A Rare Case of a Testicular Teratoma Associated with a Neuroendocrine Tumour

Virgiliu Mihail Prunoiu¹, Augustin Marian Marincas¹, Aurelia Alexandru², Mădălina Radu³, Tudor Marian Proca¹, Maria Manuela Răvaș¹, Eugen Brătucu¹, Sinziana Ionescu¹

¹"Carol Davila" University of Medicine and Pharmacy, First Clinic of General and Oncologic Surgery,

"Al. Trestioreanu" Oncology Institute, Bucharest, Romania

²"Second Clinic of Medical Oncology, Al. Trestioreanu" Oncology Institute, Bucharest, Romania

³Pathology Department, "Al. Trestioreanu" Oncology Institute, Bucharest, Romania

Corresponding author:

Augustin Marian Marincas, MD
"Carol Davila" University of Medicine
and Pharmacy, First Clinic of General
and Oncologic Surgery, "Al. Trestioreanu"
Oncology Institute, Bucharest, Romania
E-mail: marian_marincas_11@yahoo.com

Rezumat

Caz rar de teratom testicular asociat cu tumoră neuroendocrină

Introducere: Lucrarea își propune să prezinte cazul rar al unui teratom testicular combinat cu tumoră neuroendocrină și să sublinieze dificultatea diagnosticului clinic, paraclinic, a posibilităților terapeutice și evolutive ale acestor pacienți.

Prezentare caz: Pacienții cu tumori neuroendocrine testiculare reprezintă o raritate, până în 2017 erau 22 cazuri raportate în bazele de date internaționale. Cazul operat în clinica noastră prezenta o asociere de teratom testicular cu tumoră neuroendocrină. Vârsta de diagnosticare a fost de 39 de ani, pacientul fiind internat în Clinica de Chirurgie cu o tumoră abdominală nedureroasă și prezentând o masă tumorală testiculară voluminoasă. Markerii tumorii serice (β-gonadotrofina corionică umană, α-feto proteina și lactat dehidrogenaza) au fost în limite normale. Metastazele pulmonare și osoase au fost diagnosticate prin CT. Diagnosticul a fost tranșat prin teste de imunohistochimie după orhiectomie și puncție medulară.

Concluzii: Diagnosticul carcinoidelor testiculare se bazează pe studiul imunohistochimiei. Tratamentul de alegere pentru aceste tumori este orhiectomia radicală. Chimioterapia a determinat reducerea determinărilor pulmonare și osoase și dispariția metastazelor ganglionare.

Cuvinte cheie: cancer testicular, tumori neuroendocrine

Received: 02.03.2019
Accepted: 12.04.2019

Abstract

Introduction: We report a rare case of testicular teratoma combined with a neuroendocrine tumour, emphasizing the difficulty of the following aspects: the clinical and laboratory diagnosis, the treatment options and the evolution of patients suffering from this disease.

Case presentation: The patients with testicular neuroendocrine tumours represent a rarity, considering that as of 2017, only 22 cases had been reported in the literature. The case operated on in our clinic presents an association between a testicular teratoma and a neuroendocrine tumour. A 39-year-old patient was admitted in our Department for a non-painful abdominal tumour and concomitant testicular tumour. The serum tumour markers (β -human chorionic gonadotropin, α -fetoprotein and lactate dehydrogenase) were within normal limits. Lung and bone metastases were diagnosed CT scan. The histopathological diagnosis consisted of immunohistochemical study of the orchidectomy specimen as well as of the bioptic material from bone marrow puncture.

Conclusions: The diagnosis of testicular carcinoids is based on immunohistochemistry study. Radical orchidectomy is the only potentially curative treatment for this type of malignancy. Adjuvant chemotherapy determined size reduction of the lung and bone metastases and the disappearance of the lymph node metastases.

Key words: testicular cancer, neuroendocrine tumours

Introduction

Neuroendocrine tumours (NET) include tumours with heterogeneous clinical and biological manifestations, and, also in which regards the primary site, the hormonal secretion and the differentiation degree (tumour grading).

World Health Organization (WHO) classifies the neuroendocrine tumours into 3 grades:

- well-differentiated neuroendocrine carcinomas (corresponding to the classic carcinoid);
- moderately-differentiated neuroendocrine carcinomas (corresponding to the atypical carcinoma);
- poorly-differentiated neuroendocrine carcinomas (corresponding to the small cell carcinoid) (1).

