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Testicular Mixed Germ Cell Tumor Combined with Malignant Transformation to Chondrosarcoma: A Very Rare and Aggressive Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1 Mohammad Alrehaili
EF 2,3 Emad Tashkandi

1 Department of Internal Medicine, King Abdullah Medical City, Makkah, Saudi Arabia
2 Department of Internal Medicine, Umm Alqura University, Makkah, Saudi Arabia
3 Department of Medical Oncology, King Abdullah Medical City, Makkah, Saudi Arabia

Corresponding Author: Mohammad Alrehaili, e-mail: dr.rehaili@hotmail.com
Conflict of interest: None declared

Patient: Male, 31-year-old
Final Diagnosis: Testicular mixed germ cell tumor
Symptoms: Hemoptysis • shortness of breath • testicular mass
Medication: —
Clinical Procedure: Chemotherapy • CT guided lung biopsy • CT scan • orchiectomy
Specialty: Oncology

Objective: Unusual clinical course

Background: Testicular mixed germ cell tumors (GCTs) represent a spectrum of malignancies that differ in terms of histopathology, clinical complications, and overall outcome. A variety of aggressive combinations containing different histological types have been described among such testicular tumors. However, a histopathology characterized by a combination of teratoma and choriocarcinoma, as seen in this case, in which the teratomatous component shows a secondary transformation to chondrosarcoma, is considered very rare.

Case Report: The patient presented with progressive hemoptysis and dyspnea secondary to bilateral pulmonary cannon-ball lesions indicative of a metastatic process. His workup was remarkable for primary testicular cancer complicated by liver metastasis and very high levels of B-HCG at more than 175 000 mlU/ml. He deteriorated quickly with no improvement following the first cycle of Etoposide/Cisplatin (EP) chemotherapy regimen and died 15 days after starting cancer treatment. Such non-seminomatous GCTs with extrapulmonary visceral metastasis associated with very high tumor markers are deemed poor risk based on the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria, with a reported 5-year overall survival rate reaching up to 73%.

Conclusions: This case is considered unique in terms of rapid clinical deterioration and lack of improvement following the standard EP chemotherapy regimen. This unusual dramatic presentation should draw attention to the possible association between the aggressiveness of the disease and its very rare histopathology.

MeSH Keywords: Chondrosarcoma • Choriocarcinoma • Mixed Tumor, Malignant • Teratoma • Testicular Neoplasms

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Background

Primary testicular malignancies are the most common solid malignant tumor in men 20–35 years of age in the United States. Mixed GCTs of the testis contain 2 or more germ cell components and constitute around 30% of the primary testicular neoplasms [1]. Although they are considered the second most common type after pure seminoma in terms of prevalence among GCTs in adults, there are some histological subtypes which were rarely reported. In this article, we present an extremely aggressive case with very rapid deterioration, which was found to be a mixed GCT consisting of teratoma and choriocarcinoma, in which the teratomatous component showed a secondary transformation to chondrosarcoma. There are a few cases described in the literature with a similar histological combination [2], but the malignant transformation of the teratomatous component into chondrosarcoma was lacking. These unique histopathological findings should be considered as a contributing factor to the severity and aggressiveness of testicular cancer, as seen in this case.

Case Report

A 31-year-old Saudi man was referred to our medical center for 1-month history of blood-tinged sputum. His chest x-ray revealed bilateral cannon-ball lesions suggestive of metastases (Figure 1). Upon evaluation, the patient reported dyspnea and required 3 liters of oxygen. His performance status, based on Eastern Cooperative Oncology Group (ECOG) scale, was 1. CT chest was performed and showed multiple large pulmonary nodules and masses with central necrosis causing

