

Challenging presentations of germ cell tumours in routine clinical practice

Navya Bezawada¹, Arthur Norton², Karen Mactier³, Graham MacDonald⁴, Ashita Waterston⁵, Walter Mmekwa⁶, Jahangeer Malik⁷, Alistair Law⁸, Colin Barrie⁹, Allan Drummond¹⁰, Colin Muir¹¹, Jeff White¹²



Testicular cancer is the most common malignancy in young men. We discuss four cases of germ cell tumours (GCTs) presenting to general practitioners and physicians where there were notable preventable delays in the diagnosis and management. This diagnostic delay is associated with a more advanced stage of disease, and subsequent increased treatment-related morbidity and decreased survival. Our series highlights the variety of ways in which GCTs may present and we discuss the importance of prompt diagnosis through a thorough history and examination, early measurement of serum tumour markers and appropriate multidisciplinary team discussion. GCTs are highly curable cancers in the majority of patients and delays in management can, therefore, have devastating consequences.

Keywords: diagnostic delay, GCTs, germ cell tumours, testicular cancer

Financial and Competing Interests: No conflict of interests declared

Correspondence to:

Navya Bezawada
Beatson West of Scotland
Cancer Care Centre
NHS Greater Glasgow and
Clyde
1053 Great Western Road
Glasgow G12 0YN
UK

Email:

navya.bezawada@nhs.scot

Introduction

Although considered rare in the general population, testicular cancer is the most common malignancy affecting males between 25 and 49 years of age in the UK, accounting for 3 in 20 (15%) new diagnoses in this age group.¹ Germ cell tumours (GCTs) account for the majority of all testicular cancers.² The diagnosis of GCTs depend on physical examination, ultrasonography, measurement of serum tumour markers (STMs) and pathological assessment. STMs are vital in the diagnosis, staging, risk stratification and surveillance of patients. These include α -fetoprotein (AFP), human chorionic gonadotropin (hCG) and lactate dehydrogenase (LDH).² Management generally involves orchidectomy and/or chemotherapy with or without retroperitoneal lymph node dissection (RPLND).

GCTs are highly curable tumours in the majority of cases, owing to their sensitivity to platinum-based chemotherapy, even patients with advanced disease have an estimated 5-year survival of 89–93%.^{3,4} The International Germ-Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system for testicular cancers and categorises patients into three groups: ‘good’, ‘intermediate’ or ‘poor’ prognosis.⁴ Delays in diagnosis are associated with a more advanced stage of disease, and subsequent increased treatment-related morbidity and decreased survival.⁵

Patients generally present with an enlarged testicle or a painless unilateral scrotal mass. Scrotal pain is present in

around 20% and some may describe a dragging sensation in the scrotum.⁶ Gynaecomastia appears in approximately 10% of cases owing to tumours that secrete hCG leading to an increase in the circulating ratio of oestrogen to androgens.⁷ Back and flank pain due to metastasis is present in 11% of cases.^{8,9}

We present a review of cases of GCTs presenting to general practitioners (GPs) and physicians where there was diagnostic uncertainty and/or preventable diagnostic delay, which may have led to adverse outcomes.

