

Choriocarcinoma Syndrome: Bleeding of Distant Metastatic Tumors from a Testicular Germ Cell Tumor

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ABSTRACT

The massive hemorrhage at metastatic sites distant from a testicular choriocarcinoma is called choriocarcinoma syndrome. The syndrome occurs mostly common in patients with lung or brain metastases, developing complication of acute pulmonary or cerebral hemorrhage respectively, and that indicates a rapidly progressive and high-component choriocarcinoma within the testicular tumors. The choriocarcinoma syndrome usually happens before and during the onset of systemic treatment with chemotherapy. Choriocarcinoma is a unique and aggressive germ cell malignancy, and these patients require early aggressive treatment to improve their chance of survival. The β -human chorionic gonadotropin (β -hCG) is a well-established marker of syncytiotrophoblast proliferation and marked elevation of serum β -hCG level is a useful tool for screening choriocarcinoma. Successful treatment should incorporate a radical orchiectomy, retroperitoneal lymph node dissection, and chemotherapy. Standard induction chemotherapy regimen includes bleomycin, etoposide and cisplatin. Treatment should be directed towards a goal of tumor marker normalization, and shrinkage of tumor size. Patients with refractory disease should be considered for advanced combination chemotherapies like methotrexate,

etoposide and actinomycin D. Furthermore, high-dose chemotherapies of ifosfamide, carboplatin and etoposide with peripheral blood stem cell transplantation could be alternatively used for intractable choriocarcinoma with multiple lung metastases.

INTRODUCTION

Epidemiology

A germ cell tumor (GCT) is a common malignancy derived from germ cells that make up the reproductive system as testicular cells in the scrotal sac of males or ovarian cells in the pelvis of females. Most testicular and ovarian tumors are of germ cell origin. Testicular GCTs account for between 1% and 1.5% of male neoplasms and 5% of urological tumors in general, with 3-10 new cases occurring per 100,000 males per year in Western society [1]. The incidence of testicular carcinoma in Denmark had a high crude rate of 8 to 9 per 100,000 males per year [2]. Testicular GCTs are the most frequent solid tumor of Caucasian adolescents and young adult males. The peak incidence of diagnosis and presentation to GCTs in men is between the ages of 15-35 years [1].

Classification

GCTs constitute a heterogeneous group of tumors. They are classified broadly into seminomas and non-seminomas which are either undifferentiated embryonal carcinoma or differentiated patterns including embryonic teratoma, yolk sac tumor, and choriocarcinoma [3]. An increased incidence of testicular GCT over time was reported to be 1.6 cases per 1 million person-years in boys aged 0 to 14 years in the United States (US) from 1973 to 2000. Yolk sac tumor was the most common, followed by teratoma. Rates of choriocarcinoma and seminoma were equally rare [4]. While from 1955 to 1992, the age-specific incidence rate of testicular GCT (51% seminomas and 45% non-seminomas) increased from 2.7 to 8.5 per 100,000 in Norway, but the increased incidence was most marked in the younger population [5]. The incidence of mixed type of GCT is rising, whereas rates of the pure types of embryonal carcinoma, teratoma and choriocarcinoma have declined in the US and Germany [6]. Furthermore, in Germany almost all tumors were teratomas during infancy, while yolk sac tumor was the predominant histology during childhood. After the onset of puberty, GCTs often presented as mixed tumors with choriocarcinoma and embryonal carcinoma components [7].

Choriocarcinoma

Choriocarcinoma could present as a pure or a varying component (about 50% to 95%) of a mixed testicular GCT. Nonetheless, choriocarcinoma of testis is more commonly associated with other germ cell tumors, whereas pure choriocarcinoma is rare in testis, accounting for less than 1% of testicular GCT [8, 9]. Teratoma is considered a less aggressive type of GCT, while choriocarcinoma is the most malignant among GCTs in the testis [10]. Mixed GCT with a predominant choriocarcinoma component has similar aggressive behavior to pure choriocarcinoma with markedly elevated serum β -human chorionic gonadotropin (β -hCG)

levels (median, about 200,000 IU/L or mIU/mL) at presentation, easy lymphovascular invasion, distant organ metastasis, and highly fatal outcome [11]. On the contrary, a small component of choriocarcinoma ($\leq 5\%$) in a mixed GCT is typically associated with relatively low-level elevations of serum β -hCG levels (mean, $< 5,000$ mIU/mL), and is not associated with aggressive disease [12]. According to a large series of 1,058 consecutive testicular GCTs, increasing size of the tumors was associated with increasing frequency of metastatic disease but this association was not directly proportional [13]. Although choriocarcinoma mostly often involves metastases in the lungs and liver, occasional brain metastasis from testicular tumor with massive intratumoral hemorrhage carries a high risk of fatality [14]. As highly vascular nature, cerebral hemorrhages related to metastatic choriocarcinoma may be easily confused with occult vascular malformations [15]. The cases of extremely rare confluence of choriocarcinoma metastasis to arteriovenous malformation in the brain were ever reported [16, 17].

