Metachronous Germ Cell Tumors of the Mediastinum

Running Head: METACHRONOUS MEDIASTINAL GERM CELL TUMORS

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Word Count: 1616 words

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Abstract

We herein report a rare case of mediastinal nonseminomatous germ cell tumor (NSGCT) arising after 2 complete resections of mediastinal mature teratomas 18 and 10 years prior. After three cycles of chemotherapy for the mediastinal NSGCT, the serum alpha-fetoprotein and beta human chorionic gonadotropin levels were normalized. However, chest radiography revealed that the mediastinal tumor had remarkably increased in size, and thus growing teratoma syndrome was diagnosed. He underwent urgent resection of the tumor, and a pathologic examination showed an encapsulated mature teratoma without any malignant viable cells. The patient was well without disease 54 months after the third operation.

There have been few reports on multiple germ cell tumors (GCTs) arising primarily in the mediastinum. We herein report a rare case of mediastinal nonseminomatous GCT (NSGCT) that developed after two complete resections of metachronous mediastinal mature teratomas.

A 69-year-old man was referred to our hospital because of a large anterior mediastinal mass. Chest roentgenogram performed during a medical checkup showed a mass 10 cm in diameter on the left side of the anterior mediastinum (Figure 1a). He had undergone 2 complete resections of mediastinal mature teratoma at 18 years and 10 years prior to this presentation without any preoperative treatment. The first one was 5 cm in size and removed by tumorectomy via median sternotomy, while the second one was 8 cm in size and noted on the right side of the mediastinum at a follow-up radiological examination 8 years later. He underwent complete surgical removal of the second tumor by tumorectomy via right thoracotomy. Notably, the preoperative serum tumor markers were within normal ranges on both occasions.

The metachronous third mediastinal tumor was revealed as a lobulated cystic mass measuring 10.0 × 9.0 × 8.0 cm with calcification on computed tomography (CT) (Figure 1b). Positron emission tomography-computed tomography (PET-CT) showed the intermediate accumulation (maximal standard uptake value [SUVmax], 4.1) of fluorodeoxyglucose (FDG) heterogeneously within the tumor (Figure 1c). Although no malignant tumor cells were

detected on a preoperative needle biopsy, the serum alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (HCG) levels were elevated (839 ng/mL [normal range: < 20 ng/mL] and 7.7 IU/L [normal range: < 5.0 IU/L] respectively), and the tumor was clinically diagnosed as mediastinal NSGCT such as yolk sac tumor, embryonal carcinoma, or these mixtures.

After the patient received three cycles of chemotherapy consisting of bleomycin, etoposide and cisplatin, the serum levels of both tumor markers returned to the normal ranges, but chest roentgenogram and CT revealed that the mediastinal mass had remarkably increased in size, measuring 15 × 13 × 10 cm (Figure 2a, b). In contrast, PET-CT revealed that the SUVmax of the tumor had decreased to 2.5 following chemotherapy (Figure 2c). Thus, a diagnosis of growing teratoma syndrome (GTS) was made, and the patient underwent an urgent operation.

The surgical approach undertaken was re-median sternotomy with left anterior thoracotomy (hemiclamshell incision). The tumor consisted of an apparently intact fibrotic capsule firmly attached to the pericardium. En-bloc resection of the tumor with the residual thymus tissue, left upper lobe of the lung, left phrenic nerve and pericardium was performed, and the resected specimen weighed 576 g. A pathologic examination of the tumor revealed an encapsulated mature teratoma without any other malignant components, such as NSGCT (Figure 3).

The patient developed a postoperative complication of severe respiratory distress that required mechanical ventilation for one week after the operation. He was discharged on the 14th postoperative day and received no adjuvant therapy. Fifty-four months after the third operation, he was well with no evidence of disease on CT, and the serum tumor marker levels were within normal limits.

Comment

GCTs are a group of neoplasms that characteristically arise in the testes and ovaries. They occasionally develop in extragonadal sites, however, usually along the body midline, including the mediastinum, retroperitoneum, pineal gland and other sites. GCTs are hypothesized to migrate to these sites during embryonic gonadal ridge development. Mediastinal GCTs account for approximately 10% to 15% of all anterior mediastinal tumors. In terms of the origin of mediastinal GCTs, Knapp et al. incidentally found a small encapsulated GCT within the thymus tissue during an autopsy [1], and Lattes et al. reported that most mediastinal GCTs arise near the thymus or within the thymic parenchyma [2].

