Brain Metastases as Presenting Feature in 'Burned Out' Testicular Germ Cell Tumor

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Abstract

Testicular germ cell tumors (TGCTs) are the most common malignancy in males aged 20 to 39, and the incidence is increasing. TGCTs have a tendency to grow rapidly with a high risk of metastatic spread. TGCTs generally present with a palpable testicular mass, yet may present less commonly with symptoms arising from metastatic disease.

A 24-year-old otherwise healthy male presented with progressive headaches. Initial imaging reported a single mass in the right frontal lobe. Complete surgical resection revealed suspicion for metastatic poorly differentiated carcinoma with an inconclusive immunohistochemical profile. Further staging scans revealed pulmonary and pelvic tumor deposits. Tumor markers with alpha-fetoprotein, beta-human chorionic gonadotropin, and lactate dehydrogenase were not elevated. Follow-up cranial magnetic resonance imaging revealed intracranial disease progression and he underwent whole brain radiation therapy. Additional outside pathology consultation for chromosomal analysis revealed features consistent with a TGCT. A scrotal ultrasound revealed a minimally atrophic right testicle. With evidence supporting the potential for response to chemotherapeutic treatment in TGCT, the patient was started on cisplatin and etoposide. Bleomycin was planned for the second cycle of chemotherapy if his pulmonary function improved.

A salient feature of all invasive TGCTs is a gain in material in the short arm of chromosome 12, and is diagnostic if present. Although the initial pathology revealed a non-diagnostic metastatic tumor, further testing revealed amplification of chromosome 12p. The examination of poorly differentiated carcinomas of an unknown primary site using light microscopy and immunohistochemical profiling alone may be inadequate, and should undergo molecular chromosomal analysis.

This case is presented for its unconventional presentation and rarity of occurrence. It brings forward the discussion of both the commonality of TGCT in young male adults, as well as the anomaly of a 'burned out' phenomenon. With unreliable tumor markers, nonspecific symptoms, and pathological findings, 'burned out' TGCTs may account for a challenging diagnosis in a variety of cases, especially with the presenting symptom arising from a less common metastatic site. This case adds to the increasing literature on a rare entity of the 'burned out' TGCT, and upon literature review, presents itself as the first reported case presenting with brain metastasis.

Introduction

Testicular germ cell tumors (TGCTs) are the most common malignancy diagnosed in males aged 20 to 39, and the incidence is increasing [1-3]. TGCTs have a tendency to grow rapidly with a high risk of metastatic spread. TGCTs generally present with a palpable testicular mass, yet, less commonly may present with symptoms arising from metastatic disease. Specifically, TGCTs have a propensity to metastasize to retroperitoneal lymph nodes, lungs, liver, bone, and less frequently, to the brain [4].

The phenomenon of a primary TGCT outgrowing its blood supply and undergoing auto-infarction has been described as a 'burned out' TGCT. The regressed testicular lesion is not appreciable on physical exam, and the incidence is increasing [4]. TGCTs have a tendency to grow rapidly with a high risk of metastatic spread. TGCTs generally present with a palpable testicular mass, yet, less commonly may present with symptoms arising from metastatic disease. Specifically, TGCTs have a propensity to metastasize to retroperitoneal lymph nodes, lungs, liver, bone, and less frequently, to the brain [4].

Imaging can be helpful in making the diagnosis, with scrotal ultrasonography revealing evidence of a regressed tumor. Possible findings consist of a hypoechoic area, atrophic testicle, or microcalcifications [7-
Macroscopic evidence of a fibrotic scar in the parenchyma and microscopic findings of intratubular germ cells or seminomatous foci may be seen on pathological evaluation [9-11].

Of significance, extra-gonadal germ cell tumors (EGCT) are a known entity that also present with biochemistry and histological findings of a germ cell tumor in the absence of primary testicular or ovarian tumor. However, EGCT are differentiated from "burned out" TGCT by their characteristic midline location, from the pineal gland to the coccyx. Furthermore, in EGCT no radiologic nor pathologic evidence of a primary malignancy is present in the primary reproductive organs [12].

