

Case Report

Metastatic Primary Testicular Neuroendocrine Carcinoma Associated with Somatic Malignant Transformation of Teratoma: A Rare Case Report

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Keywords

Testicular neuroendocrine tumor · Testicular teratoma · Somatic malignant transformation · Chemotherapy · Case report

Abstract

Testicular neuroendocrine tumor associated with teratoma is a rare disease. Very few cases have been reported in the literature, particularly cases involving visceral metastasis. Teratoma with somatic malignant transformation (SMT) is associated with a worse prognosis compared to teratoma without SMT. Previous data have suggested that chemotherapy regimens should be directed toward the transformed histology; however, those suggestions were based on patients with rhabdomyosarcoma, adenocarcinoma, and primitive neuroectodermal subtypes. To the best of our knowledge, only 2 cases with visceral metastasis have been reported, and a better outcome with the bleomycin/etoposide/cisplatin regimen, which responds strongly to germ cell tumors, has been reported in these cases. In contrast, 2 others with lymph node metastasis did not respond to these regimens. Here, we report a case of a patient with testicular neuroendocrine carcinoma associated with teratoma who achieved a good response to chemotherapy.

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Introduction

Testicular cancer is the most common cancer in young males who are aged between 14 and 44 years [1]. Although testicular cancer is uncommon and has an overall incidence of only 0.4% globally, the mortality rate of this disease is as high as 25% [2]. There is diverse histology among testicular cancer; nevertheless, germ cell tumors (GCTs) account for 95% of all testicular cancers [3]. The most common histologic classification of testicular GCTs (TGCTs) is pure seminoma. Nonseminomatous subtypes, which include embryonal carcinoma, teratoma, and yolk sac tumors, as well as mixed seminomatous and nonseminomatous component types, are less common but exhibit more aggressive behavior. Only 11% of all TGCTs are pure testicular teratomas [4].

Teratoma with somatic malignant transformation (SMT) is rare, occurring in only 3–6% of TGCTs. The most frequently transformed histologic types are rhabdomyosarcoma, adenocarcinoma, and primitive neuroectodermal tumor (PNET). Generally, they are more aggressive than teratomas without SMT and typically show metastasis at presentation with a high rate of recurrence [5]. Surgical resection is the mainstay therapy for localized disease due to its chemotherapy- and radiotherapy-resistant nature [6], whereas chemotherapy regimens directed toward either GCTs or transformed histology are the preferred treatments for metastatic disease.

Neuroendocrine tumors (NETs) are neoplasms that arise from the cells of neuroendocrine systems. Only 0.5% of all new cases are diagnosed with this malignancy. The most common primary sites of NETs are the gastrointestinal tract (62%–67%) and the lung (22%–27%). A primary genitourinary tract NET is rare, and it is more common in women than in men. Prostate is the most frequent site of a genitourinary NET in men, and testicular NET (TNET) accounts for only 0.2% of all testicular cancers [7]. Hence, TNET is an extremely rare malignancy.

TNETs are classified into pure primary NETs (76.5%), NETs associated with a testicular teratoma (16.7%), and testicular metastasis from other primary sites (6.8%), and the gastrointestinal tract is the most common (88.9%) primary site of testicular metastasis [8]. In the largest systematic review and meta-analysis in the literature, which included 132 patients with TNET, 22 patients were diagnosed with TNET associated with teratoma. Interestingly, no patient developed visceral metastases [8]. Until now, only 2 other cases of TNET arising from teratoma with visceral metastasis to the lungs have been reported in the English literature [9, 10]. Of note, one of those cases showed small-cell carcinoma histology. Accordingly, no epidemiologic information is available for TNETs associated with teratoma, and therefore, no standard treatment has been established. Herein, we report a rare case of testicular neuroendocrine carcinoma (TNEC), the most aggressive NET subtype arising from teratoma involving visceral metastasis, in a patient presenting with a right testicular mass.