All the classification systems show a clear difference between well differentiated tumours and poorly differentiated ones (neuroendocrine carcinomas of the G3 type, including the small and large cell variations). The emphasis of this difference is useful due to the different behaviour patterns of the tumours, as the poorly differentiated forms are very aggressive.

The Ki67 proliferation marker offers a good evaluation of the proliferation rate and is used to separate the well-differentiated neuroendocrine tumours from (low/intermediary degree) from the poorly differentiated ones (high degree) (1).

Only 22 cases of testicular teratomas associated with a neuroendocrine testicular tumour were reported between 1930 and 2017 in the literature. This particular tumour form represents only 1% from the total of the testicular tumours (2).

The mean age at the time of diagnosis is 39 years. The initial complaint consists of: testicular mass (38.4%), carcinoid syndrome (10.6%), and abdominal mass (44.7%), respectively. The testicular and abdominal tumours are non-painful. The tumour markers (β -chorionic human gonadotropin, α -fetoprotein and lactate dehydrogenase) are within normal limits in the majority of the patients. Also, chromogranin, synaptophysin and cytokeratin levels can be measured, and they can be positive in 90-100% of patients. Metastases are diagnosed in 6% of the cases. The recommended treatment in these cases is orchidectomy. The 5 year survival rate is approximately 84% (2).

Case Report

A 39-year-old patient, was admitted in The First Clinic of General and Oncologic Surgery of the "Al. Trestioreanu" Bucharest Oncology Institute in Bucharest, for a testicular tumour. The clinical exam confirmed the presence of a left testicular tumour with a diameter of 10/8 cm, with a normal contralateral testicle. Palpation of the abdomen, revealed another tumour with diameter of 10/7 cm, situated in the left hypochondrium and adherent to the more profound layers. Both the testicular and the abdominal tumour were not painful.

The patient initially presented to the neurologist for lumbar pain and right facial paresis. A MRI of the spine was performed and osteolytic lesions were found at the C3-T3 and T11-S2 levels. A clinical suspicion of multiple myeloma was ruled out via blood smear analysis. The histopathological analysis of a bone marrow biopsy showed bone metastasis of poorly differentiated neuroendocrine carcinoma and also ruled out multiple myeloma (positively diffuse for pan-cytokeratin AE1/AE3, CD56 and Synaptophysin, but negative for Chromogranin, positive for CD117, negative for Vimentin – a mesenchymal marker).

A repeat whole body MRI showed, besides

the known bone lesions, a bulky retroperitoneal mass located anterior to the left kidney. The tumour had a few necrotic areas and was intensely heterogenic. A 19/17 mm metastasis was described in the superior lobe of the right lung. Multiple lymph node metastases were found in the lumbar aortic, left iliac and left supraclavicular areas. An intensely heterogeneous tumour with a diameter of 9.5/8.3 cm was described in the left testicle infiltrating the sperm cord up to the level of the inguinal canal (*Fig. 1*).

Tumour markers: β -human chorionic gonadotropin, α -fetoprotein and lactate dehydrogenase were within normal limits. The patient was mildly anaemic, with a haemoglobin level of 10.9 g/dL

Clinically, the patient did not describe manifestations similar to the carcinoid syndrome and 5-hydroxy-indolacetic acid (5-HIAA) was negative in the urin. Serum serotonin and vanillylmandelic acid were not tested.

The tumour board meeting decided for surgical intervention as the first therapeutic step. Consequently, left orchidectomy was performed, with the sectioning of the sperm cord at the level of its entrance into the deep inguinal orifice (*Fig. 2*).

Figure 1. MRI exam of the thorax, abdomen and pelvis which shows a bulky testicular tumour and a left lateral-aortic retroperitoneal tumour

Figure 2. The testicular tumour; the specimen is photographed after orchiectomy and initial sectioning for the pathology exam

Results

The definitive result of the pathology exam was: tumour proliferation constituted from immature and mature neural-ectodermal elements, with rare pearls of keratin. On other fragments, it was found sclerosis tissue and seminiferous tubes, adjacent, intact. Conclusion: immature teratoma with the recommendation to perform immunohistochemistry (IHC). The sperm cord was infiltrated at the base, with neural-ectodermal tissue, but the rest of it was intact (*Fig. 3*).