Chemotherapeutic strategies implemented in the 1970s for the treatment of advanced stage TGCTs represents a paradigm shift to a curable disease [13-15]. Here we discuss a rare case that highlights the challenges of diagnosing a 'burned out' TGCT.

**Case Presentation**

A 24-year-old previously healthy male presented with progressive nausea, vomiting, visual changes, and memory impairment. His only significant finding on history was a strong family history of factor V Leiden mutation. The physical exam was grossly unremarkable. The initial magnetic resonance imaging (MRI) reported a single mass in the right frontal lobe (Figure 1).

![Initial Brain MRI](image)

**FIGURE 1: Initial Brain MRI**

Single intra-axial heterogeneously enhancing mass in the inferior aspect of the right frontal lobe.

With high suspicion for primary brain tumor, total resection of the intracranial lesion was performed and revealed a metastatic, poorly differentiated carcinoma with an inconclusive immunohistochemical profile.

Staging investigations with computed tomography (CT) and positron emission tomographic (PET) scans revealed pulmonary and pelvic tumor deposits. A scrotal ultrasound revealed a minimally atrophic right testicle with no further abnormalities detected. A follow-up cranial MRI revealed enhancement in the surgical bed and new metastatic foci (Figures 2, 3).
Pathological and imaging findings were consistent with metastatic carcinoma with progressive brain lesions from an unestablished primary focus. At this time the brain lesions were increasingly symptomatic. Further treatment options with chemotherapy and whole brain radiation therapy (WBRT) were discussed with the patient. The patient refused palliative intent chemotherapeutic intervention for unknown primary, but agreed to WBRT with a prescribed dose of 30 gray in 10 fractions delivered. Subsequent to this, additional remote pathological consultation with chromosomal analysis revealed isochrome 12p.
amplications, consistent with a TGCT. Tumor markers with alpha-fetoprotein (aFP), beta-human chorionic gonadotropin (BhCG), and lactate dehydrogenase (LDH) were not elevated. With evidence supporting the potential for response to chemotherapeutic intervention in TGCT, the patient was started on cisplatin and etoposide, with the plan to include bleomycin in subsequent cycles if his pulmonary function improved. Unfortunately the patient’s clinical course consisted of progressive brain metastases (Figure 4), seizures, and pulmonary embolism.

FIGURE 4: MRI Five Months After Initial Presentation
Marked progression in a multiple ring-enhancing lesions with vasogenic edema.

He rapidly deteriorated before receiving a full course of treatment and succumbed to his disease only five months after initial presentation. Informed consent was obtained from the patient initially and from the patient’s family after he passed away.

Discussion
Literature review

English publications of "burned out" TGCT case reports were identified from Medline and EMBASE databases via OVID engine without restrictions on year of publication. The keywords were "germ cell tumor," "burned out phenomenon," and "testicular tumor." Additional studies were identified from reference lists of retrieved papers and review articles. Studies that did not discuss primary testicular origin were excluded. The search yielded 38 results and each abstract was reviewed. A total of 27 articles were thoroughly reviewed and 79 cases of "burned out" TGCTs were identified. The presenting sites, age of patient, tumor markers, histology, treatments employed, and outcomes were tabulated (Table 1) [5, 7-8, 17-40].

| First Author/Citation | Year of Study | Presenting/Metastatic Site | Age of Patient | Tumor Markers | Histology | Treatment | Outcome |
|-----------------------|--------------|---------------------------|----------------|---------------|-----------|-----------|---------|
| Balalaa N [17]        | 2011         | Retroperitoneal (n=1)     | 31             | aFP N         | NR        | DEP       | Treatment response |
|                       |              | Retroperitoneal (n=20)    | 17-67          | BhCG N        | +         | LDH +    |         |
|                       |              | Widely disseminated tumor (n=2) |              |              |           |           |         |

