Late recurrence of an embryonal carcinoma of the testis. Case report

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Abstract

We present the case of a 32-year old male, diagnosed in 2003 (at the age of 22) with stage IIB testicular cancer. After orchiectomy he had received 4 cycles of chemotherapy (BEP protocol). In 2013 the disease relapsed (S2-level tumor markers, multiple lung metastases, compressive and invasive abdomino-pelvic adenopathy). Performance status (PS) at presentation was poor (ECOG PS 2), he reported diffuse abdominal pain (VAS 5) and deep vein thrombosis in the right leg. Salvage chemotherapy (TIP protocol) was administered for 6 cycles, with grade 2-3 hematologic toxicity.

Post-treatment evaluation revealed a good partial response: single pulmonary nodule (no FDG uptake), and 4.4-cm intraabdominal mass (SUV 6.0). Non-nerve-sparing salvage right retroperitoneal lymph node dissection was decided, and one microscopic focus of embryonal carcinoma was the only postoperative pathology finding. The patient is currently disease-free.

Keywords: *NSGCT, late relapse, salvage chemotherapy, response evaluation*

Introduction

Testicular cancer is the most common malignancy in men between the ages 20 and 40, the risk in those with cryptorchidism being increased 10 to 40-fold [1]. Dependent on tumor stage and prognosis (good, intermediate or poor), surveillance, chemotherapy (usually BEP protocol) or/and nerve-sparing retroperitoneal lymph node dissection (RPLND) are recommended for early stage NSGCT, while the standard treatment for recurrent and/or metastatic tumors is multi-agent platinum-based chemotherapy (Cisplatin, Ifosfamide, Etoposide or Paclitaxel), with an overall cure rate of around 80% [3, 4, 5]. The vast majority of relapses occur in the first two years since diagnosis of the advanced disease. The prognosis of patients progressing/relapsing after first line chemotherapy has been notably improved with multimodality approach, the optimal setting being the close collaboration between oncologist, urologist/surgeon, and radiation oncologist in experienced centers [6].

Case report

A 32-year old patient was diagnosed in 2003 (at the age of 22) with a stage IIB nonseminomatous testicular tumor, by the occurrence and progression of a right testicular mass, inter-aortico-caval adenopathy (cN2) and slightly elevated β-hCG and AFP (S1). After orchiectomy (HP: embryonal carcinoma, pT1), he had received 4 cycles of chemotherapy (BEP protocol: Cisplatin 75 mg/m^2/d, day 1; Etoposide 130 mg/m^2/d, days 1-3; Bleomycin 30 U/d, days 1, 8, 15) in

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another oncology center. Chemotherapy was apparently well tolerated, and a post-treatment CT scan revealed a partial response (PR) in the retroperitoneum. No further treatment was proposed, and no record of long-term clinical or biologic follow-up is available. After 10 years since the initial diagnosis (July 2013), the patient presented in bad physical condition (ECOG PS 2, severe asthenia, grade 3 dyspnea as per the modified Medical Research Council (mMRC) criteria, and chronic deep vein thrombosis of the upper left leg). Further investigation revealed S2-level elevated serum markers, multiple lung metastases, a 9-cm compressive adenopathy in the abdomen and pelvis, with inferior vena cava invasion and bilateral iliac and femoral vein thrombosis (computed tomography). Hematology and biochemistry panels indicated mild anemia, kidney and liver functions within normal parameters. The IGCCCG-2 prognostic score (Table 1) of this patient was considered as 1 (intermediate-risk) at this stage.

Table 1. IGCCCG-2 (Lorch-Bayer) Prognostic Score for testicular germ cell tumors (modified from Lorch A et al, 2010) [11]

Points / Variable	–1	0	1	2	3
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
1st line therapy response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	< 3 months		
AFP (relapse)		Normal	< 1000 ng/ml	> 1000 ng/ml	
β-hCG (relapse)		< 1000 mIU/ml	> 1000 mIU/ml		
Liver/bone/brain Mets		No	Yes		

AFP, alpha-fetoprotein; β-hCG, beta-chorionic human gonadotropin; CR, complete response; IGCCCG, International Germ Cell Cancer Collaborative Group; PD, progressive disease; PFI, platinum-free interval; PR, partial response; SD, stable disease.