Case Report/Case Presentation

A 37-year-old male with unknown underlying disease presented with a painless right testicular mass that had appeared 4 months earlier. The patient had no history of cryptorchidism and no family history of cancer. The patient was treated for orchitis with oral antibiotics from a private clinic, but his condition had not improved. The patient subsequently developed dyspnea on exertion, fatigue, and significant weight loss over a 2-week period. Therefore, he visited a provincial hospital for further investigation. Physical examination revealed a large right testicular mass around 8 cm in size with a firm consistency, mild tenderness, and no warmth or redness of the mass, while the left testis was normal. The liver could be palpated 4 cm below the right costal margin, and the liver span was 14 cm. Splenic palpation was negative,

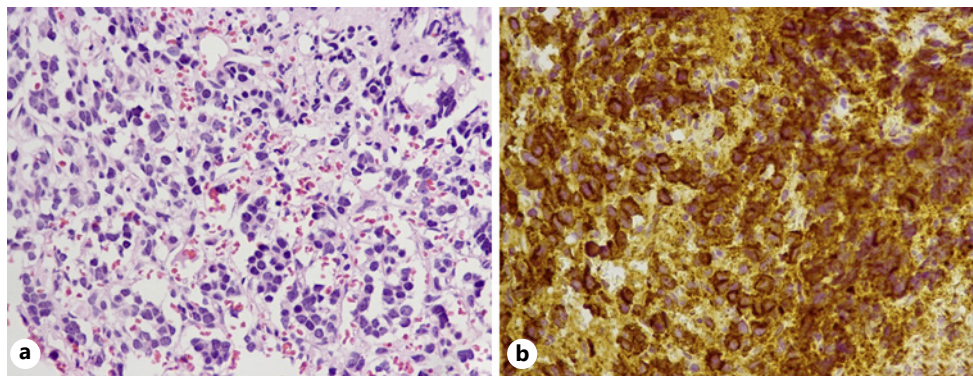


Fig. 1. Bone marrow pathology. **a** Extensive involvement by metastatic neuroendocrine carcinoma, high grade. **b** Tumor cells marked with chromogranin A.

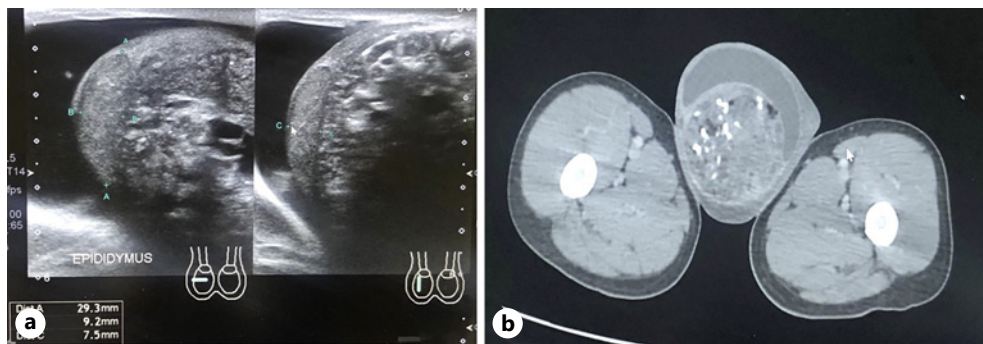


Fig. 2. Imaging. **a** Scrotal ultrasonography: Heterogeneous echogenicity of the right testicle with multiple calcifications with large cystic portion and a large amount of hydroceles. **b** CT scan: a 7.6 × 7.3 cm heterogeneous enhancing mass at the right testis with multiple internal calcifications and some small fat components, which are surrounded by hydroceles.

but he presented with positive splenic dullness. He also exhibited cachexia with moderately pale conjunctivae. Other measurements were within normal limits.

