



ELSEVIER

CASE REPORT

# Progression from an Immature Teratoma with Miliary Gliomatosis Peritonei to Growing Teratoma Syndrome with Nodular Gliomatosis Peritonei

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A 4½-year-old girl presented with an incompletely resected, huge, immature abdominal teratoma, elevated serum alpha-fetoprotein (AFP), and numerous miliary gliomatosis peritonei (GP). Two courses of chemotherapy resulted in normalization of her AFP level and marked tumor shrinkage. Further chemotherapy was interrupted by complications. During treatment for these complications, ascites increased and the tumor enlarged, but serum AFP remained within the normal range. Second-look surgery revealed that the tumor had changed histologically to a mature teratoma, and GP had enlarged to nodular size, causing massive ascites. The still incompletely resected, growing mature teratoma was reduced with interferon. Nodular GP and ascites slowly regressed with interferon use, and finally disappeared after several months. One residual mass thought to be GP was reduced by gamma-knife surgery 3 years later.

## 1. Introduction

Immature teratomas (IMT) in children are potentially malignant, especially when they present with elevated levels of alpha-fetoprotein (AFP) or human chorionic gonadotropin (hCG).<sup>1</sup> Chemotherapy is necessary in such situations.<sup>1–3</sup> Histologic grading seems less predictive than tumor markers in children.<sup>1</sup> Chemotherapy changes the features of IMT to those characteristic of mature teratomas (MT), and reduces levels of tumor markers.<sup>3–5</sup> Curiously, however, the tumor mass sometimes increases in size while tumor marker levels decrease,<sup>3,6–9</sup> and further chemotherapy is unable to shrink this growing tumor. Here we report a case, initially diagnosed as IMT

and associated with elevated AFP, which changed to growing teratoma syndrome (GTS) after two courses of chemotherapy, and was then stabilized with interferon. The gliomatosis peritonei (GP) was miliary in size at the first surgical examination, but had increased to nodular size at second-look surgery, after cessation of chemotherapy. The GP and ascites eventually regressed.

## 2. Case Report

This 4½-year-old girl was diagnosed with a grade 3 IMT, 13×15×14 cm in size, originating from the left ovary and containing neuroepithelium and glial tissue.

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Numerous miliary foci of glial implants, known as GP, each  $<0.5$  mm in diameter, were detected over the omentum and lower pelvic wall. Ascites of  $170\text{cm}^3$  was noted. Maximal tumor removal was performed leaving residual tumor at the base where it adhered tightly to the retroperitoneum. The GP were too numerous to remove, and were only biopsied. Because of an elevated serum AFP level of  $4222\text{ng/mL}$ , the patient received chemotherapy with ifosfamide  $1.2\text{g/m}^2$  for one dose, mesna  $1.2\text{g/m}^2$  for one dose, cisplatin  $20\text{mg/m}^2/\text{day}$  for 5 days, and etoposide  $75\text{mg/m}^2/\text{day}$  for 5 days. The patient subsequently developed severe neutropenic infection, acute renal failure, and persistent hyponatremia lasting for a period of 8 months. The second course of chemotherapy consisted of cyclophosphamide  $1\text{g/m}^2$  for one dose and epirubicin  $30\text{mg/m}^2/\text{day}$  for 2 days. The patient subsequently developed *Legionella* pneumonia and carditis with acute congestive heart failure.

After the two courses of chemotherapy, the tumor shrank considerably and AFP levels fell, but the tumor failed to continue to shrink after normalization of AFP. In contrast, the ascites and tumor volumes progressively increased (Figure 1). Second-look surgery revealed many nodular GP, each  $>0.5$  cm in diameter,  $2700\text{cm}^3$  ascites, and an enlarged, incompletely-excised main tumor with gross residuals. Histopathologic examination revealed that the main tumor had changed to a MT. Interferon  $\alpha\text{-2b}$   $3\text{MIU/m}^2$  three times per week was given for