MANIFESTATION

Choriocarcinoma Syndrome

Choriocarcinoma is the most aggressive type of testicular GCT and characteristically metastasizes to the retroperitoneal lymph nodes and less frequently to the lungs, liver, brain, kidney or bone [18]. Hemorrhage from metastatic sites of tumors containing choriocarcinoma is named choriocarcinoma syndrome. The primary site of GCT in this syndrome may be advanced pure or mixed GCT containing large elements of choriocarcinoma [19]. For example, a patient of lung metastatic choriocarcinoma presented with bilateral massive hemothorax and hemorrhagic shock, whose primary lesion was mediastinal mixed GCT of mixed choriocarcinoma and teratoma [20]. A patient may bleed from his liver metastases leading to hemorrhagic shock [21]. In clinical practice, patients may experience fainting, generalized headache, spontaneous pain in the flank and bone, hypovolemic shock, consistent with symptoms in the brain, thorax and abdomen metastases, and die in retroperitoneal bleeding [22]. Clinician should also know the signs and symptoms of choriocarcinoma syndrome, which represents a medical emergency and is associated with high morbidity and mortality [23].

Non-traumatic simultaneous intracerebral hemorrhages in a background of tumorous lesions and highly elevated β -hCG ($> 300,000$ IU/L) are rare clinical presentations of choriocarcinoma syndrome [24]. Nonetheless, among the causes of hemorrhage from brain tumors, primary and metastatic choriocarcinoma and primary embryonal carcinoma seemed to the most frequent ones [25]. The choriocarcinoma syndrome usually occurs before and during the onset of systemic treatment with chemotherapy [19]. Hemorrhage occurs in two distinct settings: immediately after chemotherapy and in patients with rapidly progressive advanced disease [26]. On the one hand, physicians need to consider the risk of this syndrome while dealing with patients who presents with massive hemoptysis, and that indicates a rapidly progressive and high-component choriocarcinoma within the testicular tumors. On the other hand, physicians who treat advanced

testicular tumors with lung metastases should be aware of the potential complication of acute pulmonary hemorrhage [27]. Just after the induction of chemotherapy, massive hemorrhage at metastatic sites of choriocarcinoma occurs; for example, life-threatening hemothorax may ensue in a man with testicular GCT metastatic to the lung [28]. The choriocarcinoma syndrome is usually associated with life-threatening tumor lysis syndrome in huge tumors, resulting in additional acute renal failure and hyperuricemia [29-31]. Furthermore, choriocarcinoma syndrome may even occur after resection of primary pulmonary choriocarcinoma [32].

Burned-out Phenomenon

Burned-out testicular tumors refer to partial or complete histological regression of the primary testicular lesions. The most frequent GCT type involved in this kind of histological regression is choriocarcinoma, followed by embryonal carcinoma [33]. From immune histochemical studies of testicular choriocarcinoma in the early stage of development, some choriocarcinomas regress spontaneously in the early stage [10]. Therefore, it sometimes happens that primary choriocarcinoma at distant site with only fibrous scar or absence of the tumor in the testis, which has probably undergone early spontaneous regression [34].

Cerebral Metastasis

The mean age at presentation of cerebral metastasis from testicular choriocarcinoma is usually 25.5 years. Neurologic symptoms account for the initial presentation of 60% patients. Patients commonly manifest with headaches, drowsiness and vomiting. Patients may present with hemianopia when the lesions occur in the occipital lobe [17]. Cerebral metastases are prone to hemorrhage and associated with high morbidity. Outcomes are predominantly poor, with 67% patients expiring shortly after their initial diagnosis. Most causes of deaths are related to mass effect from metastasis-related massive hemorrhages or cerebral herniation even after emergent decompressive craniectomy [15, 24]. In an extremely rare condition, a metastatic choriocarcinoma may converge into a brain arteriovenous malformation [16, 17]. Early aggressive surgical removal of bleeding metastases and intracranial hematoma is advisable before general deterioration and may be beneficial in selected instances [14, 26].