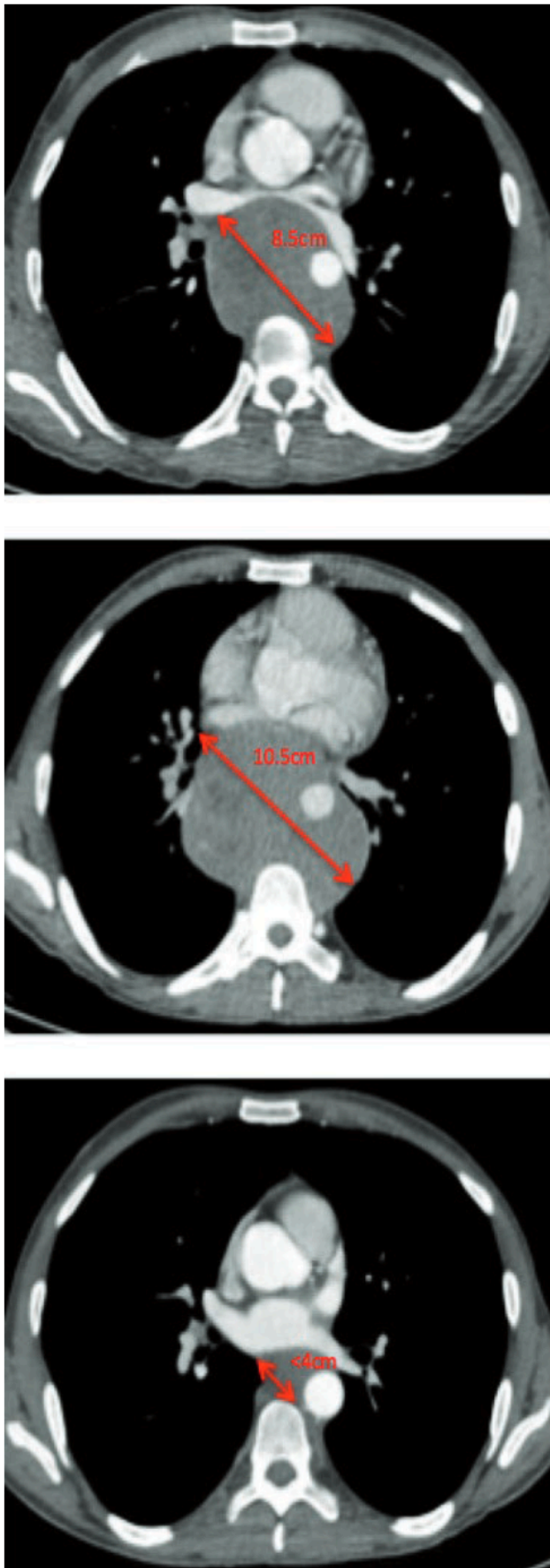
Case 1

A 43-year-old male presented to his GP with a 6-month history of weight loss and chest wall pain. He had a background of 20 pack-year smoking history and chronic schizophrenia. Initial examination revealed a mass on his posterior chest wall. Chest X-ray (CXR) demonstrated a left mid-zone opacity and subcarinal lymphadenopathy. Lung cancer was suspected and he went onto have a CT chest/abdomen, which revealed a 37 × 26 mm lesion in the left oblique fissure, pleural lesions, and a large necrotic mass encasing the tenth rib and in the posterior mediastinum (Figure 1). Initial investigation included a referral to respiratory physicians and a rib biopsy.

Rib biopsy was suggestive of a poorly differentiated neoplasm of epithelial origin. Immunohistochemical (IHC) analysis was performed and two of the five epithelial tumour markers were weakly positive: CD138 (plasma cell marker) and Bcl2

¹Clinical Development Fellow, ⁵Consultant Medical Oncologist, ¹²Consultant Medical Oncologist, Beatson West of Scotland Cancer Care Centre, Glasgow, UK; ²Rural Medicine Registrar, Oamaru Hospital, Oamaru, New Zealand; ³Clinical Oncology Registrar, ^{7,8}Consultant Clinical Oncologist, ⁹Consultant Medical Oncologist, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK; ⁴Consultant Clinical Oncologist, Aberdeen Royal Infirmary, Aberdeen, UK; ⁶Consultant Medical Oncologist, Raigmore Hospital, Inverness, UK; ¹⁰Acute Medicine Consultant, ¹¹Acute Medicine Registrar, Queen Elizabeth University Hospital, Glasgow, UK

Figure 1 CT images demonstrating progression of mediastinal disease at presentation, initial diagnosis and post chemotherapy



(lymphoma marker). It was felt this could be a plasmablastic neoplasm and the case was referred to the national lymphoma group; however, due to negative serum light chain analysis, a further biopsy was undertaken. A biopsy of the lung mass yielded cells with similar morphology. Additional IHC was positive for CD117, indicating a GCT. Placental alkaline phosphatase (PLAP) was strongly positive confirming germ cell origin. STMs undertaken at this stage showed an elevated hCG at 337 U/L (0–5 U/L) and normal AFP, indicating a GCT (seminoma). Examination showed a grossly enlarged right testicle, confirmed to be a tumour by ultrasound scan (USS). A CT pelvis showed a large pelvic mass infiltrating the right acetabulum (Figure 2).

