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

Kate Johnson [1] , Bryan Brunet [2]

1. Radiation Oncology, Cancer Care Manitoba, University of Manitoba, Canada 2. Radiation Oncology, Saskatoon Cancer Center

Corresponding author: Kate Johnson, kate.johnson@usask.ca
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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.

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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, bones, 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 spontaneous regression occurs without treatment [5]. Despite the regression of the primary testicular tumor, approximately 50% of 'burned out' primary testicular tumors continue to harbor malignant cells and distant metastatic disease can progress [6-7]. A 'burned out' TGCT can arise, regress, and metastasize within the same testicle. Cases within the literature describe pathological evidence of tumor regression of a testicular mass with a focus of GCT within a clinically unremarkable testicle [4,8]. This can lead to difficulty in making a diagnosis as the metastasis can be mistaken for a primary tumor.

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 [7-8]. 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*).

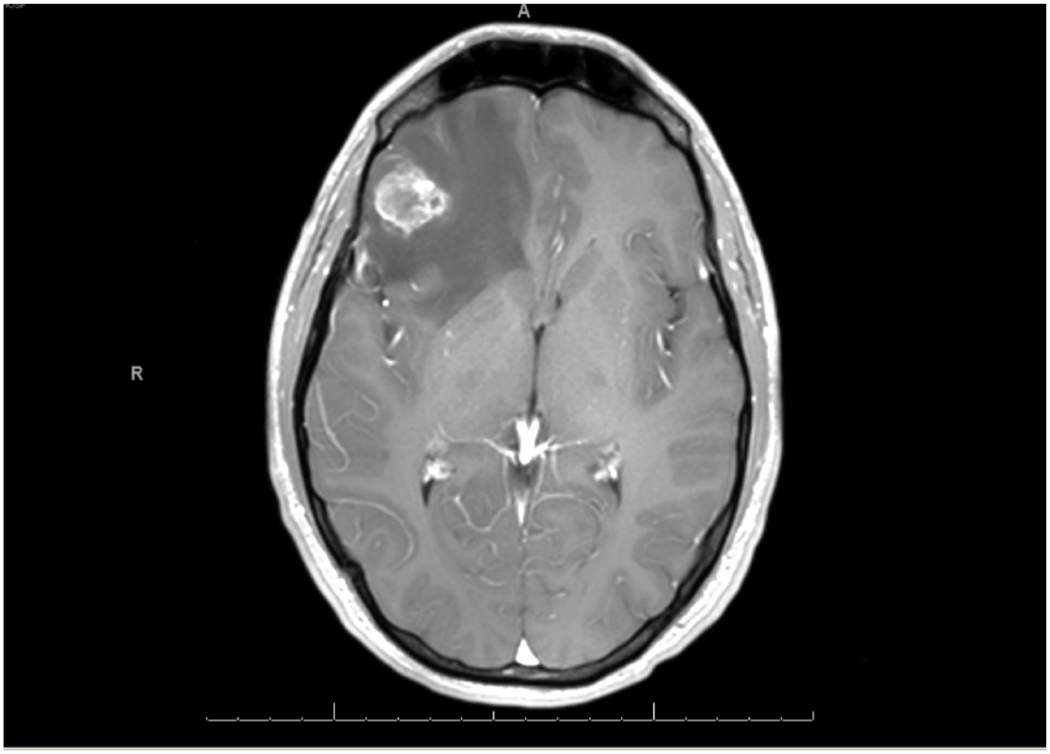

FIGURE 1: Initial Brain MRI

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*).