Lung Metastasis

Of autopsy findings for 154 patients treated for testicular GCT, the most common sites of distant metastasis were lung (89%), liver (73%), brain (31%) and bone (30%) [35]. Patients with lung metastasis of choriocarcinoma typically present with hemoptysis and a lung mass [8]. Isolated pulmonary metastases from testicular tumors could be treated by surgery. Mortality and morbidity rates after thoracotomy are minimal [36]. Widespread lung metastases of choriocarcinoma may occur and the chest CT features show diffuse distribution of nodules in oval shape with peripheral enhancement and airspace consolidation in both lungs. Patients may present with hemoptysis, dry cough, chest pain and progressive dyspnea [37]. Pulmonary metastasis of choriocarcinoma could

be early detected by measurement of β -hCG during the earlier stages, in which some atypical cells positive for β -hCG proliferate in the pulmonary arteries, confirming the diagnosis of pulmonary embolic metastasis of choriocarcinoma [38].

Gastrointestinal Bleeding

Testicular GCT could be metastatic to the gastrointestinal tract and the most frequent site of gastrointestinal involvement is the proximal small intestine [39]. Cases of primary choriocarcinoma of the jejunum were also reported [40]. However, a primary lesion in other organs than intestine may be difficult to identify as it at times regresses spontaneously [41]. Although testicular mixed GCTs could be the primary lesions, element of choriocarcinoma is usually pure or highly present in the metastatic sites [42, 43]. The most common gastrointestinal tract manifestations are intestinal obstruction and upper gastrointestinal bleeding [44]. Young patients may have suffered from severe intestinal hemorrhage for several weeks due to metastatic choriocarcinoma to the jejunum [45, 46]. Several cases of duodenal metastasis from a testicular choriocarcinoma have been reported [41, 47-49]. Even rarer cases of metastatic choriocarcinoma to stomach or spleen have still been reported [50-54]. Acute hemoperitoneum or intraperitoneal hemorrhage may be due to spleen bleeding or ruptured spleen, liver, intestine or retroperitoneal lymph node caused by a metastatic choriocarcinoma [55-57]. Choriocarcinoma of the colon could present as life-threatening lower gastrointestinal bleeding and immunohistochemical positivity for β -hCG and carcinoembryonic antigen (CEA) in neoplastic syncytiotrophoblasts should not be interpreted as primary colonic adenocarcinoma [58, 59].

Wunderlich Syndrome

Spontaneous renal hemorrhage or hematoma (known as Wunderlich syndrome) secondary to metastatic choriocarcinoma has previously been reported in young patients [46, 60, 61]. The renal angiogram may show multiple microaneurysms arising from the distal renal artery, mimicking systemic necrotizing vasculitis [46, 62]. The patients with choriocarcinoma of the kidney may initially present with fever, gross hematuria and/or intense flank pain [63-65].

Cutaneous Metastasis

Skin metastasis is extremely rare and could be the first sign of testicular choriocarcinoma that leads to medical consultation. Nonetheless, it could have already progressed to the advanced stage of the disease [66]. The skin presentation could include cutaneous or subcutaneous mass, angioma-like tumor or multiple reddish nodules located at the adjacent groin areas or distant sites such as scalp, chin, neck, sternum, chest or back [66-73]. The combination of highly atypical mononuclear cytotrophoblasts and multinucleated malignant syncytiotrophoblasts are characteristic of metastatic choriocarcinoma [73]. The primary site may be a pure testicular choriocarcinoma or mixed GCT [74-76]. Concurrent systemic organ metastasis is common [77, 78]. The unusual variant of testicular choriocarcinoma may imply the potential behavior of aggressive metastasis and poor prognosis [68, 69, 78].

DIAGNOSIS

Imaging studies

All patients should undergo a bilateral scrotal ultrasound. The findings of computed tomography (CT) scan and CT angiography for a testicular GCT with distant metastasis may include:

Multiple hemorrhagic metastatic tumors within the brain (Figure 1).