Based on the initial impression of end-stage lung cancer, the patient had opted for palliative management. However, following the diagnosis of metastatic seminoma, made 4 months after initial presentation, he was restarted on active treatment. He was treated with chemotherapy (cisplatin and etoposide). Given his smoking history, bleomycin was omitted as it is known to cause pulmonary toxicity; bleomycin-induced lung toxicity may affect 7–21% of patients in the long term and result in death in 1–3%.¹⁰ He had an excellent response, with significant reduction in tumour burden radiologically and his hCG normalised.

Case 2

A 25-year-old male presented to his GP with an 8-week history of increasing lumbar pain, fatigue, testicular discomfort, and swelling of the penis and scrotum. He had no past medical history of note, and on examination no discrete testicular masses were palpable. A scrotal ultrasound showed no abnormality in the testes, but abdominal ultrasound revealed extensive retroperitoneal lymphadenopathy, bilateral hydronephrosis and borderline splenomegaly.

He was transferred to the care of the regional Haematology team with a presumptive diagnosis of lymphoma and on examination there was palpable left cervical lymphadenopathy. Serum LDH was significantly elevated at 2,894 U/L (140–250 U/L). CT scan revealed extensive lymphadenopathy in the neck, chest, abdomen and pelvis; multiple pulmonary lesions; compression of the inferior vena cava; right-sided hydronephrosis; and right leg deep vein thrombosis. Fine-needle analysis cytology was undertaken of the cervical nodes and was suggestive of a GCT. STMs revealed an AFP of 2,072 kU/L (0–6 kU/L) and a hCG of 145,713 U/L (0–5 U/L).

Completion of staging with MRI of brain showed no intracranial disease and on the basis of an IGCCCG ‘poor prognosis’ non-seminomatous GCT (presumably of retroperitoneal origin), the patient was managed with CBOP-BEP chemotherapy with curative intent.^{4,11} This consists of cisplatin, carboplatin, bleomycin, vincristine and etoposide chemotherapy over the first 6 weeks followed by three cycles of modified BEP (bleomycin, etoposide, cisplatin) chemotherapy. The patient received 6 months dalteparin therapy.