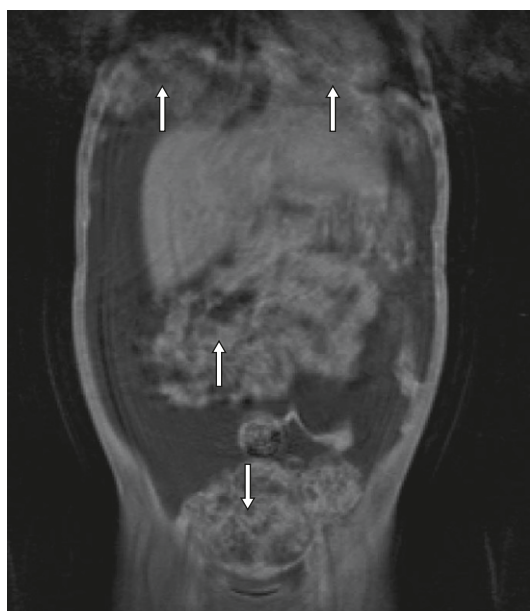
9 months, but was then stopped due to neurological complications. The size of the original main tumor was reduced during and after interferon treatment, without recurrence.

Slow regression of GP and ascites also occurred during and after interferon treatment. Three years after stabilization of a  $1.5\times 2.3$ -cm diameter subphrenic residual mass supposed to be residual GP (Figure 2), which could not be removed during second-look surgery, the patient underwent gamma-knife surgery to remove the mass. She remained free of disease 2 years after radiation therapy and 5 years after stopping interferon.

### 3. Discussion

IMT with elevated AFP often behaves in a malignant fashion, because small foci of malignant germ cell elements in the tumor can be easily overlooked in pathological specimens.<sup>6</sup> Chemotherapy is necessary in such situations.<sup>1-3</sup>

Post-chemotherapy residual masses undergo histological changes into MT.<sup>3-5</sup> Chemotherapy is ineffective against MT.<sup>1,6</sup> Curiously, teratomas are often observed to increase in size during or after chemotherapy, as tumor marker levels decrease.<sup>3,6-9</sup> This is known as GTS, a situation first described by Logothetis et al in 1982.<sup>7</sup> According to Logothetis, three criteria are required to define GTS: normalization of previously elevated serum tumor markers (AFP or hCG),



**Figure 1** Multiple gliomatosis peritonei nodules over the peritoneum, mesentery and subdiaphragm area, massive ascites, and the main mass of the growing mature teratoma over the lower abdomen.



**Figure 2** A  $1.5\times 2.3$ -cm diameter lobulated mass over the esophageal-gastric junction. Regression of ascites and multiple nodular gliomatosis peritonei.

an increase in tumor size during or after chemotherapy given for non-seminomatous germ cell tumor (NSGCT), and an absence of any NSGCT components, other than MT, at tumor resection.

GTS is characterized by an absence of malignant germ cell components, indicating that the growing tissues are benign, and not partially treated NSGCT remaining after previous chemotherapy.<sup>10</sup> Further chemotherapy is unable to shrink GTS, but interferon can control disseminated, unresectable MT or GTS, as in the current case.<sup>11–14</sup> Interferon inhibits tumor angiogenesis mediated by decreased levels of vascular endothelial growth factor and basic fibroblast growth factor.<sup>15–17</sup>

GP is a rare disease, first described in 1906 and defined as peritoneal implantations of mature glial tissue in patients with ovarian teratomas of any grade.<sup>18,19</sup> At least 86 cases of GP with teratoma have been reported.<sup>20</sup> IMT, MT, and GTS have all been reported in association with GP,<sup>10,21–25</sup> but there has been no report of any case with a combination of all these conditions, GTS responsive to interferon, and GP growing from miliary to nodular size. Waiting, or complete surgical excision, is the usual treatment for GP.<sup>24,25</sup> Our patient had numerous miliary GP at initial diagnosis, while nodular GP, which could not be excised completely, were found during second-look surgery. The responsiveness of GP to chemotherapy remains controversial,<sup>20</sup> and no mention has been made of the use of interferon to treat GP. However, a common origin has been suggested for GP, MT and GTS.<sup>10,20</sup> Miliary GP did not enlarge during chemotherapy in our patient, suggesting some inhibitory effect of chemotherapy. However, the GP enlarged to nodular size after cessation of chemotherapy in accord with GTS. In our patient, the slow regression of ascites and nodular GP during interferon treatment, originally aimed at GTS, is not sufficient to indicate interferon efficacy. Further studies are needed to determine a possible role for interferon therapy.

The outcome of GP is not always benign, as reported by Shefren et al, who described an adolescent who presented more than 5 years after diagnosis with a malignant, abdominal glial neoplasm, presumably representing a malignant transformation of mature gliomatosis.<sup>26</sup> Although our patient remained free of disease 5 years after interferon therapy and 2 years after radiation therapy, regular follow up continues to be necessary.

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