Figure 1: Brain CT of a young man with testicular germ cell tumor is showing three hemorrhagic metastatic tumors with perifocal edema within the cerebral hemisphere, including one large hematoma (4.6 x 2.5 cm) at right frontal base, causing mass effect and midline shifting; another hematoma (2.6 x 2.0 cm) at left high parietal region; and one small hematoma(2.0 x 1.0 cm) at left high frontal region.

- ◆ Intracerebral hematoma communicating with the ventricular system
- ◆ Occlusion of the medial cerebral artery [79]
- ◆ Subarachnoid hemorrhage as ruptured oncotic aneurysms from metastasis [80, 81]
- ◆ Confluence of metastatic tumor into the brain arteriovenous malformation [16,17]
- ◆ Multiple hypervascular pulmonary masses and nodules (Figure 2).

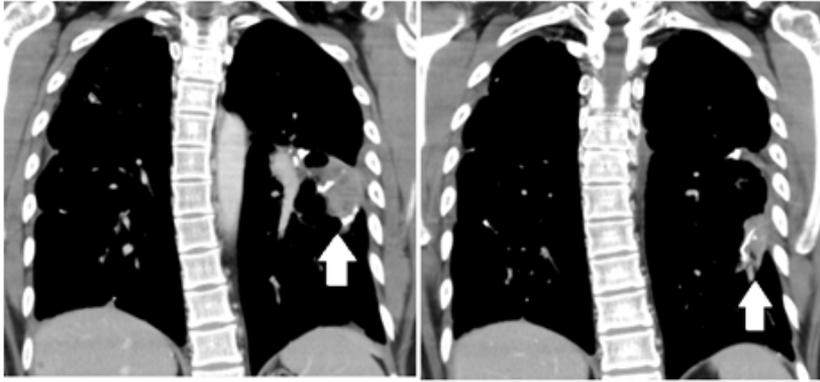


Figure 2: Chest CT of a young man with testicular mixed germ cell tumor is showing metastatic lesions including one heterogeneously-enhanced mass (arrow) and another hypervascular nodule over left lower lung (arrow).

- ◆ Acquired arteriovenous fistula in pulmonary metastases [82]
- ◆ Primary mediastinal abnormality with paraesophageal/subcarinal mass [79]
- ◆ Widespread metastatic diseases involving the head, lungs, liver, pancreas, kidneys, retroperitoneal lymphnodes and/or breast [83, 84] (Figure 3).

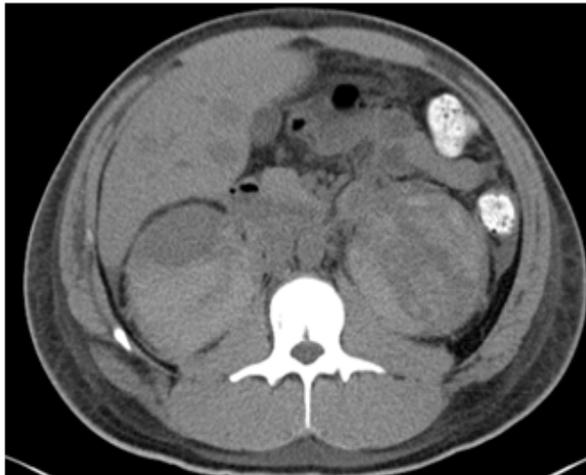


Figure 3: Abdomen CT of a young man with testicular germ cell tumor is showing metastatic diseases involving the liver (multiple hypodense nodules), kidneys (bilateral perirenal hematoma) and retroperitoneal lymph nodes (metastatic lymphadenopathy).

- ◆ A large renal and perirenal hematoma [46]
- ◆ A hypervascular renal mass with multiple small aneurysms [46]
- ◆ A huge peritoneal tumor [31]
- ◆ Intraperitoneal hemorrhage or hemoperitoneum [55, 56]
- ◆ Para-aortic lymphadenopathy [31]
- ◆ A large retroperitoneal mass [85]

Tumor Markers

The three common tumor markers including β -hCG, α -fetoprotein (AFP) and lactate dehydrogenase (LDH) will be elevated in 51% of patients diagnosed with a testicular GCT [5]. LDH is a very nonspecific biomarker. Furthermore, AFP and β -hCG display limited sensitivity and specificity, indicating yolk sac tumor (AFP) and choriocarcinoma (β -hCG), respectively. Consequently, seminoma and embryonal carcinoma are generally negative for these conventional markers [86]. In a study of 170 patients with testicular GCTs, 28% of patients with non-seminomas had raised serum AFP as well as β -hCG; 65% of patients with non-seminomas had raised serum AFP; and 29% of patients with non-seminomas had raised serum β -hCG [87].