Second line chemotherapy (TIP protocol: Paclitaxel 250 mg/m^2/d, day 1; Ifosfamide 1500 mg/m^2/d, days 2-5; Cisplatin 25 mg/m^2/d, days 2-5) was administered for 6 cycles, with a good partial response (PR) after cycle 4. Treatment encumbered grade 2-3 digestive toxicity (emesis, manageable with 5-hydroxytryptamine inhibitors, corticosteroids and metoclopramide rescue) and grade 1-2 hematological toxicity (grade 2 anemia under erythropoietin prophylaxis, and one episode of grade 1 neutropenia). Chronic low-molecular weight heparin (LMWH) treatment was also administered. Post-treatment evaluation in January-February 2014 (CT-scan, ^{18}FDG PET-CT) revealed complete response (CR) to the lung – an 8-mm nodule in the apical segment of the left lower lobe (no FDG uptake), and a very good PR at the abdominal level – a 4.4-cm precaval adenopathy with calcified inclusions (SUV max 6.0 at the postero-inferior extremity) (Figure 1). A consolidated thrombosis of the inferior vena cava (below the renal veins) with prominent collateral circulation was also described. Clinical benefit was evident (ECOG PS 1 at end of treatment), except for the persistent deep vein thrombosis and subsequent lower extremity edema. Non-nerve-sparing salvage right retroperitoneal lymph node dissection (RPLND) was decided and performed at the Fundeni Clinical Institute in Bucharest (April 2014). Histopathology

exam reported one microscopic focus of embryonal carcinoma engulfed in fibrosis and necrosis. Follow-up evaluations (July 2014, February 2015) proved the patient to be disease-free at almost two years after end of second line chemotherapy, with negative tumor marker levels, although maintaining chronic bilateral deep vein thrombosis and thus the need for chronic anticoagulant therapy.

