Mediastinal Germ Cell Tumor Exhibiting a Discrepancy between Tumor Markers and Imaging: A Case Study

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Key Words

Abstract

We report a mediastinal germ cell tumor (GCT) that exhibited a discrepancy between the time course of serum human chorionic gonadotropin (hCG) levels and clinical consequences. An otherwise healthy man, aged 34 years, was diagnosed with a nonseminomatous GCT, most likely embryonal carcinoma (EC), based on a mediastinal tumor biopsy. Standard chemotherapy resulted in an optimal decrease in serum hCG levels. However, multiple lesions in the liver continued to enlarge, which led to his death. Autopsy revealed few viable tumor cells in the liver, with the great majority of the tumor cells appearing to have undergone necrosis, suggesting that they responded to the chemotherapy. The residual tumor cells in the mediastinum and the liver were similar to syncytiotrophoblast cells, suggesting a choriocarcinoma (CC). On immunohistochemical analysis, the mediastinal tumor cells in the diagnostic biopsy specimen expressed both CD30 and hCG, whereas residual mediastinal and hepatic tumor cells in the autopsy specimen after chemotherapy also expressed hCG, but not CD30. These findings suggested that the patient suffered from a primary mixed GCT consisting of an EC and a CC. Both pre- and postchemotherapy tumors strongly expressed matrix

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metalloproteinase-2, supporting the aggressive and invasive features of the tumor phenotype. We speculate that the extremely invasive tumor destroyed normal liver structure, whereas chemotherapy and central necrosis reduced the number of viable cells themselves, causing a discordant decrease in serum hCG levels.

Introduction

Mediastinal germ cell tumors (GCTs) are rare, accounting for 3–4% of all GCTs in both adults and children. They are divided into several categories: seminoma, malignant nonseminomatous GCTs [NSGCTs; embryonal carcinoma (EC), yolk sac tumor, choriocarcinoma (CC), and mixed GCT], mature teratoma, and immature teratoma. Of these, the prognosis for NSGCTs of mediastinal origin is worse than that of tumors originating from gonadal or extragonadal sites. According to the risk classification of the International Germ Cell Cancer Collaborative Group (IGCCCG), mediastinal NSGCTs are classified as poor risk, with a 5-year relapse-free chance of survival of 40% [1], regardless of the presence or absence of metastasis, or of levels of the serum tumor markers, lactate dehydrogenase (LDH), α-fetoprotein (AFP), and human chorionic gonadotropin (hCG). The standard care for advanced NSGCTs is combination chemotherapy with bleomycin, etoposide, and cisplatin (BEP), followed by resection of the residual tumor [2]. Serum LDH, AFP, and hCG levels should be measured to monitor the response to treatment [3]. Some studies have indicated that a logarithmic decrease in these markers, consistent with their respective serum half-life time, predicts a good treatment outcome [4].

Here, we report a rare case of a mediastinal GCT that exhibited rapidly progressive disease, which eventually killed the patient, despite an optimal decrease in serum tumor markers. We also conducted a pathological and biological analysis of autopsy and biopsy specimens to gain insight into the cause of this peculiar clinical course.

Case Report

A 34-year-old man who had developed gynecomastia about 4 months previously visited a local hospital on July 10, 2013, due to hemosputum, which had developed 3 days previously. Chest radiography and computed tomography (CT) both showed a very large mediastinal tumor with multiple lung nodules. He was referred to a cancer center, where a core-needle biopsy of the anterior mediastinal tumor was performed. Since his dyspnea and hemosputum were getting worse, he was referred to our hospital on July 29, 2013.

On examination, his Eastern Cooperative Oncology Group (ECOG) performance status was 2; body temperature was 37.5°C, blood pressure 102/62 mm Hg, pulse 93 beats per min (regular), respiratory rate 28/min, and oxygen saturation 88–92% (room air, spontaneous respiration). Palpation of superficial lymph nodes and testicular tumors were negative. Bilateral gynecomastia was seen. No other abnormalities were recognized, including respiratory or cardiac sounds.

Imaging studies, including chest and abdominal-plane CT, positron emission tomography CT, and brain magnetic resonance imaging (MRI), showed a bulky anterior mediastinal tumor with liver, lung, and brain nodules (fig. 1a–e).

Laboratory findings were as follows: white blood cell count $169 × 10^6$ μ/l, hemoglobin 10.1 g/dl, C-reactive protein 13.7 mg/dl, aspartate aminotransferase (AST) 63 U/ml, alanine

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aminotransferase 76 U/ml, LDH 656 U/ml, total bilirubin 1.6 mg/dl, AFP 1 ng/ml, and hCG 289,500 mIU/ml.