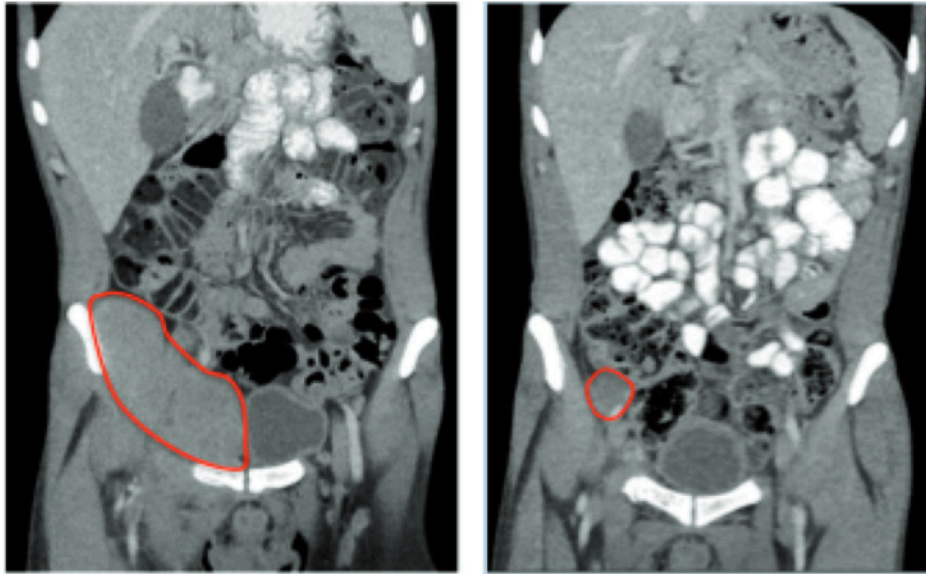


Figure 2 CT images of pelvic disease pre and post chemotherapy

The patient's STMs normalised by week 7 and there was a radiological partial response on their end of treatment CT scan, with residual small volume lung lesions and a residual 4 × 4 cm retroperitoneal mass (12 × 11 cm at presentation). The patient underwent RPLND of the mass 3 months after completing chemotherapy, pathology showed extensive necrosis with no viable teratoma or other GCT. A subsequent bilateral testis biopsy showed no germ cell neoplasia in situ. The patient has remained disease-free through 9 years follow up.

Case 3

A 31-year-old male was admitted with a 6-week history of shortness of breath, associated weight loss and occasional night sweats. On admission, the patient was noted to have a new large right-sided effusion. The patient did not have any palpable lymphadenopathy, or masses in abdomen or testis. The patient was otherwise fit and well. However, the patient had a CT pulmonary angiogram 12 months previously after presenting to cardiology with shortness of breath and chest pain. This was negative for pulmonary embolism but did comment on a small amount of lobulated soft tissue in the anterior mediastinum, thought to represent thymic pathology. No clear follow up of this was arranged at this time.

CXR showed a large pleural effusion. Owing to his history of the thymic mass, there was concern about a malignant pleural effusion and further imaging with a CT chest, abdomen and pelvis showed a large, centrally necrotic, anterior mediastinal mass (Figure 3).

Pleural fluid cytology was inconclusive and only showed inflammatory cells. Following a multidisciplinary team (MDT) discussion, STMs were checked: AFP was grossly elevated at 21,009 kU/L (0–6 kU/L), LDH was 389 U/L (140–250 U/L) and hCG was normal. The patient had a CT-guided biopsy of the anterior mediastinal mass, which showed malignant cells. IHC was positive for AFP, PLAP, glypican 3 and AE1/3, in keeping with diagnosis of a yolk sac GCT, particularly in the

context of a markedly raised serum AFP. MRI brain excluded intracranial disease.

The patient subsequently underwent treatment for a primary GCT of the anterior mediastinum with CBOP-BEP chemotherapy.¹¹ The patient had a good response with normalisation of his STMs and underwent a mediastinal resection. The patient has been on surveillance since without disease recurrence for 4 years.

Case 4

A 49-year-old male presented to his GP with a 2-month history of progressive upper abdominal pain and bilateral loin discomfort. The patient's past medical history was limited to fibromyalgia. Epigastric fullness was noted on examination and the patient was referred for imaging. USS confirmed a 5 × 6 cm nodal mass encasing the aorta. CT scan demonstrated multiple lung metastases suggestive of a metastatic testicular tumour (Figure 4). The radiologist recommended a USS testes and CT-guided lung biopsy; he was admitted for these investigations 4 days later. A 2 cm heterogeneous area was seen within left testes on USS in keeping with a primary lesion.

The patient's case was discussed with a consultant urologist who recommended awaiting discussion of the pathology results at the uro-oncology MDT the following week. Histology of the lung biopsy showed a poorly differentiated carcinoma. The pathologist felt IHC was very non-specific.

The patient was contacted by letter to arrange measurement of STMs as he could not be reached by telephone. hCG was grossly elevated at 1,156,656 U/L (0–5 U/L) and AFP was normal. There was a further 2-week delay until the patient was re-discussed at the uro-oncology MDT. The patient was then immediately transferred for urgent chemotherapy.