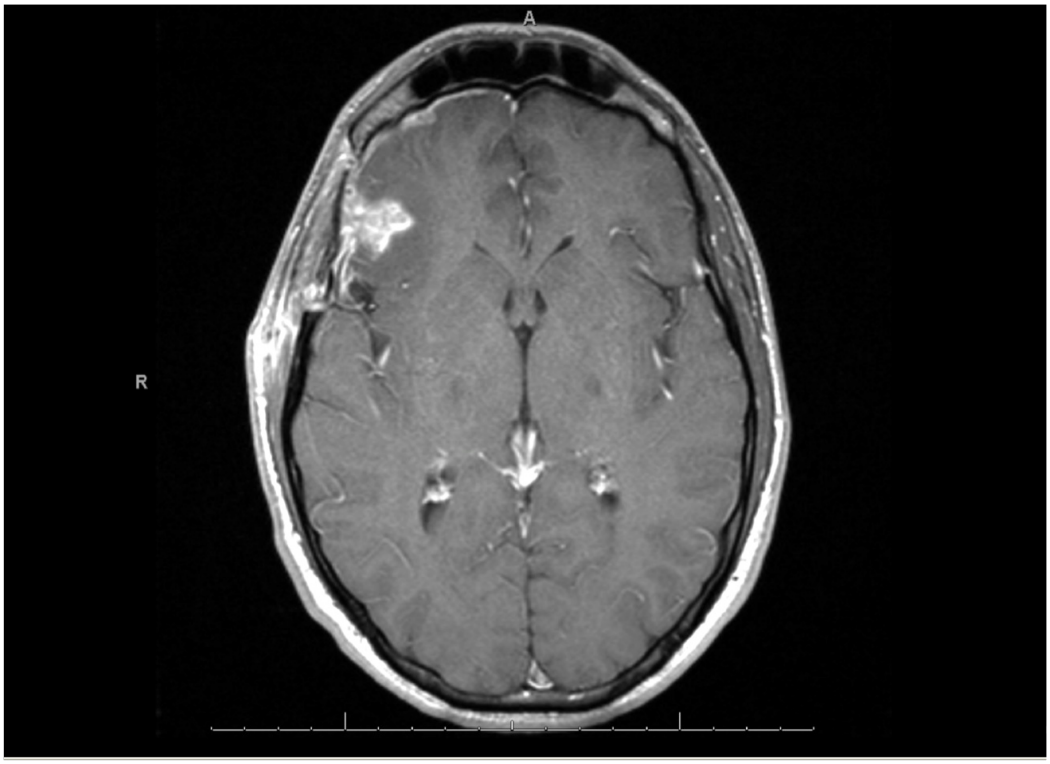

FIGURE 2: MRI One Month Post-Resection

Increased enhancement in the surgical bed.

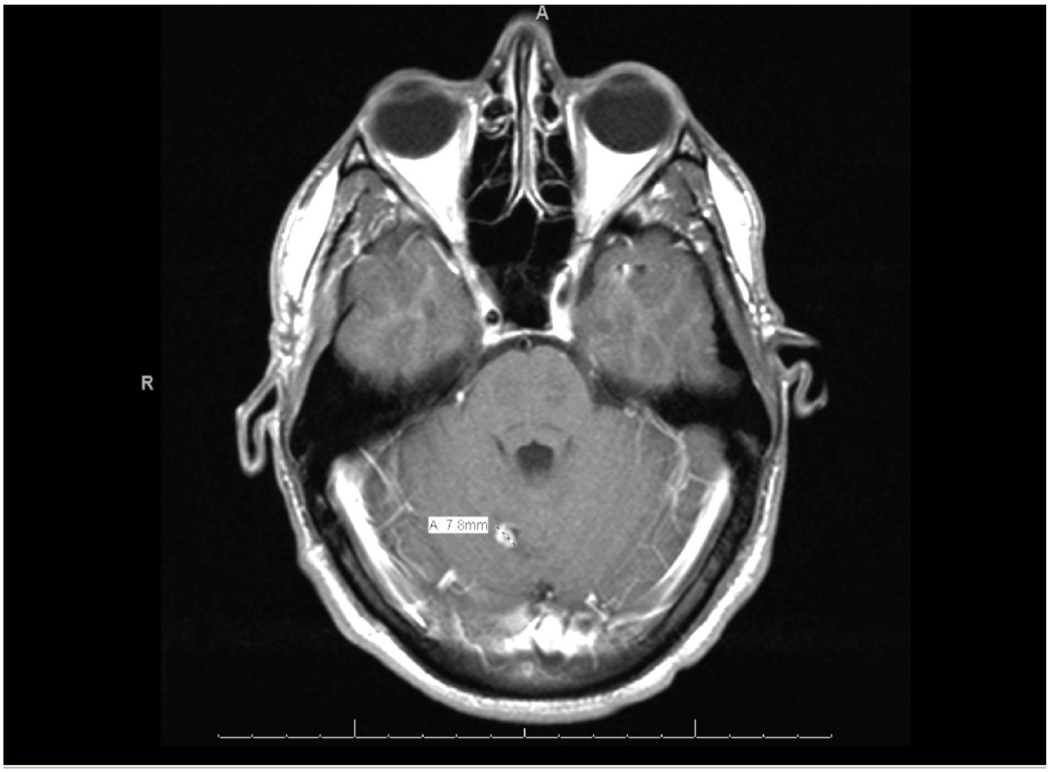

FIGURE 3: MRI One Month Post-Resection

New definite enhancing foci compatible with metastatic foci.

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 [14-16]. Unfortunately the patient's clinical course consisted of progressive brain metastases (Figure *4*), seizures, and pulmonary embolism.

