]. The initial description of benign maturation was however reported in the year 1969 by Smither *et al*. [5]. Di Saia *et al*. first reported this incidence among the gynecological settings and named it as chemotherapeutic retroconversion (CR) defined as the conversion of a metastatic immature teratoma into a mature tumor as a result of chemotherapy [6]. However, the criteria for CR did not include the component of growth as in GTS. The etiology of GTS is still not clear. The most postulated theories being that chemotherapy either destroys only the immature malignant cells, leaving the mature benign teratomatous elements or chemotherapy promotes the transformation from a totipotent malignant germ cell toward a benign mature teratoma [7].

Various authors have reviewed the cases of ovarian GTS literature published. Djordjevic *et al*. reviewed 34 cases of Ovarian GTS from the literature [8]. They observed that GTS ovary can present from age of 5 to 38years with mean age of 20 years. It was also observed that GTS nodules mostly remained confined to pelvis, abdomen or the retroperitoneum except few rare cases in contrast to testicular tumors where GTS may appear at distant sites too. They further concluded that the location of GTS nodule may be a delayed indicator of the location of invasive tumor previously. A recent literature review by Song Li *et al*. analyzed 101 cases of ovarian GTS [9]. They found that the median time interval from primary treatment to diagnosis of ovarian GTS was 26.6 months [range 1 to 264 months, n = 41]. This emphasizes the role of regular follow ups in cases of ovarian germ cell tumors after treatment for early diagnosis and treatment of GTS.

In our GTS case, the teratomatous masses were seen as pelvic, mesenteric cystic masses, also abutting the liver surface close to Gall bladder and porta hepatis, along the falciform ligament, and splenic hilar (extra capsular) lesions [Figure 1]. These masses could have been the foci of microscopic deposits at the initial presentation. The histopathology of these resected masses revealed mature teratoma components with splenic deposit showing neuroendocrine tumor grade I. The immuno-histochemical staining of this was positive for synaptophysin & cytokeratin, focally positive for

chromogranin and negative for thyroglobulin and thyroid transcription factor 1 (TTF-1) with low Ki 67 index [Figure 3].

Malignant transformation of mature teratoma of ovary is a known phenomenon. Malignancy of any 3 embryological cell lines can develop. Most common being squamous cell carcinoma followed by adenocarcinoma and carcinoid tumors [10]. The rate of secondary malignancy in mature ovarian teratomas has been reported to be 1.4% and 0.17% in the two largest studies till date by Ayhan *et al*. [10] and Comerci *et al*. [11] respectively. It is also interesting to note that the neoplasms that have been reported in mature ovarian teratomas, carcinoids form a frequent observation.

Secondary teratomas arising in GTS of the testis have been reported previously by Sonneveld *et al*. [12]. They described 3 cases of stage IV mixed germ cell tumors of testis. The patients had presented after 27, 174, and 39 months following chemotherapy followed surgery with the evidence retroperitoneal disease at the site of original retroperitoneal tumors. The histopathology revealed adenocarcinoma of unspecified type with mature teratomatous tissue in 2 patients and a somatic malignancy with neuroendocrine features in the third patient. However, all three patients had an elevation of alpha feto protein level.

Secondary tumor arising in Ovarian GTS is rare. Only one report on record demonstrates the occurrence of secondary malignancy arising in growing teratoma syndrome of ovary to the best of our knowledge. In their report by Djordjevic *et al.* they reported a patient with an immature teratoma of ovary with positive retroperitoneal lymphnodes [8]. The patient had presented with recurrent GTS presenting as abdominal and pelvic masses after 1, 6, and 19 years post initial therapy. The last recurrence showed a trabecular carcinoid tumor developing in the mature teratoma associated with the liver. It was reported that the patient had a liver mass 1year after the initial presentation which was closely followed up. They concluded that the long standing mass could have developed carcinoid over time. Similarly in our case, we observed a secondary malignancy arising in the splenic hilar teratomatous mass with carcinoid features after 11years following initial treatment. Although, the patient was regularly following up, the long standing nature of the masses cannot be determined due to the long intervals of follow up. Her previous follow up was 3 years prior to the presentation. It is interesting to note that the both cases have shown the neoplasm arising from the growing teratoma syndrome of ovary have been carcinoid tumors. The long term implications of this carcinoid tumor arising in the GTS on the prognosis is yet to determine as the patient is at present asymptomatic and under strict follow up.

CONCLUSION

Growing teratoma syndrome of ovary is a rare clinical phenomenon. A secondary malignancy arising from a growing teratoma syndrome of ovary is even rarer. Awareness, early diagnosis and prompt surgical resection remain the mainstay of the treatment for GTS. Our case demonstrates that recurrent masses can arise many years after the primary tumor, thus consolidating the importance of long term follow up in these patients.

AUTHORS CONTRIBUTION

SN: manuscript preparation, analysis, patient care, reference hunting and final editing. PSR: patient care, article design and manuscript editing. PVR: Data analysis and manuscript editing. UA: histopathological diagnosis and reporting. UDB: patient care, article design, the final corrections and manuscript editing.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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