Given that the patient's clinical condition had not improved with oral antibiotics, surgical orchiectomy was planned. However, preoperative complete blood count showed anemia with thrombocytopenia (white blood cell count 5,560/μL, polymorphonuclear granulocytes 46%, L 36%, Mono 8%, Eo 4%, Band 2%, Meta 1%, nucleated red blood cell 12%, hematocrit 21.5%, hemoglobin 6.7 g/dL, platelets 55,000/μL); hence, the planned operation was terminated. A peripheral blood smear was reviewed; it revealed myelophthistic anemia. Bone marrow biopsy was subsequently performed; it demonstrated extensive metastatic neuroendocrine carcinoma (Fig. 1). Tumor cells were marked with CD56, chromogranin, synaptophysin, and neurospecific enolase but were not marked with CD3, CD20, CD34, CD30, CD61, myeloperoxidase, placental alkaline phosphatase, alpha-foetoprotein (AFP), AE1/AE3, desmin, or MyoD1. Subsequently, the patient was referred to our hospital with a diagnosis of metastatic neuroendocrine carcinoma.

Testicular ultrasonography showed a heterogeneous echogenicity of the right testicle with multiple calcifications with cystic portions, and a large amount of hydroceles (Fig. 2a). Chest and abdominal computed tomography (CT) scan (Fig. 2b) depicted a 7.6 × 7.3 cm heterogeneous enhancing mass at the right testis surrounded by hydroceles, with multiple internal calcifications, some small fat components, multiple periaortic lymph nodes sized 2.7–2.9 cm,

Table 1. Timeline of the treatment and laboratory results

Treatment	WBC, / μ L	Hct, %	Platelet, / μ L	AST/ALT, U/L	LDH, U/L
Cisplatin week 1	5,560	21.5	48,000	108/55	2,291
Cisplatin week 2	8,900	22.6	65,000	72/81	2,047
Cisplatin week 3–8	4,720	24.3	82,000	60/66	1,016
Right radical orchiectomy					
Cisplatin week 9	4,840	23.0	117,000	37/37	491
Cisplatin plus etoposide cycle 1 (20% dose reduction)	3,960	25.6	183,000	–	–
Cisplatin plus etoposide cycle 2 (20% dose reduction)	3,080	25.3	221,000	41/43	363
Cisplatin plus etoposide cycle 3 (20% dose reduction)	4,570	25	145,000	32/30	–
CT scan: progressive nodal and liver metastases					
CAV cycle 1	3,640	28.8	144,000	28/29	–
Complicated with pancytopenia and septicemia leading to clinical deterioration					

WBC, white blood cell count; Hct, hematocrit; AST/ALT, aspartate aminotransferase/alanine aminotransferase; LDH, lactate dehydrogenase; CAV, cyclophosphamide/doxorubicin/vincristine.

diffuse hepatosplenomegaly, and moderate right pleural effusion with minimal left pleural effusion. With reference to the typical radiological findings of testicular teratoma, a diagnosis of TNEC, suspected of arising from SMT of teratoma, was made along with multiple metastases to the bone marrow, liver, spleen, and intraabdominal lymph nodes. All serum tumor markers, including AFP and beta-human chorionic gonadotropin, were within normal limits, except lactate dehydrogenase levels, which were elevated (2,291 U/L).

Given the presence of significant thrombocytopenia, palliative right orchidectomy was not performed because of the bleeding risk related to surgery. Therefore, due to baseline bicytopenia, the patient received palliative chemotherapy with weekly cisplatin (40 mg/m²) instead of the combination chemotherapy using platinum plus etoposide. The patient tolerated weekly cisplatin relatively well. His clinical condition, blood counts, and serum lactate dehydrogenase were improved (Table 1). The abdominal CT scan after 8 weeks of chemotherapy demonstrated no new lesion with a slightly decreased size of the right testicular mass and lymph nodes, indicating stable disease. The patient then underwent right radical orchidectomy after demonstrating an adequate platelet count for palliative symptom management.

