Aggressive multimodal therapy may prolong disease-free survival in recurrent primary retroperitoneal embryonal carcinoma

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Abstract

INTRODUCTION: Primary retroperitoneal extragonadal tumours relapsing after initial chemotherapy have a poor prognosis.

PRESENTATION OF THE CASE: We report a case of primary retroperitoneal embryonal carcinoma in a patient with negative open testes biopsy. After the first line of chemotherapy (4 cycles BEP) secondary surgery with extirpation of a retroperitoneal residual mass was performed. The residuum proved histologically to be a mature teratoma, and no adjuvant treatment was given according to current recommendations.

The patient had regular follow-up. 3.5 years later, patient developed recurrence in the ipsilateral adrenal gland, which was treated with surgery and 4 cycles of salvage VeIP chemotherapy. Seven months after the second surgical intervention the patient underwent multisisceral “desperation surgery” for early metastatic disease progression followed by 2 cycles of salvage TIP chemotherapy. The patient is currently disease-free at 34 months.

CONCLUSION: Initial post chemotherapy retroperitoneal lymph node dissection is crucial for local retroperitoneal disease control. Aggressively treated metastatic recurrent disease does not preclude prolonged survival. Despite a generally poor prognosis, repeated complex oncosurgical therapy for retroperitoneal extragonadal tumours may be worthwhile.

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1. Introduction

Gonadal (GGCTs) and extragonadal germ cell tumours (EGGCTs) originate from primordial germ cells. EGGCTs may develop by malignant transformation of residual, misplaced primitive germ cells in the sagittal midline, or may be a group of misdiagnosed metastatic GGCTs [1]. Metastatic retroperitoneal tumours may have their primary small and unrecognised, or spontaneously regressed (autoinfarcted, burnt-out) [2–4].

Currently, 5% of malignant GGCTs are thought to be of extragonadal origin [5]. Patients with EGGCTs are classified into good, intermediate and poor prognosis categories based on primary tumour site, serum tumour marker levels and metastatic spread [6,7]. While GGCTs are typically curable with a high five-year survival rate (more than 90% when diagnosed at early stage) [8], nonseminomatous, retroperitoneal EGGCTs present with poor prognostic features in 50%, have frequent metastases in 76% and a five-year survival rate of 62%. Based on therapy response rate (68%) and a relapse rate of 50%, retroperitoneal EGGCTs are presumed to belong to a poor prognosis group even if they fulfil the IGCCCG criteria for good, or intermediate prognosis [5]. Embryonal carcinoma is an undifferentiated, pluripotent germinal cell neoplasm. This rare and complex malignancy should be managed by an experienced multidisciplinary team (MDT) in specialised centres [9].

2. Presentation of the case

A 42-year-old, obese (BMI 34.4 kg m−2), Caucasian male presented with left sided obstructive nephropathy due to a retroperitoneal primary in 10/2007. Retroperitoneal lymphadenopathy on abdominal ultrasonography (USG) and computed tomography (CT) raised suspicion of lymphoma (Fig. 1). After ureteral stent placement laparoscopic biopsy was performed. The histopathology
revealed a germinal tumour formed predominantly by embryonal carcinoma cells (99%) and a small proportion of choriocarcinoma cells (1%) (Fig. 2). Immunohistochemistry staining was positive for CD30, PLAP and ßHCG (Fig. 3). Bilateral open testes biopsy proved negative. Based on the CT, MRI, histopathology and tumour marker level, the disease was staged as “intermediate risk” according to the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria. The case was presented at a multidisciplinary team conference for consensus decision-making on multimodal treatment.

The patient was given a course of 1st-line BEP chemotherapy (bleomycin 30 IU day 1, 8, and 15, etoposid 100 mg/qm day 1–5, cisplatin 20 mg/qm day 1–5) (4 cycles q3w) (November 2007–February 2008). After the first cycle, febrile neutropenia and septic shock occurred, but this was managed successfully. Subsequent chemotherapy was delivered with granulocyte-colony stimulating factor (G-CSF) prophylaxis–pegfilgrastim (Neulasta, Amgen Europe B.V.(NLD)) and was uneventful. In April 2008, complete extirpation of tumour residuum and retroperitoneal lymphadenectomy (RPLND) was performed and structures of mature teratoma were revealed on final histopathological examination (Fig. 4). The patient experienced complete clinical remission for almost 3.5 years. Disease progression occurred in May 2011 involving the patient’s left adrenal as a solitary lesion. Increased level of ßHCG (5.7 IU/l) was recorded and based on the MDT decision, the patient underwent surgery. Left adrenalectomy, partial pancreatectomy and splenectomy were performed in order to resect the adrenal lesion in close relation to the pancreatic tail pseudocyst (a complication after the first surgical intervention). Metastatic embryonal carcinoma with high mitotic activity (more than 10 mitoses per 10 high-power fields) was confirmed on histopathology. After the surgery, the patient received a full 4 cycles of 2nd-line VeIP chemotherapy q3w (vinblastin 0.11 mg/kg day...
Fig. 3. Immunohistochemistry staining. (A) High proliferation activity Ki 67 stain (200×). (B) Positivity for CD 30 stain (400×). (C) Positivity for PLAP stain (400×). (D) Positivity for CK AE 1/3 (400×).