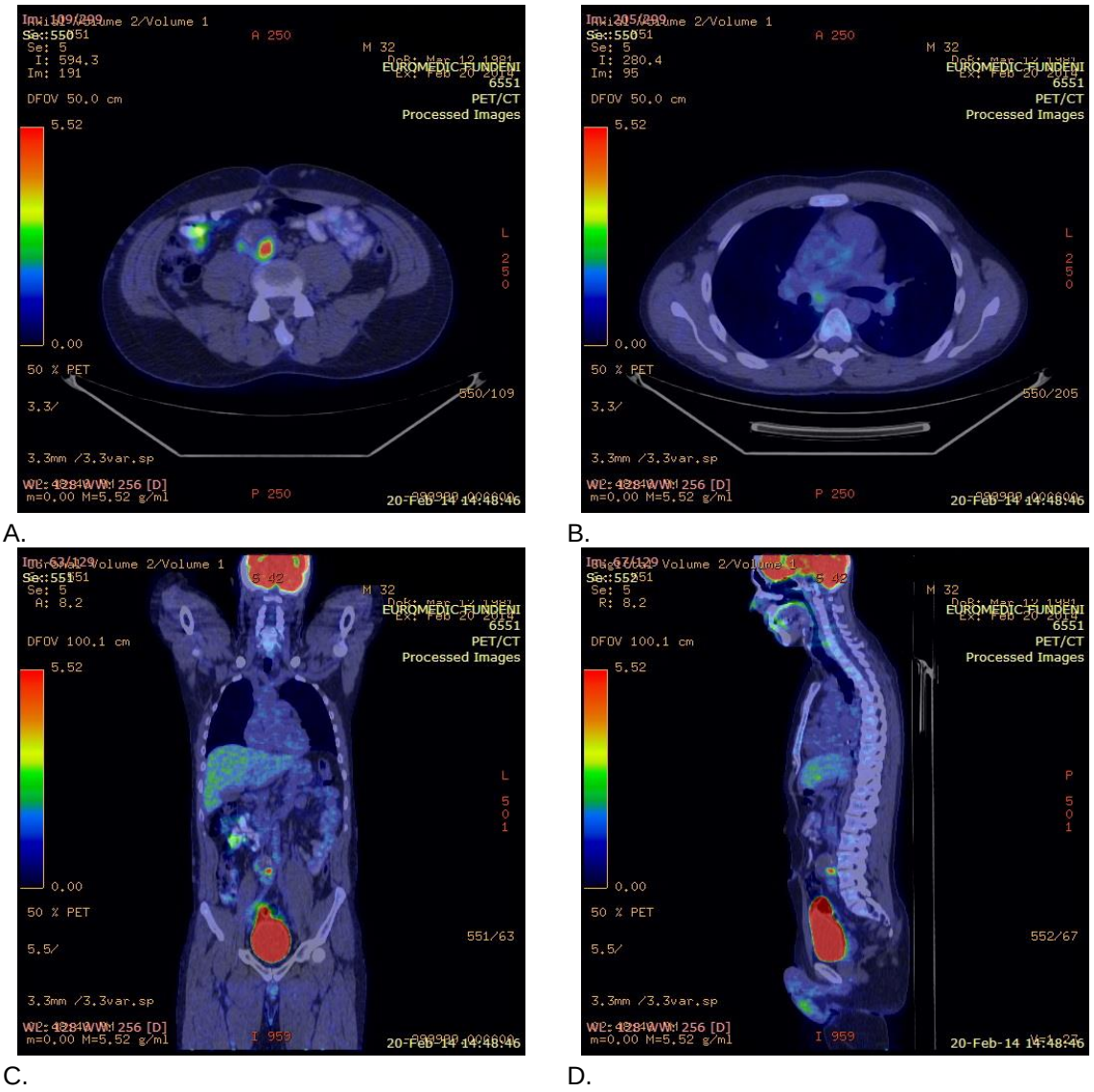

Fig. 1. Images from the ^{18}-FDG PET-CT scan performed after salvage chemotherapy: A. Axial view, residual precaval adenopathy; B. Axial view, complete response of lung metastases; C. Coronal view, residual precaval adenopathy and normal liver; D. Sagittal view, residual precaval adenopathy.

Discussion

For all stage II NSGCT with elevated tumor markers, platinum-based chemotherapy is recommended as the initial treatment after orchiectomy (standard: EP, 4 cycles, or BEP, 3 cycles). The option of primary nerve-sparing RPLND (followed by active surveillance for pN0, or by adjuvant chemotherapy for most pN+ cases) is available for highly selected cases, unable/not willing to undergo primary chemotherapy. With either approach, cure rates should be as high as 98% [3, 4]. The highest rates of recurrence are seen in the first two years, but distant relapses may occur (with lower frequency) for up to 5 years, so rigorous follow-up is warranted at least for this

interval (lifelong monitoring has also been advocated). When occurring, platinum-based combination salvage chemotherapy may still achieve long-term remissions in about a half of relapsed disease patients [3, 7]. Over the last 10 years, several trials have investigated the role of dose-dense chemotherapy (ddCT) in relapsed NSGCT. While retrospective and phase II data indicated a survival advantage in high-risk patients, phase III studies did not confirm these findings. There is currently not enough data to support the superiority of high-dose over conventional-dose chemotherapy as salvage treatment for patients with recurrent/refractory NSGCT [8, 9]. A positive PET-CT is a strong, but not definitive argument for biopsy or resection of lymph nodes or other lesions which remain clinically identifiable after first-line chemotherapy for testicular germ cell tumors (GCT). According to guidelines, PET scans have limited positive predictive value for residual disease, especially for seminoma. The negative predictive value (>90% for seminoma, lower for NSGCTs) may warrant surveillance over biopsy if the PET scan is negative in lesions >3cm. If the remnant lesions are smaller, follow-up is usually preferred even when the PET results are positive [10, 11]. Identification of circulating tumor cells (CTCs) in the peripheral blood (11-18% of patients) might be important for both the diagnosis and the treatment response or prognosis of GCTs. Research has shown that CTCs are associated with more advanced clinical and serological tumor stage, chemoresistance, and a generally poorer outcome of these patients [12]. However, to date, this approach is still considered experimental, and further data are needed to clarify the role of CTCs (and possibly other markers, such as miRNAs) in this setting.

Several studies evaluating the presence and impact of viable cancer cells in residual mass (es) after chemotherapy showed positive association with recurrence rates, hence the "mandatory" indication of RPLND. Other reasons are the "growing teratoma syndrome" and/or the fact that residual disease could undergo malignant transformation ("sarcomatization"), which is "inherently" platinum-resistant. However, RPLND should always be carried out at a center with extensive experience in vascular and digestive surgical techniques.

Our case has been initially a good-prognosis NSGCT, bearing a relapse risk of approximately 4-8%. In this respect, and considering the possible long-term side effects of chemotherapy, we should also note the slight overtreatment in the first-line (4 cycles of BEP instead of the maximum recommended 3) – but this apparently influenced neither the patient's quality of life in the following years, nor the eventual occurrence of retroperitoneal and distant relapse. Although he belonged in the 2% of good-prognosis patients not cured with first-line therapy, the time to disease progression was much longer than expected in this setting (10 years, instead of the usual 1-2 years).

In case of relapse, favorable prognosis is predicted by complete resection (< 10% viable malignant cells), a good IGCCCG score at presentation, and possibly a longer platinum-free interval [3, 4, 7, 13-16]. Multimodality salvage therapy (conventional-dose chemotherapy and surgery) is still expected to cure approximately 25% of relapsed NSGCTs and ensure long-term remissions in 50% of patients [3].

Conclusions

An individualized multidisciplinary approach is of the utmost importance in advanced/recurrent NSGCTs (perhaps especially in late relapses).

Whenever possible, patients should be enrolled in clinical studies looking to define the optimal salvage treatment, and should always be referred to experienced tertiary care centers.

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