The biopsy specimen from the anterior mediastinum was diagnosed as an NSGCT, most likely an EC based on positive hCG and CD30 staining (fig. 1g, h, respectively). According to the risk classification of the IGCCCG, the patient was classified as having a poor risk because of his primary mediastinal tumor. We immediately initiated chemotherapy with a BEP regimen (bleomycin 30 U/body, days 2, 9, and 16; etoposide 100 mg/m^2, days 1–5, and cisplatin 20 mg/m^2, days 1–5, q 3 weeks) [5] on July 30, the day after admission. Serum hCG levels decreased consistently (fig. 2a), suggesting that the tumors were responsive to the BEP therapy. Unexpectedly, we observed an increased number and size of cystic liver lesions on CT on August 22 compared to those at admission (fig. 2b–d). Because of his optimal tumor marker response and a high fever at that point, we first suspected liver abscesses in the patient and initiated meropenem treatment on August 22. Intracystic fluid aspiration and a liver biopsy were undertaken to determine whether the liver lesions were tumors or abscesses on August 23. Although the intracystic fluid was a yellowish brown, cloudy, odorless solution, compatible with an abscess, it was aseptic microscopically and on culturing, and negative for malignant cells on cytology. The liver biopsy specimen was composed of normal hepatocytes with no evidence of tumor or infection, including mycobacterium and mycosis. Consistent with the imaging study, his liver enzymes increased (fig. 2a), and we accordingly postponed the second cycle of BEP. The liver lesions had increased further in size on CT on August 28 (fig. 2e), and we initiated treatment with amphotericin B on the assumption of a fungal infection. However, his liver enzymes continued to increase. We considered his condition to indicate clinically progressive disease and decided to give gemcitabine combined with paclitaxel (GP; gemcitabine 1,250 mg/m^2, day 1; paclitaxel 135 mg/m^2, day 1) [6] on August 30. An ifosfamide-based standard salvage regimen was considered unfeasible based on his poor general condition. Though his liver enzyme levels transitionally decreased over several days after GP (fig. 2a), hepatic failure associated with increased serum total bilirubin and a rapid increase in liver enzyme levels (AST 813 U/ml on September 12; fig. 2a) were seen; multiorgan failure subsequently developed, and the patient finally died on September 13.

Autopsy findings were as follows: the liver contained cystic tumors of various sizes up to 10 cm in diameter and filled with cloudy necrotic material, where we found no evidence of infection (fig. 3a). We also observed the null formation of sperm in the testes. We later microscopically confirmed the absence of tumors in the testes.

Microscopic analysis of the mediastinal (fig. 3b) and liver (fig. 3c) tumors showed the presence of very few viable syncytiotrophoblast cells, and seemingly CC. Immunohistochemical analysis of the mediastinal tumor at autopsy showed the diffuse expression of hCG, including in necrotic areas (fig. 3d). In contrast, CD30 expression was not detected in the autopsy specimen (fig. 3e), suggesting that CD30-positive cells disappeared after chemotherapy. In the liver, the remnants of necrotic tumor cells were weakly positive for hCG (fig. 3f). Collectively, these findings suggest that this particular tumor was a mixed GCT composed of CC (hCG-positive) and EC (CD30-positive).

Given preclinical studies showing that matrix metalloproteinase-2 (MMP-2) was involved in the invasive phenotype of a CC cell line [7] and in trophoblast cell invasion [8], we conducted an immunohistochemical analysis for MMP-2. As shown in figure 3g, we found that MMP-2 was expressed in primary mediastinal tumor cells as well as in liver lesions (both viable tumor cells and debris) (fig. 3h). These results strongly suggested that the GCT was highly invasive, leading to extensive metastases and aggressive expansion in the liver.

Discussion

We report a rare case of a mediastinal GCT that exhibited a discrepancy between the time course of serum hCG levels, imaging studies, and the patient's condition. In general, an unsatisfactory decline in serum levels of tumor markers in the first 1–2 cycles of chemotherapy is associated with a worsening outcome [9–11]. In previously published papers, the cut-off value of the half-life of hCG was defined to be between 3.0 and 3.5 days [9–11]. In our case, the estimated half-life of hCG was nearly 3.3 days (between days 1 and 22 of the first cycle of chemotherapy), as calculated by a previously described method [12]. Therefore, it is surprising that the metastatic lesions in the liver were enlarged by about the third week of the first chemotherapy regimen, despite an optimal decrease in serum hCG. Since we detected no infectious pathogens in the punctatum or infectious changes in the liver specimen, we eventually speculated that this might have been due to disease progression but not to liver abscesses, which was subsequently confirmed, but only at autopsy.