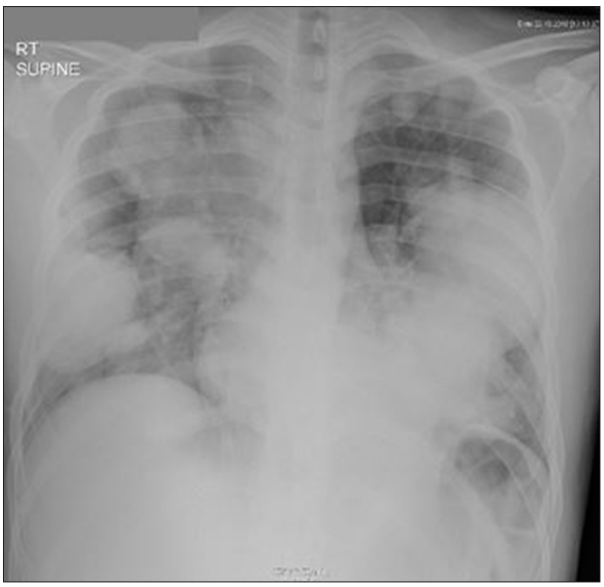

Figure 1. Chest x-ray shows bilateral cannon-ball lesions suggestive of metastasis.

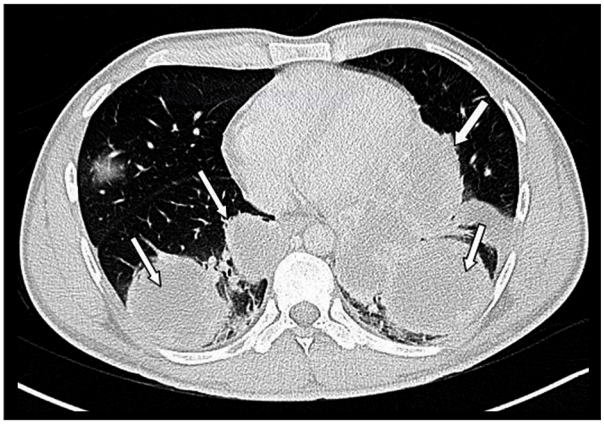

Figure 2. CT scan of the chest shows multiple large bilateral lung masses as seen by the white arrows.

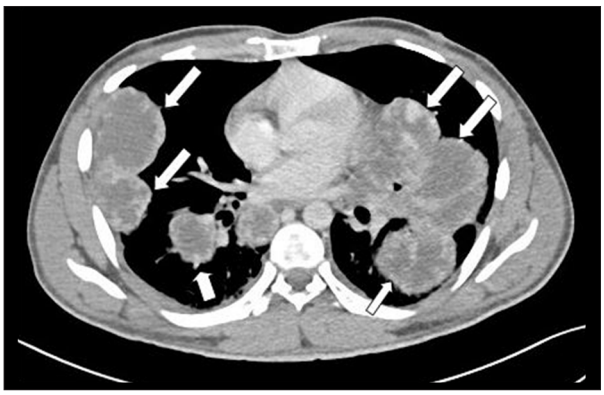

Figure 3. Chest CT mediastinal window shows large masses (white arrows) in both lungs and severe compression of the superior vena cava.

severe compression on the superior vena cava (Figures 2, 3). CT-guided core biopsy of the lung lesion showed changes consistent with a metastatic mixed germ cell tumor. Testicular physical examination was remarkable for a large mass in the right testicle, which was confirmed by a scrotal ultrasound showing a 5.5×4.1 cm lesion of increased irregular vascularity and multiple foci of calcification.

His B-HCG and LDH levels were elevated at 178 000 mIU/ml and 820 U/L, respectively. His AFP and CEA were normal. A complete blood count showed an elevated white blood cell count of 15×10^9/L and normocytic normochromic anemia with hemoglobin level at 8–10 g/dL. A tuberculosis workup including acid-fast bacilli (AFB) smear, and TB polymerase chain reaction was negative. Renal function tests were unremarkable. Liver enzymes were normal and total bilirubin was mildly elevated at 2.7 mg/dL, with direct component at 1.7 g/dL. An abdominal CT scan showed a large hypodense hepatic lesion with peripheral enhancement, measuring 3.4×2.3 cm involving segment VII, suggestive of a metastatic deposit (Figure 4).