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| Author          | Year | Location(s) | Age(s) | Marker(s)          | Diagnosis/Nature | Treatment/Outcome                          |
|-----------------|------|-------------|--------|--------------------|------------------|--------------------------------------------|
| Balzer BL      | 2000 | Lung and Liver (n=1) | (mean 32) | αFP, αHCG, βHCG | Seminoma (n=36) | Orchiectomy and BEP, NR                    |
| Castillo C      | 2003 | Retropertioneal (n=1) | 25     | αFP               | Mature teratoma | BEP + αHCG                                  |
| Comber CV       | 1995 | Supraventricular (n=1) | 22-36  | αFP               | NR              | NR                                         |
| Condino G       | 2006 | Retropertioneal (n=1) | 42     | αFP, αHCG         | Seminoma | Orchiectomy, BEP, and RPLND, NR           |
| Fabre E         | 2004 | Testicular (n=1) | 32     | αFP               | Seminoma | Orchiectomy and Radiotherapy (30Gy) | Free of disease 16 years after the diagnosis |
| Fabre E         | 2004 | Retropertioneal (n=1) | 35     | αFP               | Mature teratoma | Orchiectomy, BEP plus vincristine, and RPLND | Free of disease 6 years after the diagnosis |
| Fabre E         | 2004 | Retropertioneal (n=1) | 50     | αFP               | Seminoma | Orchiectomy, RPLND, and EP | Total remission 3 years after the diagnosis |
| Fabre E         | 2004 | Retropertioneal (n=1) | 17     | αFP               | Mature teratoma | BEP, retropertional mass resection, and orchectomy | Free of disease 4 years after the diagnosis |
| Fabre E         | 2004 | Supraventricular (n=1) | 50     | αFP               | Seminoma | BEP followed by salvage chemo (mitotane, etoposide, ifosfamide, and cisplatin) | Total remission 3 years after the diagnosis |
| George SA       | 2015 | GIST (n=1) | 24     | αFP               | Mixed GCT | Orchiectomy | NR                                         |
| Gurioli A       | 2013 | Retropertioneal (n=1) | 35     | αFP               | Seminoma | BEP and orchectomy | Free of disease 2 years after the diagnosis |
| Haitel A        | 2013 | Retropertioneal (n=1) | 50     | αFP               | Seminoma | Orchiectomy, vincristine, bleomycin, and surgical debulking of mass | Free of disease 4 years after the diagnosis |
| Hu B            | 2015 | Retropertioneal (n=1) | 37     | αFP               | Seminoma | NR | NR                                         |
| Jaber S         | 2010 | Retropertioneal (n=1) | 32     | αFP, αHCG         | Seminoma | Orchiectomy and surgical removal of the retropertional mass | NR                                         |