Several examples reporting the enlargement of a mediastinal GCT despite a decline in tumor markers have been reported. One is the 'growing teratoma syndrome', first described by Logothetis et al. [13] in 1982. This is a rare phenomenon characterized by a growing lesion despite the normalization of serum markers after chemotherapy for NSGCT. Importantly, a mature teratoma is normally involved, which is usually negative for hCG [14]. In our case, the pathological analysis showed that the viable cells in the metastatic lesion were composed of hCG-positive cells, most likely CC, making 'growing teratoma syndrome' unlikely.

Another example is a somatic type of malignancy accompanying a chemo-sensitive GCT [15]. Because GCTs with somatic malignancy are usually reported to contain teratoma components and because residual viable cells within the tumors in our case resembled CC and no teratoma component was detected, it is unlikely that the primary mediastinal GCT transformed to a somatic type of malignancy.

Most importantly, despite the enlarged liver lesion in our case, an autopsy showed that almost all tumor cells in the liver had undergone necrosis, and very few resident viable cells remained (fig. 3c). It appeared that the metastatic tumors destroyed the surrounding normal tissues in the liver by inducing necrosis. While no definitive mechanism of this phenomenon can be identified, we offer the following hypothesis: the GCT had a malignant phenotype, having cells with the capacity to aggressively invade the outer region, as indicated by MMP-2 expression, leading to enlarged liver lesions. The enlarged liver regions developed a hypoxic environment in the core region, leading to hypoxia-induced central necrosis. In addition, the tumor cells may have released inflammatory molecules or digestive enzymes such as MMP-2 when killed by chemotherapy, which we speculate led to the secondary necrosis of surrounding liver tissues. Indeed, total bilirubin and liver enzymes increased rapidly during the 10 days before his death, indicating that cystic lesion expansion caused liver destruction. In this manner, while chemotherapy and central necrosis may have reduced the number of viable tumor cells, which was associated with a decrease in serum hCG levels, the extremely invasive tumor destroyed normal liver structure, eventually leading to the death of the patient.

Retrospectively, BEP successfully reduced the number of viable tumor cells. Nevertheless, the efficacy of BEP was considered clinically insufficient because the patient's condition worsened with treatment. In cases where a discrepancy exists between the observed trend of serum tumor markers, imaging studies, and/or the patient's condition, any decision about whether to switch from BEP therapy to salvage chemotherapy will be challenging. In our case, we unfortunately missed the opportunity to administer standard ifosfamide-based

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Case Rep Oncol 2015;8:323–331

DOI: 10.1159/000438697

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salvage chemotherapy because of still decreasing serum hCG levels and the suspicion of infection, only to adopt a less intensive GC regimen on day 31 of BEP therapy. For clinicians making important clinical decisions on the best treatment strategies for NSGST, the observation that serum tumor markers for this tumor do not always precisely reflect treatment efficacy should be kept in mind.

Conclusions

We report a case of a mediastinal GCT which exhibited a discrepancy between the time course of serum tumor markers and the imaging evaluation. We speculate that the extremely invasive tumor destroyed normal liver structure, whereas chemotherapy and central necrosis reduced the number of viable tumor cells themselves, causing a decrease in serum hCG levels.

Acknowledgements

We thank the technicians in the Department of Diagnostic Pathology of Kobe University Hospital for their helpful assistance in immunohistochemistry.

Disclosure Statement

The authors declare that they have no competing interests.

Statement of Ethics

Written informed consent was obtained from the patient and his family for publication of this case report and any accompanying images.