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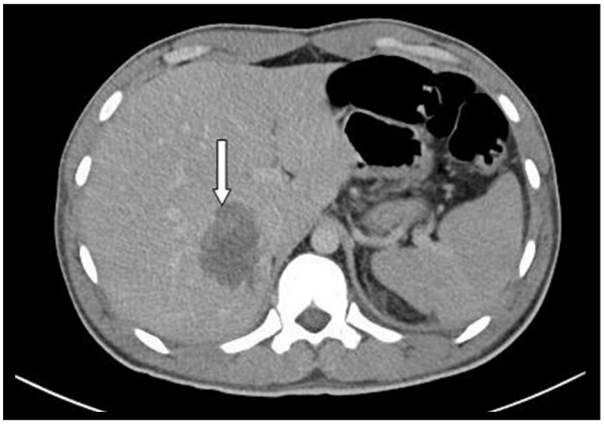

Figure 4. Abdominal CT shows a large hypodense hepatic lesion (white arrow) measuring 3.4×2.3 cm involving segment VII suggestive of metastasis.

The patient subsequently had right-sided orchiectomy, but lymph node dissection was not performed. The tumor was confined to the testis, with a size of 7×6×4 cm. The tunica albuginea and spermatic cord was grossly intact. Histopathology was compatible with the previous biopsy findings from the pulmonary lesion (Figures 5, 6). It confirmed the presence of mixed GCT containing teratoma (80%) with a somatic type malignancy and choriocarcinoma (20%). We found that 99% of the teratomatous component was composed of large lobules of hypercellular chondrocytes that were consistent with grade I chondrosarcoma, and the remaining 1% was characterized by cystic lesions lined by benign epithelial cells with occasional mucinous cells. There was lymphovascular invasion, and multifocal Leydig cell hyperplasia was observed. Immunohistochemistry stains displayed strong positivity for B-HCG, Cytokeratin 19, and placental alkaline phosphatase (PLAB) in the choriocarcinoma component.

During the patient's hospitalization, the hemoptysis was rapidly getting worse and his oxygen requirement had gradually increased. He was started on the standard EP chemotherapy protocol (5-day regimen) consisting of Etoposide and Cisplatin, with no improvement, and radiation therapy was planned. He received only 1 cycle of chemotherapy as his hospital course was complicated by increased oxygen demand requiring intubation with mechanical ventilation and hemodynamic support in the ICU.

A repeat chest x-ray showed no remarkable changes. A septic screen revealed growth of *Pseudomonas aeruginosa* in both sputum and blood. He was given broad-spectrum antibiotics including Vancomycin and Piperacillin/Tazobactam in addition to Granulocyte-colony stimulating factor (G-CSF), but he showed no signs of positive response, and then died after maximum resuscitative measures were performed.

Discussion

Mixed GCTs contain 2 or more germ cell elements, and their exact composition varies. Several distinct mixtures of these tumors have been described, but it was shown that certain combinations are more likely to occur, such as those containing teratoma and embryonal carcinoma [3,4]. In a review of 2589 patients with primary testicular tumors, of whom 1765 (68.2%) were diagnosed with mixed GCTs, the commonest histological element in mixed GCTs was embryonal carcinoma (in 84.4% of cases) and then teratoma (in 69.7%) and yolk sac tumor (in 60.1%) [1]. In contrast, the same study showed that the presence of choriocarcinoma with any other histological element was a rare finding, and its frequency was around 17.8% of cases.