Fig. 4. Mature teratoma, HE stain (100×).

1–2, ifosfamide 1.2 g/qm day 1–5, cisplatin 20 mg/qm day 1–5) plus G-CSF prophylaxis according to current EORTC (European Organisation for Research and Treatment of Cancer) recommendation (August–October 2011). Second disease progression was diagnosed early after systemic therapy completion in February 2012 (Fig. 5). The PET/CT (positron emission tomography–computed tomography) showed a lesion suspected to be a locoregional recurrence at the site of the left adrenalectomy, and metastatic mass in the gastric fundus (Fig. 6). The patient underwent “desperation surgery” in April 2012. Previous interventions made discretion of postoperative and tumour changes impossible and multivisceral resection had to be performed (en bloc gastrectomy with distal pancreatectomy, left nephrectomy and splenic flexure resection). On histopathological analysis, metastatic embryonal carcinoma in both the gastric and colonic wall was found. No locoregional recurrence was confirmed, but the metastases had close relation to severe postoperative changes. Two cycles of 3rd-line TIP (paclitaxel 250 mg/qm day 1, ifosfamid 1500 mg/qm day 2–5, cisplatin 25 mg/qm day 2–5) salvage chemotherapy were delivered (May–June 2012). The patient has had regular follow-up, is currently 34 months disease-free, and being carefully monitored in order to detect relapse, development of secondary malignancies and to assess cardiovascular events, whose frequency is higher after combination chemotherapy for germ cell tumours.

3. Discussion

EGGCTs can be difficult to distinguish from metastatic tumours of testicular origin. Thorough testes investigation to rule out testicular primary is mandatory because the unrecognised tumour may be a source of relapse. In regressed tumours, moreover, fibrosis and inadequate blood supply may render chemotherapy ineffective [2,10]. Although routine open testes biopsy is currently
not recommended [5], in our case, bilateral biopsy was performed and proved negative.

Secondary surgery after 1st-line chemotherapy is performed in 45% of patients with nonseminomatous retroperitoneal EGGCTs and currently is recommended for any postchemotherapy residual retroperitoneal mass ≥1 cm in nonseminomatous tumours [11]. Resected residuum consists of necrotic tissue in more than half of the patients, nondifferentiated tumour is found in 25% and teratoma like in our case in another 16% [5,12]. The adequacy of initial retroperitoneal lymph node dissection (RPLND) is considered to be an independent predictor of disease-free survival in both low-stage and advanced nonseminomatous germ cell tumours. The true incidence of retroperitoneal relapse after RPLND is thought to be underestimated and occurs late [13]. In our case, neither of the two subsequent surgical interventions showed disease relapse inside the operating field of initial RPLND, although this could not be ruled out preoperatively and the patient in the end underwent multivisceral resection to assure resection of all retroperitoneal disease. Histopathologically, the first disease relapse was localised within the left adrenal and the second relapse in the gastric and in colonic wall. Only final histopathological examination could define the tumour origin precisely and distinguish it from postoperative changes after previous surgeries.

In the retrospective analysis of Oldenburg et al. [14], late disease recurrence after chemotherapy and radical RPLND does not exclude prolonged survival. Twenty-two out of the 25 patients were considered tumour-free after treatment of the first relapse. In seven of them, the second relapse occurred, and the reported 10-year postrelapse survival was 68% [14]. In this analysis, however, all malignant germ cells tumours were included (seminomatous and nonseminomatous) and only 4 cases were of primary extragonadal origin. EGGCTs relapsing after initial chemotherapy have a poor prognosis [5].

In our patient, tumour recurrence occurred after a long disease-free interval of 3.5 years. Extirpation of recurrence within the left adrenal plus 4 cycles of 2nd-line VeIP chemotherapy were followed by early second tumour progression (9 months after the second surgery and 6 months after completion of chemotherapy). As a small proportion of patients with relapsed disease may achieve durable remission with surgical resection alone [15,16], the patient underwent multivisceral resection as the first therapeutic step, followed by 3rd-line adjuvant chemotherapy (2 cycles of TIP with G-CSF prophylaxis).
4. Conclusion

While standard 1st-line therapy in EGGCTs consists of chemotherapy followed by surgery in patients with residual mass, repeated tumour recurrences may pose a serious problem. “Desperation surgery” with adjunctive salvage chemotherapy may be an option for otherwise fit patients, who are able to tolerate the side-effects of repeated combined chemotherapy and surgery in a second or 3rd-line treatment. Multidisciplinary decision-making to ensure optimal timing of medical and surgical interventions in patient with recurrent tumour is mandatory.

Consent

Written informed consent was confirmed from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

All authors have made substantial contributions to all of the following: (1) acquisition of data, analysis and interpretation of data, (2) revising it critically for important intellectual content and (3) final approval of the version to be submitted.

Guarantor

Martin Straka.

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