Histopathology

Seminoma is not only the most common testicular neoplasm but it is also the only malignant testicular tumor that is commonly treated with radiation, which is ineffective in other malignancies of the testis [88]. Therefore, accurate diagnosis of testicular GCT to differentiate seminomas from non-seminomas has major important therapeutic and prognostic implications. Seminoma appears to represent the invasive derivative of intra-tubular germ cell of neoplasm. Spermatocytic seminoma is an essentially non metastasizing neoplasm. Cytoplasmic membrane immunoreactivity of immunohistochemical stains for placental alkaline phosphatase and CD117 as the receptor for stem cell factor, with usual negativity for AE1/AE3 cytokeratins, is helpful in the diagnosis of seminoma [89-91]. Embryonal carcinomas usually occur admixed with other germ cell tumor types. Yolk sac tumor is characterized by numerous patterns including glandular, myxomatous, sarcomatoid, hepatoid, and parietal variants. Glypican 3 (GPC-3) is a membrane-bound heparan sulfate proteoglycan, which has recently been identified as a useful immunohistochemical marker for liver cancer and yolk sac tumors. GPC-3 could be used as part of a panel of markers in sub typing testicular germ cell tumors in distinguishing yolk sac tumors and choriocarcinomas [92].

Choriocarcinomas classically have a biphasic pattern of syncytiotrophoblast and cytotrophoblast [93]. The majority of choriocarcinomas seem to develop initially going through the embryonal carcinoma phase. However, there are some choriocarcinomas that show no relationship with embryonal carcinoma [10]. Choriocarcinoma commonly shows hemorrhagic

nodular cysts and extensive necrosis surrounded by variable layers of neoplastic trophoblastic cells (mononucleated trophoblasts and syncytiotrophoblasts). The syncytiotrophoblasts usually cover columns or plexiform of malignant trophoblasts with abnormal mitosis and abundant amount of eosinophilic or vacuolated cytoplasm [11]. The β -hCG, made by fused villous syncytiotrophoblast cells, is a well-established marker of syncytiotrophoblast proliferation [94]. Prominent syncytiotrophoblast giant cells suggest choriocarcinoma. In mixed germ cell tumors, immunoperoxidase staining for β -hCG has been historically used to assess for the presence and burden of choriocarcinoma [95]. Immunohistochemically, cytokeratin (AE1/AE3) stains all types of trophoblastic tissue. Therefore, the tumor cells of choriocarcinoma express β -hCG and cytokeratin (AE1/AE3), but are negative for CD117 and AFP [89, 90].

MANAGEMENT

Surgery

A radical orchiectomy (also named orchidectomy) by inguinal approach (also called inguinal orchiectomy) is a definitive treatment of testicular cancer. As the testicle is drained by the retroperitoneal lymphatic system, successful treatment incorporates a number of other modalities, including retroperitoneal lymph node dissection (RPLND), chemotherapy and radiation. The mean testicular tumor size of GCT was 6.5cm (range, 1.5 to 8cm) [11]. Men with a mixed GCT with $\leq 5\%$ choriocarcinoma at radical orchiectomy revealed a median testicular tumor size of 4.5 cm (1.1 to 8.0cm) [12]. The lymphatic spread of GCTs usually involves the retroperitoneal lymph nodes. Therefore, the gold standard approach for a testicular GCT is the open surgery for radical orchiectomy and retroperitoneal lymphadenectomy [78].

Approximately 30%-50% of patients with disseminated testicular cancer who receive platinum-based chemotherapy will experience normalization of tumor markers but still have radiographically evident disease in the retroperitoneum. The retroperitoneal residual masses reveal findings of necrotic debris or fibrosis (mean mass size about 5cm), and near 50% of them contain teratoma (growing teratoma or already has undergone malignant transformation). These patients are usually subjected to RPLND, which remains the gold standard for patients with residual masses in the retroperitoneum [96]. Retroperitoneal recurrence is essentially eliminated when RPLND is performed in some select patient group with early stage GCT confined to the testis and persistently increased tumor markers [97]. Patients undergoing post-chemotherapy RPLND have a considerably smaller chance of residual viable GCT in the retroperitoneum if they have factors of absence of teratoma in the primary testicular tumor and shrinkage of 35% or more in retroperitoneal mass [96]. Robot-assisted laparoscopic RPLND has added benefits of robotic technology and is becoming more widely adopted for residual disease after completion of orchiectomy and chemotherapy [98, 99].