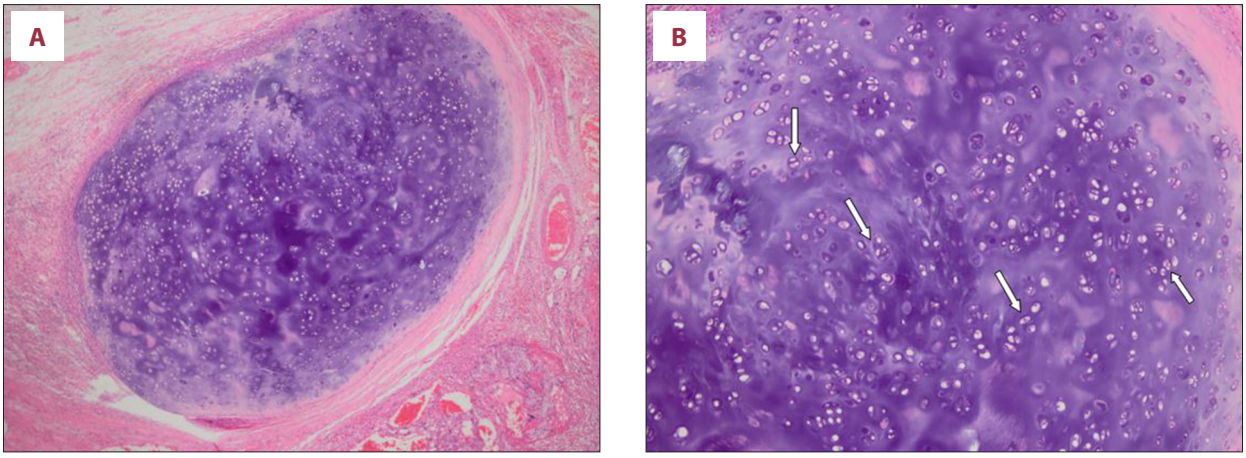

Figure 5. Teratomatous component of the testicular biopsy showing hypercellular chondrocytes consistent with grade I chondrosarcoma (**A**). A high-power image of the chondrosarcoma which demonstrates chondrocytes (white arrows) is also seen (**B**).

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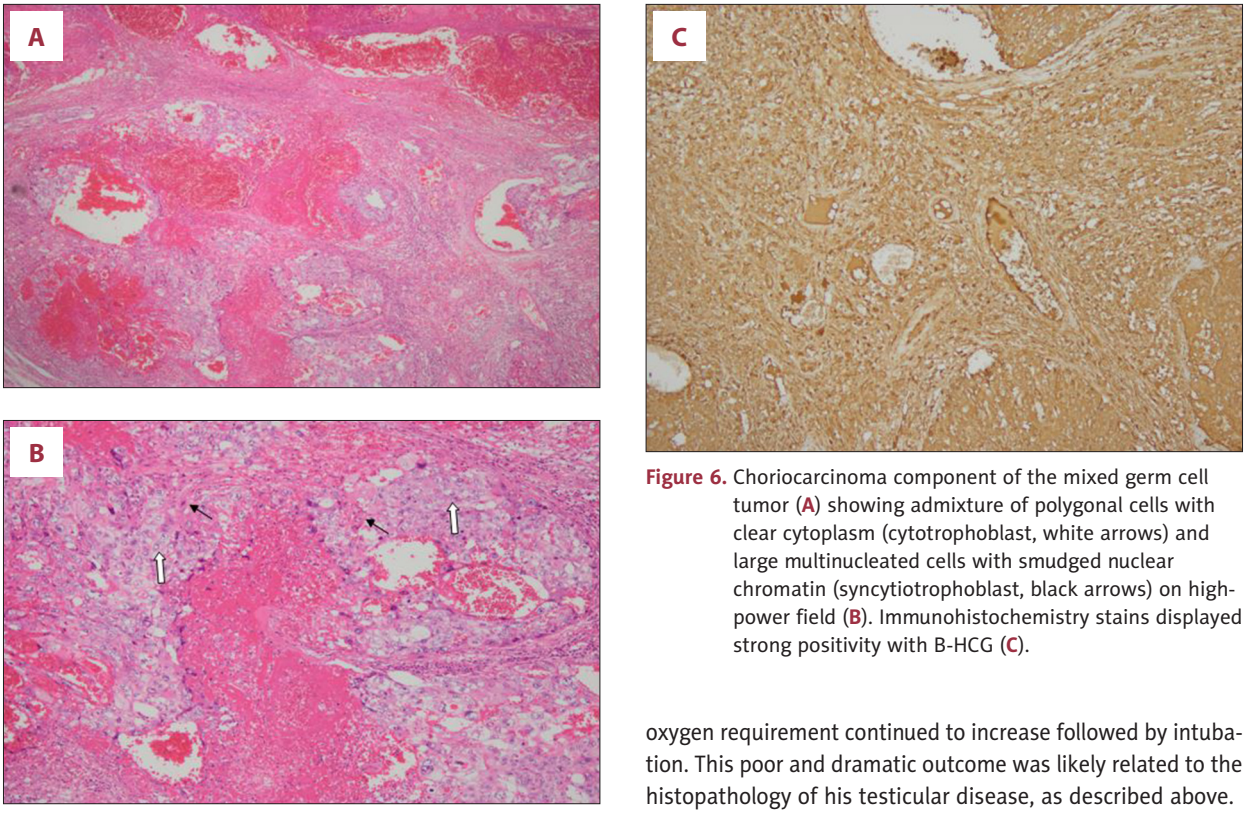