Gross pathology of the right testicular mass showed a gray-white/yellow, circumscribed, firm, solid mass, sized 8.5 × 7.0 × 6.5 cm, with fat, cartilage, sebum, and a few cystic components. The microscopic pathological report showed neuroendocrine carcinoma arising in a mature teratoma with the presence of lymphovascular invasion, spermatic cord involvement of the tumor, and a not free spermatic cord margin (Fig. 3). Tumor cells marked with CD56, chromogranin, synaptophysin, neurospecific enolase, and weak positive of desmin and S100. However, these cells were not positive for CD3, CD30, CD34, CD30, CD61, myeloperoxidase, placental alkaline phosphatase, AFP, AE1/AE3, and MyoD1. Ki-67 was 50% (Fig. 3).

Thus, the final diagnosis was neuroendocrine carcinoma of the right testis associated with SMT of a mature teratoma with bone marrow, intraabdominal lymph nodes, liver, and splenic metastasis. After improvement of clinical condition and blood count, chemotherapy was switched to a 3-week cycle of cisplatin plus etoposide, a standard regimen for NEC. Unfortunately, lymph node and liver metastases progressed after three cycles of combination chemotherapy

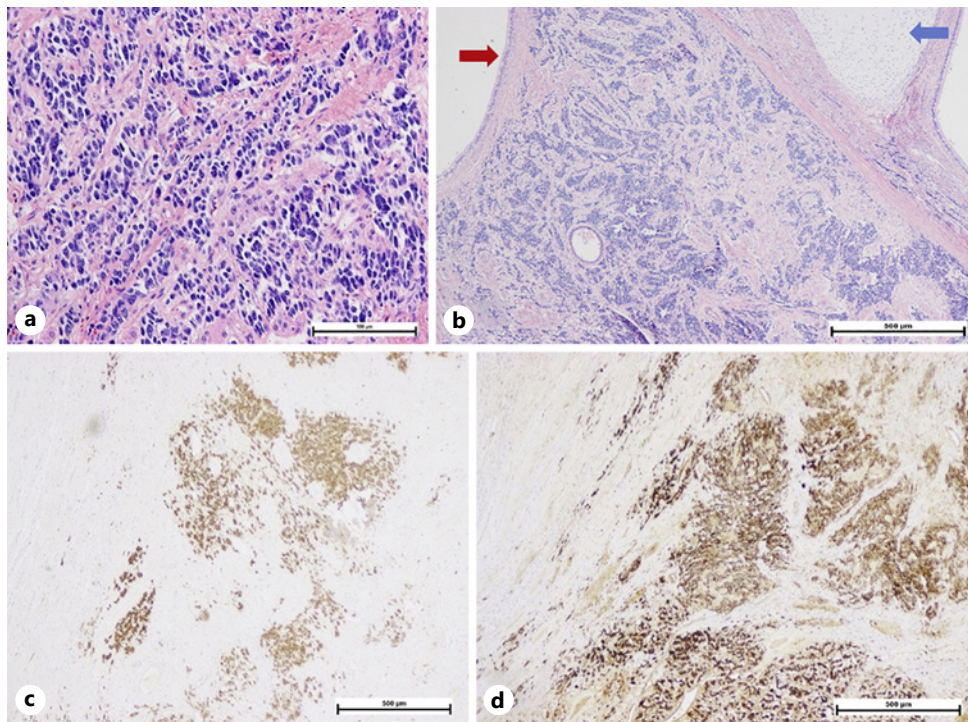


Fig. 3. Right testicular pathology. **a** Small-cell morphology with nuclear pleomorphism. Nest-like pattern with salt and pepper chromatin. Mitosis >20 /HPF. **b** Nest-like pattern comprising small-cell morphology located near the translucent and glassy matter, which is cartilage (blue arrow) and pseudo-columnar ciliated epithelium, which is consistent with respiratory epithelium (red arrow). **c** Immunohistochemistry staining is positive for synaptophysin. **d** Immunohistochemistry staining is positive for chromogranin A. HPF, high-power field.

in this patient. Consequently, the second-line palliative chemotherapy regimen, cyclophosphamide/doxorubicin/vincristine (CAV) was administered to the patient. Nevertheless, after only one cycle of CAV, the patient developed pancytopenia with septicemia leading to clinical deterioration. The patient survived for 6 months after diagnosis.