At this stage, the patient was extremely cachectic and fatigued. The patient was anaemic and hypoxic, a repeat CXR showed marked progression of metastatic pulmonary

Figure 3 CT showed a large, centrally necrotic, anterior mediastinal mass that was displacing the heart to the left and compressing the right main bronchus causing right lower and middle lobe collapse



disease. The patient was commenced on CBOP-BEP chemotherapy.¹¹

The case was re-discussed and biopsy reviewed. The appearance was consistent with metastatic choriocarcinoma but without clinical and radiological correlation it would have been difficult to draw this conclusion owing to the absence of the usual germ cell IHC markers.

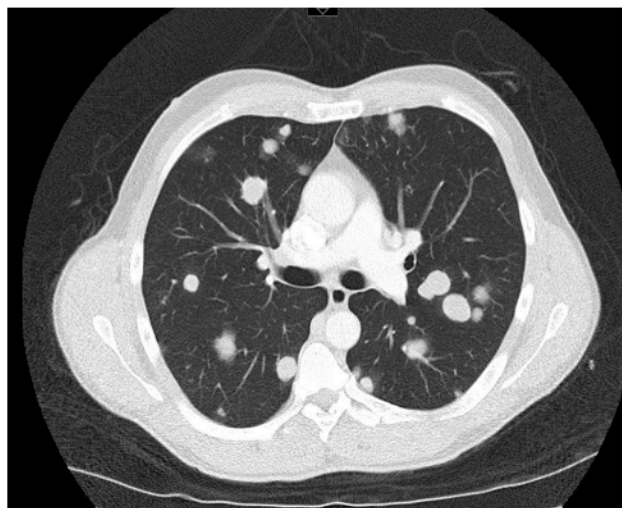
Unfortunately, the patient deteriorated rapidly in the following 48 hours. CT head demonstrated multiple brain metastases. The patient was transferred to the Intensive Care Unit and required ventilation for type 1 respiratory failure. Chemotherapy was continued in the hope of achieving tumour response. However, the patient developed multiorgan failure and the decision was made to withdraw active care, the patient subsequently died.

Discussion

Our case series highlights the variety of ways in which GCTs may present to primary and secondary care. Case 1 signifies the need for a thorough history and examination of a young male where there is a suspicion of malignancy. The investigations in this case were misdirected due to the inherent difficulties in diagnosing germ cell malignancy and the confounding risk factor of a significant smoking history. European Society for Medical Oncology (ESMO) guidelines state thorough physical examination (including rectal, pelvic and breast) should be the first step in assessing every patient with suspected malignancy.¹² ESMO guidelines also recommend that all males presenting with cancer of unknown primary should undergo serum assessment for AFP, hCG, plasma chromogranin A and prostate specific antigen (PSA) to investigate the possibility of extra-gonadal GCTs, neuroendocrine tumours and prostate cancer.¹²

Measurement of STMs is pertinent to diagnosis and management of GCTs and should be undertaken at an early stage in any patient where a GCT is in the differential

Figure 4 CT scan showing multiple lung metastases



diagnosis, especially in males with midline presentations of malignancy. In case 2, the diagnosis was delayed by 2 weeks by the failure to check STMs early in the diagnostic work up of a young male with extensive malignancy. The absence of a discrete mass in the testis led to lymphoma being considered the most likely diagnosis, pending cytology of the neck nodes. Similarly, for case 4, an early check of STMs could have expedited this patient's diagnosis and treatment.