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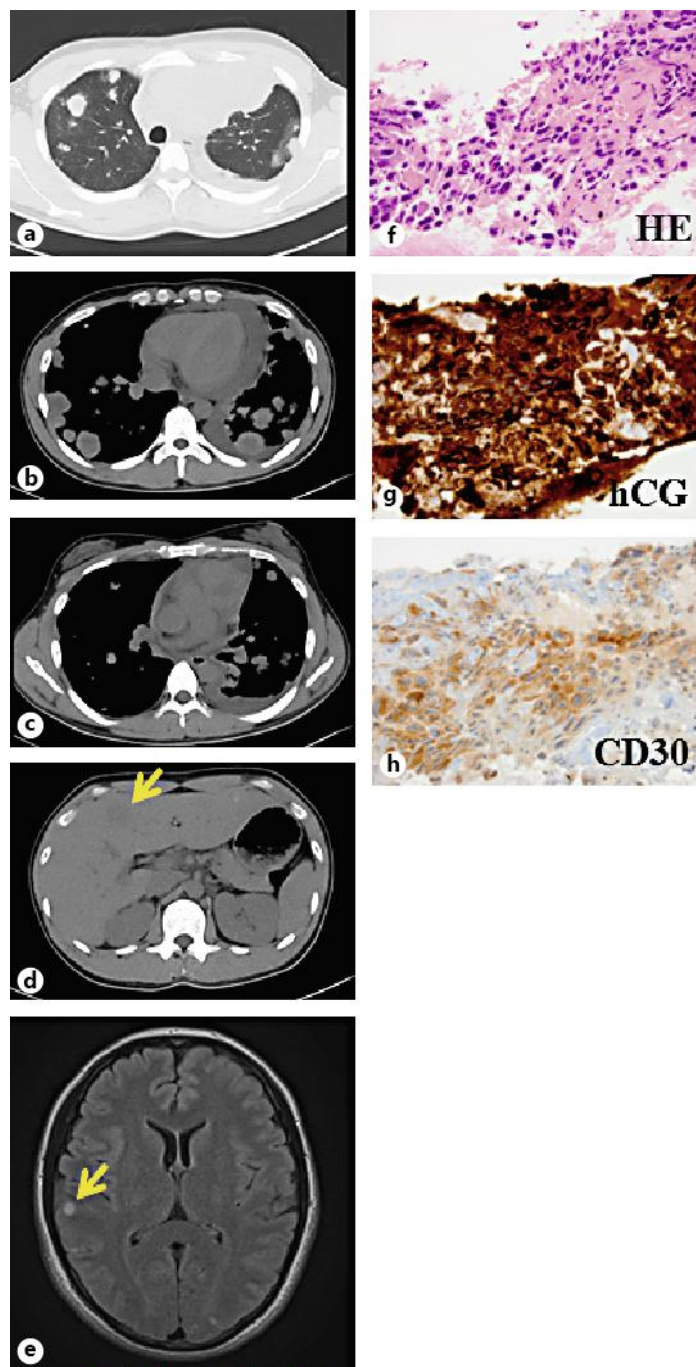
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Case Rep Oncol 2015;8:323–331

DOI: 10.1159/000438697 | © 2015 S. Karger AG, Basel
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Fig. 1. Chest (**a–c**) and abdominal- (**d**) plane CT showed an anterior mediastinal tumor, multiple lung nodules, pericardial effusion, pleural effusion, and a nodule (yellow arrow) in the liver. MRI (**e**) showed a nodule in the right temporal lobe (yellow arrow). HE stain (**f**), anti-hCG antibody stain (**g**), and anti-CD30 antibody stain (**h**) of the mediastinal tumor from biopsy.

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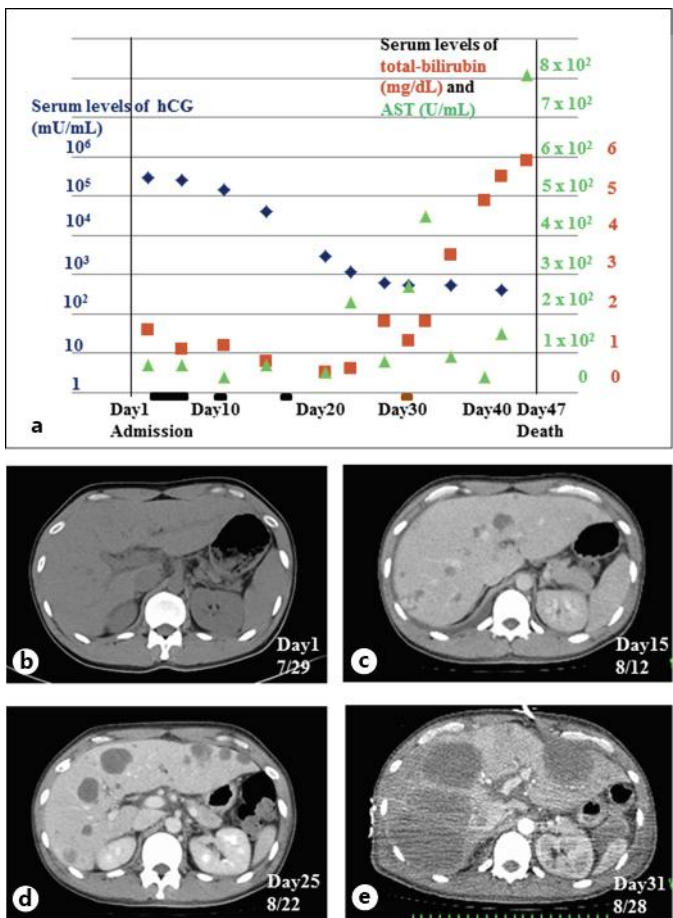Tumor Markers and Imaging: A Case Study