| Kandpal M       | 2001 | Supraventricular (n=1) | 22     | αFP               | GCT having choriocarcinoma and probable embryonal cell | Orchiectomy and BEP | NR                                         |
| Reference | Case Description | Age | aFP | LDH | nodule Type | Treatment | Outcome |
|-----------|------------------|-----|-----|-----|-------------|-----------|---------|
| Leleu O [27] | Pulmonary (n=1) | 50 | | | Malignant germ cell tumor | Orchiectomy and BEP | Stable 3 years after the diagnosis |
| Lopez JA [28] | Retroperitoneal (n=1) | 20 | | | Choriocarcinoma | Orchiectomy, biopsy of retroperitoneal masses, BEP plus vincristine | Deceased 7 months after initial complaints |
| Mesa H [29] | Gastric ulcers (n=1) | 55 | | | Poorly differentiated adenocarcinoma- further studies revealed seminoma | Orchiectomy, vincristine, bleomycin and cisplatin | Free of disease 1 year after the diagnosis |
| Onishi K [30] | Para-neoplastic neurological syndromes (n=1) | 41 | | | | | Free of disease 15 months after the diagnosis |
| Patel MD [8] | Testicular (n=1) | 23 | | | Mixed GCT | Orchiectomy | NR |
| Perimenis P [31] | Retroperitoneal (n=1) | 40 | | | | | Free of disease 2 years after the diagnosis |
| Persua E [32] | Retroperitoneal (n=1) | 18 | | | Non-seminoma NOS | | Full remission |
| Preda O [33] | Retroperitoneal (n=1) | 40 | | | | | Free of disease 1 month after the diagnosis |
| Qureshi JM [34] | Retroperitoneal and Pulmonary masses (n=1) | 20 | | | Teratoma GCT | BEP followed by orchiectomy, RPLND, and hepatic mass resection | Free of disease 3 years after the diagnosis |
| Rozsosz M [35] | Spermatic cord (n=1) | 56 | | | | | Free of disease 6 months post operatively |
| Sahoo PK [36] | Retroperitoneal (n=1) | 33 | | | Seminoma vs poorly differentiated carcinoma (seminoma confirmed on IHC) | Orchiectomy and BEP | Patient under observation at time of publication |
| Suzuki K [37] | Mediastinum (n=1) | 27 | | | Teratoma GCT and sarcomatous elements | SEP | NR |
| Taeu J [7] | Retroperitoneal (n=1) | 23 | | | | | |
| | Retroperitoneal (n=1) | 35 | | | Non-seminoma NOS (n=3) | | |
| | Retroperitoneal (n=1) | 50 | | | Seminoma (n=3) | | |
| | Supraventricular (n=1) | 53 | | | | | |
| | | | | | Non-seminoma NOS BEP (n=3) | | |
| | | | | | Non-seminoma NOS BEP (n=3) | | |
| | | | | | Metastatic seminoma radiotherapy and RPLND (n=1) | | |
| | | | | | Seminoma orchiectomy (n=1) | | |
| | | | | | Complete remission | | |
| | | | | | Free of disease after 5 year follow up (n=1) | | |
| | | | | | Free of disease after 7 year follow up (n=1) | | |
| Yamamoto H [38] | Gastric tumor (n=1) | 59 | | | Seminoma | Orchiectomy and GP | Free of disease 2 years after the diagnosis |
TABLE 1: Reported Cases of ‘Burned Out’ TGCT