Multiple mediastinal GCTs have seldom been reported because of their rarity. To our knowledge, this is the first case of the development of mediastinal NSGCT after two resections of metachronous mediastinal mature teratomas. In this case, because the two prior tumors were completely resected with negative margins and represented a favorable histology

(mature teratoma without evidence of malignancy), we assessed that this sequential arising of tumors was not local recurrence but rather metachronous multiple primary GCTs developing from the residual thymic tissue. Alternatively, some parts of the third teratoma may have transformed into malignant NSGCT due to long-standing mature teratoma over a period of 10 years, chronic inflammation and irritation due to 2 previous instances of surgical treatment [3].

The third mediastinal tumor was suspected to be mature teratoma based on a transthoracic needle biopsy conducted before chemotherapy. However, the tumor was clinically diagnosed as mediastinal NSGCT because the serum levels of the tumor markers were significantly elevated. Nichols et al. reported that patients with benign teratoma are, by definition, marker negative, and that significant elevations of HCG or AFP imply that the tumor has a malignant component [4]. They also noted that the significant elevation of AFP is diagnostic of a nonseminomatous component in malignant tumors. In the present case, PET-CT was also useful for clinically differentiating NSGCT from teratoma. Stephens et al. reported that a significant association was found between the SUV and the histology when viable NSGCTs were compared to teratomas [5]. In addition, the small amount of tumor tissue obtained by a needle biopsy does not always enable a pathologist to accurately differentiate teratoma from malignant GCTs [6].

Mediastinal teratoma is generally treated by complete excision of the tumor via median

sternotomy or thoracotomy, and this is usually curative [7]. No reports have suggested that patients with mediastinal mature teratoma should undergo total thymectomy combined with tumor resection. However, if total thymectomy had been performed at the first operation in the present patient, he would not have developed the second teratoma or the malignant NSGCT. To prevent the development of second or more tumors, total thymectomy may be appropriate in patients with mediastinal teratoma if resection can be performed without excision of the adjacent structures.

GTS, which is characterized by the enlargement of masses despite the administration of appropriate systemic chemotherapy and the normalization of serum marker levels, was first described by Logothetis et al. in 1982 [8]. It represents a rare event among mediastinal NSGCTs patients. The diagnosis is confirmed by both the presence of mature teratoma and the absence of any malignant germ cells in the final pathological results. Our patient mostly met these criteria. We considered that surgical excision in this setting was advisable because of the confirmation of viable malignant cells and the risk of cardiopulmonary deterioration secondary to mediastinal compression of the adjacent structures [9].

In conclusion, we herein described a 69-year-old male with metachronous mediastinal mature teratomas and mediastinal NSGCT that developed GTS after chemotherapy. Total thymectomy with resection of the primary teratoma may be preferable to prevent the development of multiple GCTs.

Conflict of interest

The authors declare no conflicts of interest in association with this study.

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8. Logothetis CJ, Samuels ML, Trindade A, et al. The growing teratoma syndrome. Cancer 1982;50:1629-35.

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Figure legends

Figure 1. Disease condition before chemotherapy. (a) Chest radiograph showed an abnormal shadow on the left side of the mediastinum. (b) Computed tomography revealed a tumor in the anterior mediastinum. (c) Positron emission tomography-computed tomography showed the intermediate accumulation (SUVmax of 4.1) of fluorodeoxyglucose heterogeneously within the tumor.

Figure 2. Disease condition after three courses of chemotherapy. (a) Chest radiograph showed an enlarged mass shadow. (b) Computed tomography also demonstrated that the tumor shadow had remarkably increased in size. (c) Positron emission tomography-computed tomography revealed that the SUVmax on the tumor had decreased to 2.5.

Figure 3. Resected tumor with polycystic appearance and calcifications.