Fig. 2. Time course of serum levels of hCG (blue diamonds), total bilirubin (red squares), and a liver enzyme (AST; green triangles) (**a**) and repeated imaging of the liver lesion (**b–e**) are shown. Black and brown squares indicate the days of BEP and GP regimens, respectively.
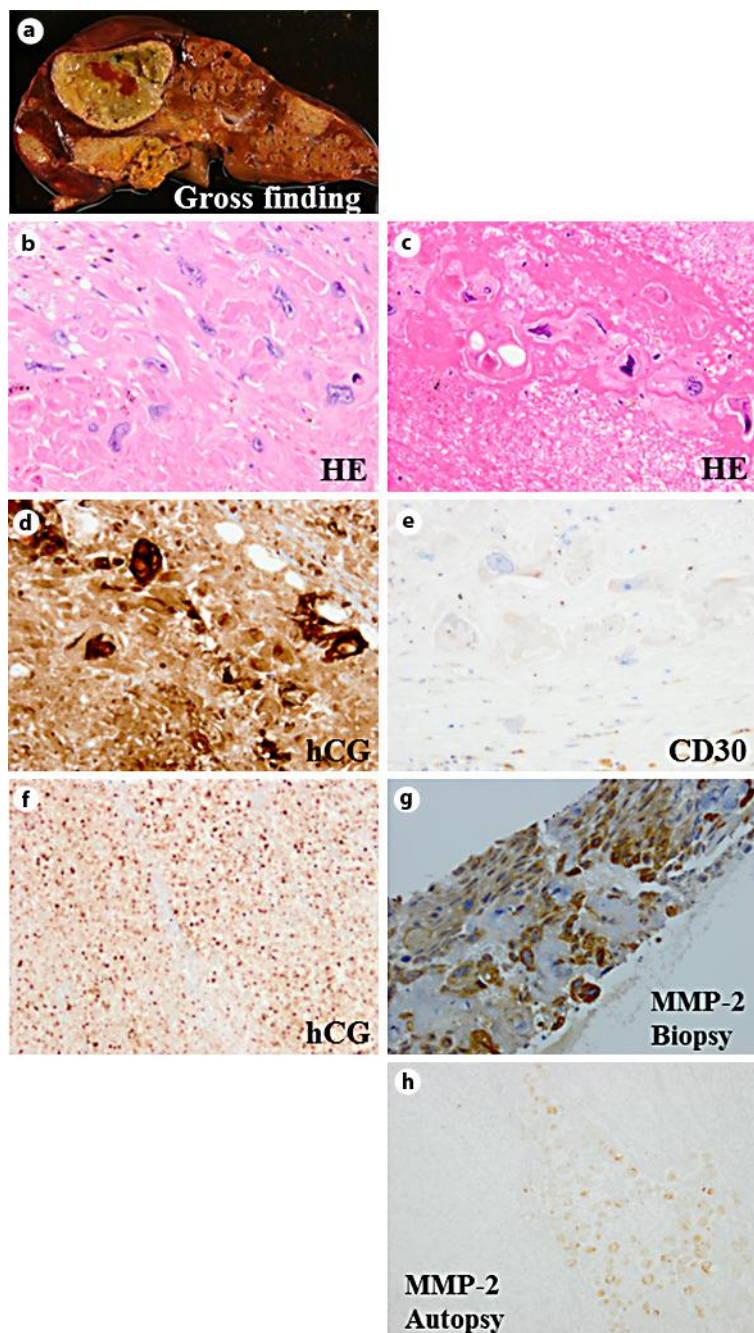
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Case Rep Oncol 2015;8:323–331

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Fig. 3. The liver contained cystic tumors of various sizes up to 10 cm in diameter (**a**). HE stain of the mediastinum (**b**) and liver (**c**). Immunohistochemical analysis of hCG and CD30 of the mediastinum from autopsy (**d**, **e**) and hCG of the liver (**f**). Anti-MMP-2 antibody staining was performed on a specimen of the mediastinum from the biopsy (**g**) and on a specimen of the liver from the autopsy (**h**).