Figure 6. Choriocarcinoma component of the mixed germ cell tumor (**A**) showing admixture of polygonal cells with clear cytoplasm (cytotrophoblast, white arrows) and large multinucleated cells with smudged nuclear chromatin (syncytiotrophoblast, black arrows) on high-power field (**B**). Immunohistochemistry stains displayed strong positivity with B-HCG (**C**).

Somatic type malignant transformations (SMTs) in mixed GCTs is a well-known phenomenon, but is very rare. It occurs in around 3–6% of these tumors and is believed to develop as a result of malignant transformation of the teratomatous components, although other mechanisms might exist such as abnormal differentiation of primordial germ cells [2,5,6]. Tumors accompanied by malignant transformation are more likely to metastasize at presentation and have further aggressive potential than those without this phenomenon [7]. Among the most frequently delineated histologic transformations are sarcomas, mainly rhabdomyosarcoma, and carcinomas [8]. However, malignant transformation to chondrosarcoma, as seen in this report, is considered unusual and its association with choriocarcinoma has rarely been reported in the English literature.

Testicular tumor outcome depends largely on clinical stage. According to the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria [9], our patient would be classified to the poor risk group given the presence of non-seminomatous GCT, extrapulmonary visceral metastasis, and B-HCG >50 000. The 5-year overall survival can reach 73% [10] and the presence of pulmonary metastases usually does not imply an unfavorable risk group or staging of the disease. However, since his initial presentation, our patient had had bulky lung metastases in both sides with high tumor burden leading to progressive and rapid deterioration in his respiratory status. He received 1 cycle of EP chemotherapy without any improvement and his oxygen requirement continued to increase followed by intubation. This poor and dramatic outcome was likely related to the histopathology of his testicular disease, as described above.

We felt that the unusual histological types found in his testicular tumor should be considered as a significant factor that could critically influence the clinical course and contribute to further risk stratification of the disease. Our assumption was based on studies that show a significant association between SMTs to sarcomatous elements and increased disease aggressiveness with shortened survival compared to tumors without malignant transformation [6,11]. Moreover, choriocarcinoma is found to be the most aggressive histological type of all pure GCTs as it is fast-growing and can spread rapidly through the hematogenous route [12].

The development of SMTs in mixed non-seminomatous GCTs is a challenge in treating such cases. Several studies demonstrated chemoresistance in patients with transformed histology to Cisplatin-based chemotherapy regimens [11,13] that are usually associated with good outcomes in non-transformed malignant germ cell tumors. It was also suggested that chemotherapy should be adapted and targeted against the most aggressive histology for better outcome and disease control [5,13]. However, there is still no consensus regarding the optimal treatment of mixed non-seminomatous GCTs with malignant transformation [14], and further research is needed to establish clear treatment guidelines.

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Conclusions

Mixed GCT consisting of teratoma with SMT to chondrosarcoma associated with choriocarcinoma is a very rare type of testicular tumor. It seems to have a highly aggressive potential, which can critically influence the clinical course and prognosis. The optimal treatment for such tumors is poorly defined due to insufficient information.

Conflict of interest

None.

Acknowledgment

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