As seen from cases 2 and 3, male GCTs can arise out with the testes, with retroperitoneal and mediastinal primary sites recognised. Therefore, a normal scrotal USS does not exclude a GCT. Extragonadal GCTs are a rare subgroup of GCTs, most of which arise in the retroperitoneum, followed by anterior mediastinum.¹³ Primary mediastinal GCTs account for less than 5% of germ cell malignancies and are more common in males.¹⁴ Certain anterior mediastinal tumours can be reliably identified by imaging alone but many have suggestive but inconclusive features on imaging alone.¹⁵ Therefore, clinical correlation is important. Mediastinal masses have a wide differential and include thymoma, GCTs, lymphoma and benign cysts.¹⁵ Thymomas are the most common anterior mediastinal masses but account for less than 1% of all adult cancers; around 20% of anterior mediastinal masses are diagnosed as lymphomas whilst GCTs account for 10–15%.^{16,17}

Case 4 highlights the importance of a complete assessment and MDT discussion. Tissue diagnosis was perhaps secondary in this case to the clinical and radiological picture, which was highly suggestive of a GCT although IHC did not support this initially. Finally, this case undoubtedly highlights how delays in management may result in devastating outcomes.

Conclusion

There are several learning points to be gained from these cases. As the most common malignancy in the young male population, testicular cancer should be high in the differential diagnosis. A thorough clinical assessment and directed investigation including STMs would significantly aid the diagnostic process. Diagnostic

delays lead to a higher stage and adverse prognosis group, the need for more treatment, and worse survival outcomes. It is, therefore, important that a prompt diagnosis is made in these young patients with GCTs, as with the appropriate management they generally have an excellent prognosis. **1**

Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient/guardian for publication of this paper, including accompanying images.

References

- 1 Testicular cancer incidence statistics. Cancer Research UK. 2015. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/incidence> (accessed 01/11/2019)
- 2 Baird DC, Meyers GJ, Hu JS. Testicular cancer: diagnosis and treatment. *Am Fam Physician* 2018; 97: 261–8.
- 3 Ko JJ, Bernard B, Tran B et al. Conditional survival of patients with metastatic testicular germ cell tumors treated with first-line curative therapy. *J Clin Oncol* 2016; 34: 714–20.
- 4 International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997; 15: 594–603.
- 5 Öztürk Ç, Fleer J, Hoekstra HJ et al. Delay in diagnosis of testicular cancer; a need for awareness programs. *PLoS One* 2015; 10: e0141244.
- 6 Scottish Intercollegiate Guidelines Network (SIGN). Management of adult testicular germ cell tumours. Edinburgh: SIGN; 2011. (SIGN publication no. 124). <http://www.sign.ac.uk> (accessed 01/11/2019)
- 7 Tseng A, Homing SJ, Freiha FS et al. Gynecomastia in testicular cancer patients. Prognostic and therapeutic implications. *Cancer* 1985; 56: 2534–8.
- 8 Albers P, Albrecht W, Algaba F et al. Guidelines on testicular cancer. http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Testis_Cancer.pdf (accessed 01/11/2019)
- 9 Moul JW. Timely diagnosis of testicular cancer. *Urol Clin North Am* 2007; 34: 109.
- 10 O'Sullivan JM, Huddart RA, Norman AR et al. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol* 2003; 14: 91.
- 11 Huddart RA, Gabe R, Cafferty FH, et al. A randomised phase 2 trial of intensive induction chemotherapy (CBOP/BEP) and standard BEP in poor-prognosis germ cell tumours (MRC TE23, CRUK 05/014, ISRCTN 53643604). *Eur Urol* 2015; 67: 534–43.
- 12 Fizazi K, Greco FA, Pavlidis N et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011; 22 Suppl 6: vi64–68.
- 13 McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. *Adv Anat Pathol* 2007; 14: 69–92.
- 14 Juanpere S, Cañete N, Ortuño P et al. A diagnostic approach to the mediastinal masses. *Insights Imaging* 2013; 4: 29–52.
- 15 Carter BW, Okumura M, Detterbeck FC et al. Approaching the patient with an anterior mediastinal mass: a guide for radiologists. *J Thorac Oncol* 2014; 9: 110–8.
- 16 Takahashi K, Al-Janabi NJ. Computed tomography and magnetic resonance imaging of mediastinal tumors. *J Magn Reson Imaging* 2010; 32: 1325–39.
- 17 Marom EM. Imaging thymoma. *J Thorac Oncol* 2010; 5: S296–S303.