Discussion/Conclusion

Almost all testicular cancers (95%) are GCTs [3]. Testicular teratoma is found in only 11% of TGCTs [4]. Generally, the overall prognosis in testicular teratoma is excellent with a 5-year survival rate of almost 100% after curative resection for localized disease. Nonetheless, patients with metastatic teratoma have a poorer outcome due to chemotherapy- and radiotherapy-resistance, and curative resection is not applicable [11].

Testicular teratoma can be divided into various subtypes. A rare presentation is a testicular teratoma with SMT, which is associated with specific prognosis and treatment. The most frequently transformed histologic types are rhabdomyosarcoma, adenocarcinoma, and PNET, whereas the NET subtype is rare [5]. To date, only 24 cases of TNET arising in testicular teratoma have been reported, and only 2 of these cases involved visceral metastasis [8–10].

Our patient had similar clinical and radiological findings to the previously reported cases of TNET with teratoma in terms of age, presenting symptoms, and normal serum tumor markers (AFP, beta-human chorionic gonadotropin). Both ultrasonography and CT scans were also

typical of testicular teratoma. However, our patient had a larger testicular mass (8.0 cm) than that of the previously reported patient (3.69 cm). In addition, our patient developed widespread metastasis, involving the bone marrow, intraabdominal lymph nodes, the liver, and the spleen, whereas no visceral metastasis was reported in the previous study. This finding might be explained by the differences in NET subtypes, and NEC, the most aggressive form of NET, was seen in our patient. The more favorable prognosis of well-differentiated NET was reported in the previous study [8]. In another report on 2 TNET cases with lung metastasis, the tumor sizes were 12.0 and 10.8 cm. Of note, small-cell carcinoma transformation was reported in one of them [9, 10]. Taken together, teratoma with SMT, especially with high-grade malignant histology, should always be suspected in the case of a young male presenting with rapid growth of a huge testicular mass with typical imaging findings for testicular teratoma, particularly with metastatic disease.

The prognosis of GCT in patients with SMT is worse than in those without SMT. Metastasis is a feature in majority of the cases. Review of the literature suggests that large tumor size, low degree of tumor differentiation, and evidence of carcinoid syndrome are associated with a poor prognosis and the development of metastasis [8]. However, the clinical stage is the most important prognostic factor, suggesting that if the SMT is confined within the testis, there may be no differences in outcome between GCTs and GCTs with SMT [11, 12]. Unlike other GCTs, a teratoma, a histologic subtype representing terminally differentiated somatic tissue, is chemotherapy- and radiotherapy-resistant; hence, surgical resection remains the primary treatment for localized disease [13]. For patients with metastatic disease, radical orchiectomy is still beneficial in terms of symptomatic treatment and local tumor control because the testis is a sanctuary site, and the effects of chemotherapy are comparatively less in these areas [14]. Thus, radical orchiectomy is always recommended for any stage of teratoma.

Regarding metastatic teratoma with SMT, whether the preferred chemotherapy regimen is one directed at transformed histology or one directed at the GCTs remains controversial. However, the previous reports revealed good responses and long-term survival in selected patients who were treated with transformed histology-guided regimens. In such cases, SMTs, such as rhabdomyosarcoma, adenocarcinoma, PNET, and leukemia, received chemotherapy with the ifosfamide-based, fluoropyrimidine-based, P6 (CAV alternating with ifosfamide/etoposide), and high-dose cytarabine regimens [6, 15]. Meanwhile, data comparing the outcomes of chemotherapy in patients with teratoma and SMT to that of patients with TNET are limited. The largest meta-analysis of 24 cases with TNET reported only 2 patients with TNET associated with teratoma and lymph node metastasis. They received adjuvant chemotherapy with a BEP (bleomycin/etoposide/cisplatin) regimen after radical orchiectomy. However, chemotherapy generated no effect on the size of the metastatic lymph nodes after three cycles of BEP. The remaining patients in that report had localized disease, where radical orchiectomy was the only mainstay treatment applied [8].