The IHC tests showed: Synapto – immature nervous tissue Synapto positive – diagnostic teratoma, S100 – positive intra-tumour, CROMO – negative, AE1/AE3 – positive, 34 BE 12 – positive, WT1 – negative, TTF1 – negative, Desm – negative, CD 30 – negative, Melan A – positive, Celretinin – positive, Ki67 – positive 15%, P6p9.5 – positively diffuse, INHIBIN – negative.

Conclusion: the tests are suggestive for an immature post-pubertal teratoma, with somatic type malignancy suggestive of neuroblastoma, and for the carcinoid part of the tumour it was

requested supplementary IHC testing and also MIC 2 FLI1 (PNET malignancy). Other tests which showed the following: VIM positive in rare tumour cells, AE1/AE3 positive, MIC2/CD99 positive, SYN positive, CD56 positive, Ki67 positive in 15% of the tumour cells, CD 117 positively diffuse, 34 beta E12 positive in the periphery of the tumour zones. The IHC tests suggest a PNET tumour, developed probably on a post-pubertal teratoma. The analysis established the tumour was stage IV, M1PUL, M1OSS. Postoperatively, the patient received Etoposide, Cisplatin, Bleomycin and zoledronic acid, with no major complications.

The following MRI and CT scan showed a substantial decrease of the left supraclavicular lymphadenopathy. The left lung nodule previously described shrunk to 6/5 mm. The inter-aorto-caval, the left pre-renal tumour mass as well as the spine metastases also regressed.

One year after the diagnosis, the patient was clinically well, with reduction in size of the abdominal mass to 7/5 cm and the disappearance of the left supraclavicular

Figure 3. 1. Seminiferous tubules (left) and cancerous cells (right). 2. Spermatic cord section with muscle cells and tumoral cells (upper left). 3. Ectodermal component representative for a teratoma (left). 4. Immunohistochemistry stain - Cytokeratin AE1/AE3 positive.

lymphadenopathy. Nevertheless, he still presented recurrent pain at the level of the spine, for which he received radiotherapy sessions.

Discussions

The mixed teratoma and neuroendocrine type testicular tumours are rare (under 1%) and have been reported in only 22 cases in literature. The majority occurred in patients between 38.5-39 years (2, 3). The diagnosis of this type of tumour is difficult and the IHC testing is crucial in establishing the precise diagnosis.

The particularity of the present case lies in the fact that he presented for the pain at the level of the spine and right facial paresthesia, rather than the testicular mass. The former complaints mandated the repeated MRI scans. The osteolytic images of the spine were the reason why the patient was referred to the haematology department, where a bone marrow biopsy was performed in order to rule out a suspicion of multiple myeloma.

The literature documents the fact that there is a delay between the tumour-oedema transformation and the moment of self-referral to medical care. In this particular patient 6 years

have passed between the two moments.

The blood tests, the pathology exam and the IHC of the tissue sampled from the bone marrow excluded the myeloma, and further study of the IHC from the bone marrow documented the neuroendocrine carcinoma.

The clinical exam, which documented the bulky left testicular tumour and the abdominal tumour, determined the whole body MRI exam at the level of the head, the cervical level, the abdomen and the pelvis and confirmed a testicular tumour but also the extension of the disease (lung and bone metastases, cervical and lateral aortic increased lymph nodes). The patient was staged as a stage IV of disease, M1PUL, M1OSS. In the multidisciplinary tumour board session, it was decided for the orchiectomy. Again, IHC is the one to determine the diagnosis: teratoma and testicular neuroendocrine tumour. The patient begins, after the surgical intervention, a chemotherapy regimen with good clinical outcome, and, in repeated check ups the CT scan and MRI found the decrease and even disappearance of the retroperitoneal tumour masses and of the lung metastasis. For the pain and the bone metastases, radiation therapy was applied.

The presence of carcinoid syndrome was described in 10.6% of the testicular tumours especially in those who developed metastases. The final diagnosis was established through IHC testing. The specific markers for testicular tumours (beta chorionic human gonadotropin, alfa-fetoprotein and lactate dehydrogenase) are usually within normal limits. The association between immature teratoma and neuroendocrine tumour was described only in one case (2).