Chemotherapy, followed by an aggressive surgical resection of residual disease, can result in eradication of testicular GCTs. Serial serum levels of β -hCG and AFP are useful for monitoring

disease activity of the tumors. After induction chemotherapy, the transition of elevated serum tumor markers to normal levels suggests that malignant disease has been eliminated or converted to teratoma. Elevated markers indicate persistent or recurrent GCTs and mandate further chemotherapy [100]. If normalization of tumor markers occurs, any distant residual mass in the abdomen, chest, or neck should be surgically resected [101]. Selective neck dissection can be safely performed for cervical lymph node metastasis [101,102]. Resection of a distant lung metastasis of choriocarcinoma may be performed if no evidence of multiple pulmonary metastases and mediastinal lymph node metastasis. However, patients might develop choriocarcinoma syndrome with massive hemoptysis even after lobectomy with lymphadenectomy [32]. For Wunderlich syndrome, emergency partial nephrectomy and angioembolization could be carried out for successful control of renal hemorrhage [46].

Chemotherapy

First-line induction chemotherapy with bleomycin, etoposide and a platinum analogue cisplatin (BEP) combination chemotherapy (bleomycin 30U/week, etoposide 100 mg/m²/d x4d, cisplatin 25 mg/m²/d x4d) should be started the day after an orchiectomy [27]. After 3 cycles of BEP chemotherapy, the tumor marker β -hCG levels are almost restored to normal levels, and radiography could show a clinical partial response. A regimen of reduced BEP dose regimen may reduce the risk of acute respiratory failure with intra-alveolar hemorrhage related to post-chemotherapy early tumor necrosis [103]. On the contrary, if normalization of tumor markers could not be achieved, salvage chemotherapy with methotrexate, etoposide and actinomycin D (MEA) could be used for a choriocarcinoma component with resistance to intensive conventional chemotherapies. The MEA regimen includes methotrexate, 450mg/body on day 1; actinomycin D, 0.5mg/body on days 1-5; and etoposide, 100mg/body on days 1-5 [104].

Furthermore, for choriocarcinoma with multiple lung metastases, a patient has achieved continuous remission for 2 years after BEP combination induction chemotherapy and sequential high-dose chemotherapy with autologous peripheral stem cell transplantation rescue. The high-dose chemotherapy regimen consisted of ifosfamide 2,500mg/m², carboplatin 500mg/m² and etoposide 600mg/m² (ICE); this was intravenously given for 3 consecutive days [105]. The high-dose ICE with peripheral blood stem cell rescue for intractable choriocarcinoma is effective and tolerable [106, 107]. For malignant GCTs in children with predominance of germinoma and teratoma, chemotherapy with carboplatin, etoposide, and bleomycin (JEB) produced high cure rates and few serious complications [108]. For nonseminomatous germ cell tumor of the testis, even when extensive metastatic disease is present, it is very sensitive to chemotherapy with cisplatin, vinblastine, and bleomycin (PVB). But multiple brain metastases need whole brain radiation therapy plus a rigorous chemotherapeutic regimen that penetrates the blood-brain barrier better than PVB [109]. Cisplatin and large doses of methotrexate with the leucovorin rescue method has shown a remarkable response against the brain metastasis of choriocarcinoma [110].

CONCLUSION

Testicular GCTs often present as mixed tumors with choriocarcinoma component. Among GCTs in the testis, choriocarcinoma is the most malignant and easily metastatic, often involving in the lungs, liver and occasional brain metastasis. Non-traumatic simultaneous intracerebral or organ hemorrhages in a background of tumorous lesions and highly elevated serum β -hCG are characteristic presentations of choriocarcinoma syndrome, which should highly alert the physicians as a medical emergency and a high risk of mortality. Early aggressive surgical removal of bleeding metastases and intracranial hematoma is advisable before general deterioration. Isolated intracranial or pulmonary metastases from testicular tumors could be treated by surgery. The gold standard approach for a testicular GCT is the radical orchiectomy, retroperitoneal lymphadenectomy and adjuvant chemotherapy. Serum β -hCG and retroperitoneal mass are useful for monitoring disease activity and tumor recurrence.

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