Figure 1

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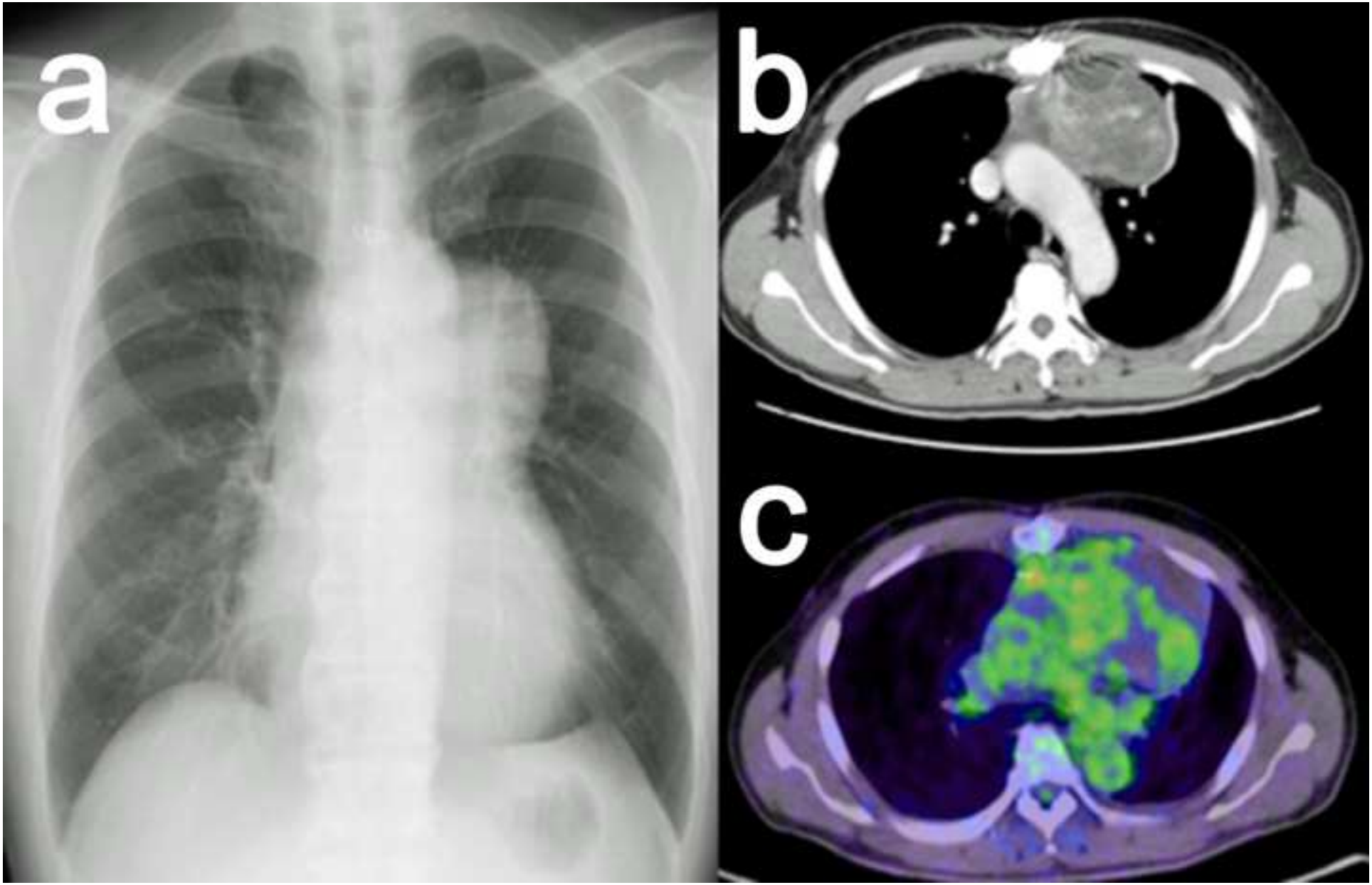