The presence of bone metastases is rare: 2 patients were diagnosed through PET-CT scan. Neuroendocrine testicular tumors associated with teratomas are rare, 22 patients were diagnosed between 1930 and 2017 (2,4,5) which represented 16.67% of the total number of neuroendocrine tumors of testicular origin. Literature data showed that no patient with a mixed-type teratoma and neuroendocrine tumour developed visceral metastases, those being described only in the case of pure

testicular tumors and localized at the level of the lungs (2). Our patient had a solitary right superior lobe metastasis as well as multiple metastases at the level of the spine.

All patients, had radical orchidectomy via inguinal approach. Lateral aortic lymph node dissection was also performed in the patient with teratoma and neuroendocrine tumour. However, the pathology exam did not reveal cancer infiltration (6). The role of retroperitoneal lymph node dissection is controversial in patients with pure testicular tumours and concomitant metastases, other anatomical locations. Adjuvant chemotherapy was possible in only 2.27% of the patients, as there were also patients without any response at the level of the lymph nodes and of the lungs, especially in those with pure neuroendocrine tumors. All patients with both neuroendocrine tumors and testicular teratomas received 2-3 cures of Etoposide, Cisplatin, and Bleomycin, as was the case of our patient. Neo-adjuvant radiotherapy has not been described in the literature (7). Only 3 patients with pure neuroendocrine testicular tumours and concomitant metastases were given radiotherapy for the inter-aorto-caval and inguinal, lymph nodes, and the spine metastases, respectively (4). Some of the patients with pure testicular neuroendocrine tumours and visceral metastases were given Octreotide (2). Patient survival at 5 years was 84% and was considered better in associated tumours (teratoma and neuroendocrine tumour) compared to pure tumour forms (2,8,9).

Conclusions

1. Testicular tumors represented by the association between teratoma and neuroendocrine tumour are rare (< 1%) and have a good prognosis when they are not diagnosed in advanced stages.
2. IHC is essential in establishing the diagnosis and treatment. Specific markers offers diagnostic accuracy and provides prognostic orientation.
3. The recommended treatment is radical orchidectomy; adjuvant chemotherapy is only administered in patients with

metastases.

4. The prognosis and survival are similar to those of patients with testicular teratomas.

Conflict of Interest

The authors declare no conflicts of interests.

References

1. Tomulescu V, Stanciulea O, Dima S, Herlea V, Stoica Mustafa E, Dumitrascu T, et al. Diagnosis and surgical management in gastrointestinal neuroendocrine tumors. *Chirurgia (Bucur)*. 2011; 106(2):151-161.
2. Amine MM, Mohamed B, Mourad H, Majed H, Slim C, Mehdi B, et al. Neuroendocrine Testicular Tumors: A Systematic Review and Meta-Analysis. *Curr Urol*. 2017;10(1):15-25.
3. Ulbright TM, Amin MB, Young RH. Tumors of the Testis, Adnexa, Spermatic Cord and Scrotum. *Atlas of Tumor Pathology, Third Series*, vol. 161, Fascicle 25: Armed Forces Institute of Pathology. Washington, DC, USA; 1999.
4. Sasaki M, Emura M, Kim U, Shinbo M, Shima T, Suzuki N, et al. Primary carcinoid tumor of the testis metastatic to the para-aortic lymph nodes in six years after the first operation: a case report. *Hinyokika Kyo*. 2009;55:233-236.
5. Stroosma OB, Delaere KP. Carcinoid tumours of the testis. *BJU Int*. 2008;101:1101-1105.
6. Frank RG, Gerard PS, Anselmo MT, Bennett L, Preminger BI, Wise GJ. Primary carcinoid tumor of the testis. *Urol Radiol*. 1991; 12:203-205.
7. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. *Ann Oncol*. 2001;12(suppl 2):S111-114.
8. Epperson JR, Pope NM, Abuzeid MJ. Rare testicular tumor discovered by assault: an unusual presentation of a primary testicular neuroendocrine tumor grade 2. *Case Rep Pathol*. 2013; 2013:709352.
9. Fujita K, Wada R, Sakurai T, Sashide K, Fujime M. Primary carcinoid tumor of the testis with teratoma metastatic to the para-aortic lymph node. *Int J Urol*. 2005;12:328-331.