Late Recurrent Testicular Seminoma: Histological Evidence Is Required

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Abstract

Introduction: Over the past 3 decades, the appropriate management of metastatic germ cell tumours (GCT) has been defined by several phase III trials. Many follow-up recommendations have been published based on expert consensus. However, common clinical scenarios can still be vexing for clinicians who are less experienced at managing patients with testicular cancer. Case Report: We highlight the arduous diagnostic work-up of a suspected late relapsing metastatic GCT in a patient suffering from fatigue, weight loss and prominent retroperitoneal lymph nodes, 4 years after first-line chemotherapy for metastatic seminoma. The various explorations finally led to the diagnosis of Whipple’s disease. Conclusion: This unusual clinical case strongly highlights the need to perform an exhaustive evaluation, with a biopsy, if a late recurrent GCT is suspected to avoid pointless and potentially harmful treatment.

Keywords
Seminoma · Testicular cancer · Lymph node status · Recurrence

Established Facts
• There are several differential diagnoses to late recurrent testicular seminoma.

Novel Insights
• Histological evidence is required for late recurrent testicular seminoma.
and cisplatin (P) 20 mg/m² on days 1–5) or 4 cycles of EP (etoposide (E) 100 mg/m² on days 1–5 and cisplatin (P) 20 mg/m² on days 1–5) every 3 weeks are the recommended treatment options for patients with good prognosis metastatic seminoma. 4 cycles of BEP or VIP (etoposide (V), ifosfamide (I), cisplatin (P)) should be offered to patients with intermediate prognosis disease. Unlike the case of non-seminomatous germ cell tumours (NSGCT), residual masses after completion of chemotherapy should not be immediately treated surgically but rather according to the metabolic response status depicted on a PET-FDG scan [7] performed at least 6 weeks after the last course of chemotherapy. Many follow-up recommendations have been published based on expert consensus. However, common clinical scenarios can still be vexing for clinicians who are less experienced at managing patients with testicular cancer [8], and a full physical examination is mandatory.

Patients with a late relapse form a very rare population (the incidence of late relapse after treatment of seminoma is 1.6% [9]) with a variable prognosis, histological proof is mandatory to confirm the relapse (teratoma, non-GCT component), and to establish the prognosis for those patients. Prognosis depends more strongly on histology of relapse than initial histology, and furthermore an initial seminoma GCT may relapse as NSGCT and vice versa. Teratoma or necrosis at late relapse confer a 100% cause-specific survival, compared to a 50% cause-specific survival in patients with viable malignant tumour [10]. We highlight the arduous diagnostic work-up of a suspected relapsing metastatic GCT in a patient suffering from fatigue, weight loss and prominent retroperitoneal lymph nodes, 4 years after first-line chemotherapy for metastatic seminoma.

Whipple’s disease caused by Tropheryma whippelii affects middle-aged men, and begins with recurrent arthritis followed several years later by digestive problems associated with other diverse clinical signs. The diagnosis is based on PCR analysis of bodily fluids or tissues. Pathological examination revealed sheets of foamy macrophages. Periodic acid-schiff (PAS) staining showed numerous PAS-positive granular or rod-shaped inclusions distending their cytoplasm. Occasionally, involved tissues contained sarcoid-like, non-caseating granulomas often in contact with lipid vacuoles. Antibiotics eradicate the bacteria but an immune reconstitution syndrome and recurrence remain possible. This curable disease may, nonetheless, be fatal if diagnosed late or in an extensive systemic form with heart or central nervous system involvement [11].

Case Report

In 2010, a 37-year-old man, a marble cutter, was diagnosed with a metastatic seminomatous GCT arising from the left testis with an enlarged retroperitoneal lymph node. The prognosis was good according to the IGCCCG classification and disease was stage IIC according to the American Joint Committee on Cancer (AJCC) staging system. Tumour markers (a-fetoprotein (AFP), human chorionic gonadotrophin (hCG), and lactate dehydrogenase (LDH)) were normal. A left orchiectomy was performed, he received 4 cycles of EP according to the international recommendations [3], and achieved a complete response depicted on the CT scan. Tumour markers remained normal during the follow-up period.

After 4 years of normal clinico-radiological monitoring every 6 months, he experienced chronic diarrhea with 6 stools per day and a weight loss of 20 kg. He weighed 51 kg for 1.78 m, and he was afebrile. A physical examination showed dehydration and severe malnutrition. Abdominal palpation was painless. He complained of chronic axial and peripheral joint pains. Abdominal ultrasonography depicted splenomegaly (140 × 560 mm) with intraperitoneal effusion. An abdominal CT scan demonstrated centimetric coeliac-mesenteric lymph nodes and ascites. A chest CT scan revealed a mammillated appearance of the pleura associated with pleural effusion. Serum AFP and hCG were normal. Testicular ultrasound and gastroduodenal endoscopy were normal (duodenal biopsies were normal).

A complete colonoscopy found right erythematous colitis and lymphoid hyperplasia of the terminal ileum. Multiple biopsies revealed non-specific inflammation. Stool standard bacteriology was negative. Extensive biological examinations found malnutrition syndrome with microcytic anaemia (Hb 7.1 g/dl), hypoproteinaemia (48 g/L) and biological inflammation with C-reactive protein (CRP) of 139 mg/l. The leucocyte count was normal at 7,970/mm³ (170/mm³ polymorphonuclear eosinophils, 1,340/mm³ lymphocytes). A biological examination of ascites showed inflammatory sterile fluid without atypical cells. A lumbar puncture yielded aseptic liquid rock water without hypercellularity.

An exploratory laparoscopy collecting multiple biopsy samples was performed to eliminate recurrent seminoma. The intraoperative appearance revealed peritonitis with clear fluid of average abundance, and the peritoneum exhibited a mammillated appearance. A diagnosis of Whipple’s disease was made based on the presence of non-caseating lipogranulomas and clusters of epithelioid histiocytes in the mesenteric lymph node biopsy sample, with PAS-positive and Ziehl-negative staining (fig. 1). PCR analysis of serum, saliva and the mesenteric lymph node showed positivity for T. whippelii.

Ceftriaxone antibiotherapy was administered intravenously (2 g/day) for 2 weeks followed by oral doxycycline and hydroxychloroquine, scheduled for 1 year of treatment duration. After 1 month of antibiotics, complete regression of diarrhea, weight regain, and partial relief of joint pains were observed. Abdominal and testicular ultrasounds were normal without ascites or prominent abdominal/retroperitoneal lymph nodes.

Discussion

This unusual clinical case (to our knowledge, the first case of Whipple’s disease after a diagnosis of metastatic seminomatous GCT described to date) strongly highlights the need to perform an

![Fig. 1. Lymph node showing cortical localisation of histiocytes containing large amounts of PAS-positive granulations (PAS, × 800).](image)
exhaustive evaluation with a biopsy if a late recurrent GCT is suspected, especially in the absence of elevated serum markers, in order to avoid pointless and potentially harmful treatment [12, 13]. Most patients with metastatic GCT will be cured with platinum-based chemotherapy and surgery in the case of NSGCT, and without surgery in patients with seminomatous GCT. Young patients with a history of GCT may have other concomitant diseases such as infection, granulomatosis (sarcoidosis), inflammatory disease, or other cancers. One of the major goals of the next decade will be to ‘maintain the high success rate’ as stated by the European consensus [12], probably through increased centralized care in centres with experience in treating such patients and especially those with intermediate- and poor-risk disease at initial presentation and all patients with a relapsed GCT.

**Disclosure Statement**

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