Figure 2

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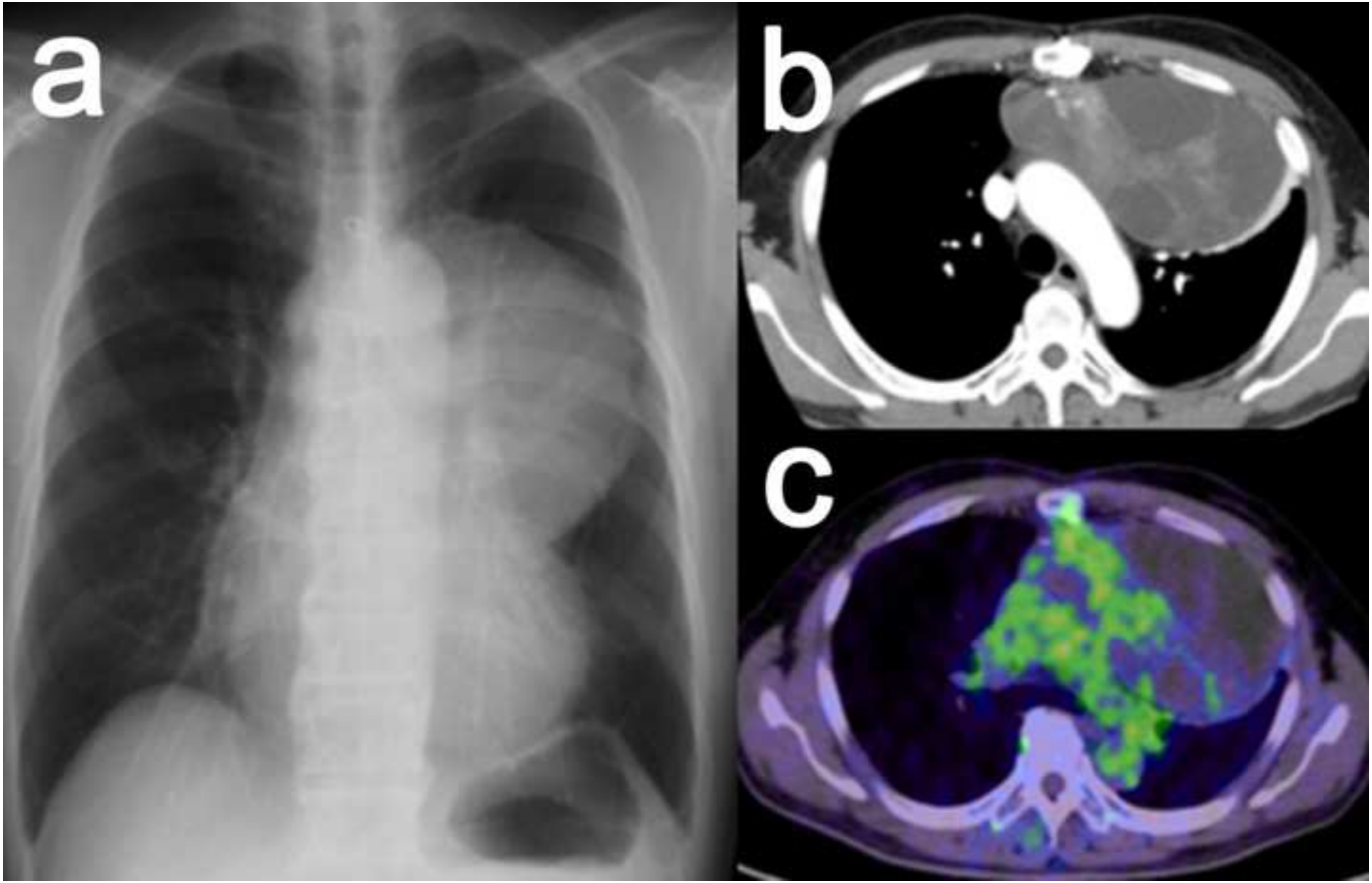