n = number of cases

aFP = alpha-fetoprotein

BhCG = beta-human chorionic gonadotropin

LDH = lactate dehydrogenase

N = normal level

+ = elevated level

BEP = bleomycin, etoposide, cisplatin

RPLND = retroperitoneal lymph node dissection

NR = not reported

NOS = not otherwise specified

Results

The sites of symptomatic metastasis identified were retroperitoneal (51.9%), testicular (12.7%), mediastinal (5.8%), pulmonary (3.8%), gastric (3.8%), and others (24.1%) consisting of prostate, supraclavicular, head and neck, and widely disseminated. The average patient age at presentation was 32.7 years old. Tumor markers were not found to be consistently elevated, with only 12.7%, 10.2%, and 5.1% of the cases found to be increased for BhCG, aFP, and LDH respectively. The most common treatment employed was orchiectomy with chemotherapy (57.5%), followed by chemotherapy alone (32.5%). Radiation therapy was utilized in four (10%) cases, all of which were seminoma [5,7,31,40]. The majority of reported cases had a good treatment response with only one reported death in the literature [28]. Tabulated case details are summarized in Table 2 [5, 7-8, 17-40].
### TABLE 2: Summary of ‘Burned Out’ TGCT Cases

NSGCT = non-seminomatous germ cell tumors  
+BhCG = elevated beta-human chorionic gonadotropin level  
+aFP = elevated alpha-fetoprotein level  
LDH = elevated lactate dehydrogenase level  
Orch = orchiectomy

| Presenting Site of ‘Burned Out’ TGCT | Total Cases | Age (Mean, Range) | +BhCG | +aFP | +LDH | Orch Alone | Chemo Alone | Orch + Chemo | Radiation Therapy Included | Treatment Unknown | Treatment Response, Death, Outcome Unknown |
|--------------------------------------|-------------|-------------------|-------|------|------|-----------|------------|-------------|---------------------------|------------------|-----------------------------------------|
| Retroperitoneal                       | 41          | 32 (17-67)        | 4     | 0    | 2    | 21        | 13         | 16          | 4                         | 38               | 23,1,31                                 |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| Testicular                           | 10          | 33, (23-56)       | 2     | 1    | 7    | 2         | 1          | 2           |                           |                  | 2,0,8                                  |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  | 0,0,3                                  |
| Mediastinum                          | 3           | 30,3 (27-32)      | 1     |      |      |           |            |             |                           |                  |                                         |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| Pulmonary                            | 3           | 27,3 (20-32)      | 2     |      |      |           |            |             |                           |                  | 2,0,1                                  |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| Gastric                              | 3           | 39 (34-55)        | 1     | 2    | 2    |           |            |             |                           |                  |                                         |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| Other                                | 19          | 32 (20-48)        | 1     | 3    | 1    | 8         | 1          | 1           |                           |                  | 4,0,13                                 |
| Seminoma                             |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   |       |      |      |           |            |             |                           |                  |                                         |
| Total                                | 79          | 32,7 (17-67)      | 10    | 4    | 8    | 4         | 13         | 16          | 4                         | 38               | 23,1,31                                 |
| Seminoma                             |             |                   | 0     |      |      |           |            |             |                           |                  |                                         |
| NSGCT                                |             |                   | 4     |      |      |           |            |             |                           |                  |                                         |
| Other/Unknown                        |             |                   | 2     |      |      |           |            |             |                           |                  |                                         |

**Case discussion**

A salient feature of all invasive TGCTs is a gain in material in the short arm of chromosome 12, and is diagnostic if present [41]. Although the initial pathology revealed a non-diagnostic metastatic tumor, further testing revealed an amplification of chromosome 12p leading to the diagnosis of TGCT. This suggests that the examination of poorly differentiated carcinomas of an unknown primary site using light microscopy and immunohistochemical profiling may be inadequate, and should undergo additional testing modalities with molecular chromosomal analysis [41-42].

The behavior and aggressive nature of the tumor discussed throughout this case combines the complexity of the evolving field of tumor biology and unique patient characteristics. Interestingly, the patient had a
confirmed family history of factor V Leiden mutation. It has been suggested that clotting factor polymorphisms such as factor V Leiden are associated with cancer onset and progression. The theoretical mechanism behind such adverse effects stems from the involvement of tissue factor and thrombin in tumor angiogenesis, which is essential for tumor growth and metastasis [43]. Furthermore, such factors may contribute to a more radio-resistant tumor profile despite advanced diagnostic techniques and treatment modalities. Thus, this case reflects the need for further research to explore the dynamic interplay of tumor biology and patient characteristics for targeting tumor response.

Conclusions

This case is presented for its unconventional presentation, rarity of occurrence, and difficulty in diagnosis. It brings forward the discussion of both the commonality of TGCT in young male adults, as well as the anomaly of a 'burned out' TGCT. With unreliable tumor markers, nonspecific symptoms, and pathological findings, the 'burned out' phenomenon accounts for a challenging diagnosis, particularly with the presenting symptom arising from a less common metastatic site. This case adds to the increasing literature on the rare entity of the 'burned out' TGCT, and upon literature review, presents itself as the first reported case presenting with brain metastasis. By establishing a strong foundation of 'burned out' TGCT in the literature leading to familiarity of the diagnostic process, a deeper understanding into medical management may arise.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Consent for the use of case details with intent of publication was obtained from the individual described in the case study. Consent was discussed and documented by the first author of the case report. As the patient unfortunately was deceased at the time of publication, further written consent was also obtained by the family of the patient.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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