So far, there are only 2 other case reports in the literature concerning patients with TNET associated with teratoma involving visceral metastasis. Türkmen et al. [9] reported a 44-year-old man with metastatic small-cell carcinoma associated with mature testicular teratoma and embryonal-cell carcinoma involving lung and lymph node metastasis. There was no information on Ki-67 reported. He underwent left orchiectomy and received a BEP chemotherapy regimen postoperatively. After four cycles of BEP, a partial response had been achieved. Two additional cycles of cisplatin/etoposide were administered, while bleomycin was omitted to prevent bleomycin toxicity. After 6 cycles of chemotherapy, no residual disease was observed on the positron emission tomography/CT scan (complete response), and no recurrence of disease occurred for 15 months [8]. Another case report from Prunoiu et al. [10] involved a 39-year-old man with metastatic TNEC associated with immature teratoma involving the lung, bone marrow, lymph nodes, and retroperitoneal metastasis. The histopathological analysis

from bone marrow showed poorly differentiated neuroendocrine carcinoma, but the Ki-67 was only 15%. Left orchiectomy was performed, followed by administration of a postoperative BEP chemotherapy regimen. The following magnetic resonance imaging and CT scan showed a substantial decrease in size at all metastatic sites. The patient had been clinically well 1 year since diagnosis [9]. Altogether, due to the inconsistent responses to the BEP regimen reported previously, the standard chemotherapy regimen for TNET associated with teratoma still cannot be established. However, the BEP chemotherapy protocol for GCTs should also be effective for NEC where the standard regimen involves a combination of platinum plus etoposide. In our report, we also demonstrated that the patient achieved a good response to chemotherapy containing platinum plus etoposide with the improvement of clinical status and bone marrow function.

Compared to patients in previous reports, our patient had a shorter overall survival of 6 months. This outcome in our case could be because of several reasons. First, the tumor in our patient had more aggressive pathological features with a high Ki-67 of 50% and a poorly differentiated histology. Second, our patient had a higher tumor burden with widespread metastasis at the time of diagnosis, which is common in this aggressive type of NEC. Finally, our patient had inadequate bone marrow function at baseline leading to the limited use of chemotherapy. The patient received only cisplatin weekly, which is less effective than combination with etoposide. Although he achieved good response to weekly cisplatin with the improvement of clinical status and blood work, this response occurred over a relatively short time. The patient developed rapidly progressive disease after three cycles of cisplatin and etoposide, confirming the aggressive nature of this disease.

In conclusion, we report a rare case of a patient with TNEC associated with teratoma who underwent radical orchidectomy and achieved a response to chemotherapy. Although almost all testicular cancers are GCTs, teratoma with SMT should be suspected in cases of rapidly enlarged testicular mass in young males with typical imaging of teratoma, especially with high-grade transformed histology, including NEC.

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Statement of Ethics

This study protocol was reviewed and approved by the local Ethic Committee at Research Center of Prince of Songkla University, approval number REC.64532143. Written informed consent was obtained from the patient's relative for the publication of this case report. Information revealing the subject's identity was avoided. All identifying information has been removed from this case report to protect patient privacy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.W. searched the literature and wrote the manuscript. A.D. edited the manuscript. P.S., C.S., and A.D. supervised the patient treatment. K.K. provided the pathology images. All authors have made significant contributions to the manuscript and have reviewed it before submission. All authors have approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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