Figure 3

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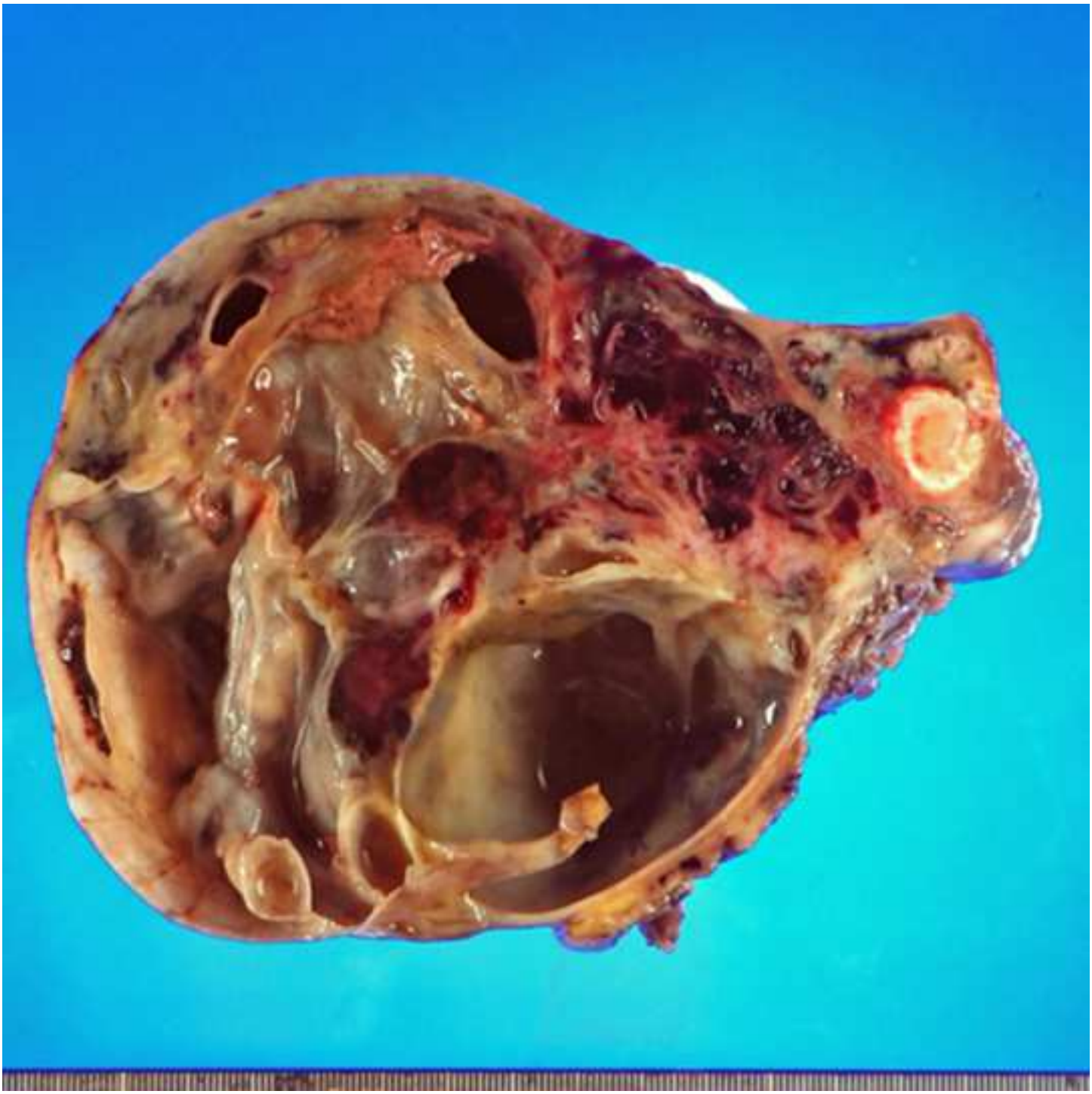

Response to Reviewer's comments:

To the Reviewer,

Q1. Page 5, line 18, the sentence that begins "In this case…." the wording "lack of any remarkable pathological results and no malignant lesions" is a bit ambiguous. It may be clearer to say something along the lines of "Because the prior tumors represented a favorable histology (mature teratoma without evidence of malignancy) and were completely resected with negative margins, we felt the likelihood of local recurrence was low".

Q2. Page 7 line 12, the sentence that begins "Clinically…. unavoidable" It is unclear what the authors are trying to communicate here. I suspect the authors are suggesting that , "surgery is this setting is advisable because….."

Reply) Thank you very much for reviewing our revised manuscript and offering helpful advices. We changed the couple of sentences as suggested. (Q1; page 5-6, line 18-3, and Q2; page 7, line13-15).

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