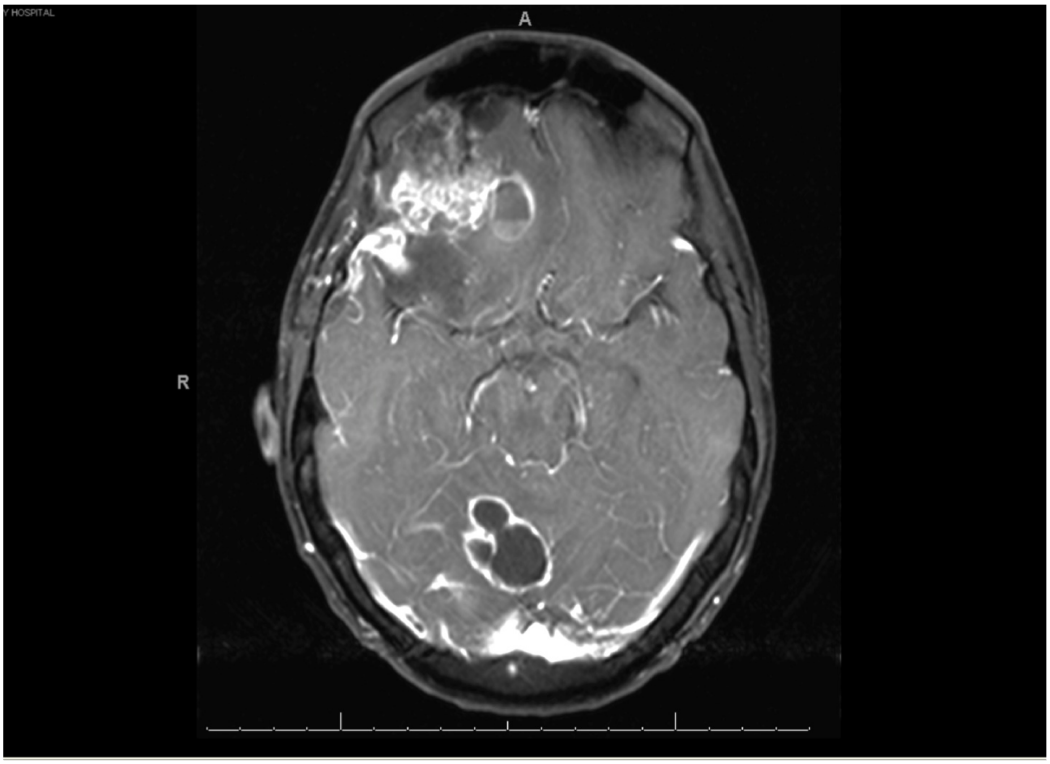

FIGURE 4: MRI Five Months After Initial Presentation

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 BhCG LDH	N N +	NR	BEP	Treatment response
Balzer BL [18]	2006	Retroperitoneal (n=20) Widely disseminated tumor (n=2) Lung and Liver (n=1) Mediastinum (n=1) Other (thyroid, neck thoracic cavity) (n=1) Testicular mass (n=7)	17-67 (mean 32)	BhCG	+ (n=2)	Seminoma (n=26)	NR	NR
Castillo C [19]	2003	Retroperitoneal (n=1)	25	aFP BhCG	+ +	Mature teratoma	BEP	Initial clinical response
Comiter CV [20]	1995	Retroperitoneal (n=1) Supraclavicular (n=1)	22-36	NR		NR	NR	NR
Curigliano G [21]	2006	Retroperitoneal (n=1)	42	aFP BhCG LDH	N + N	Seminoma	Orchiectomy, BEP, and RPLND	NR
		Testicular (n=1)	32	aFP BhCG LDH	N N N	Seminoma	Orchiectomy and Radiotherapy (30Gy)	Free of disease 16 years after the diagnosis
		Retroperitoneal (n=1)	35	aFP BhCG aFP	+ + N	Mature teratoma	Orchiectomy, BEP plus vincristine, and RPLND	Free of disease 6 years after the diagnosis

Fabre E [5]	2004	Retroperitoneal (n=1)	50	BhCG LDH	N +	Seminoma	Orchiectomy, RPLND, and EP	Total remission 3 years after the diagnosis
		Retroperitoneal (n=1)	17	aFP BhCG LDH	N N N	Mature teratoma	BEP, retroperitoneal mass resection, and orchiectomy	Free of disease 4 years after the diagnosis
		Supraclavicular (n=1)	39	aFP BhCG LDH	N N N	Seminoma	BEP followed by salvage chemo (vinblastine, etoposide, ifosfamide, and cisplatin)	Total remission 3 years after the diagnosis
George SA [22]	2015	GIST (n=1)	24	aFP BhCG LDH	N N N	Mixed GCT	Orchiectomy	NR
Gurioli A [23]	2013	Retroperitoneal (n=1)	35	aFP BhCG LDH	N N +	Seminoma	BEP and orchiectomy	Free of disease 2 years after the diagnosis
		Retroperitoneal (n=1)	50	aF BhCG	N +	Seminoma	Orchiectomy, vincristine, ifosfamide, bleomycin, and surgical debulking of mass	Free of disease 4 years after the diagnosis
Hu B [24]	2015	Retroperitoneal (n=1)	37	aFP BhCG LDH	N N N	Seminoma	NR	NR
Jaber S [25]	2010	Retroperitoneal (n=1)	32	aFP BhCG	N N	Seminoma	Orchiectomy and surgical removal of the retroperitoneal mass	NR
Kebapci M [26]	2001	Supraclavicular (n=1)	22	aFP BhCG	N +	GCT having choriocarcinoma and probable embryonal cell carcinoma components	Orchiectomy and BEP	NR
Leleu O [27]	2000	Pulmonary (n=1)	30	aFP BhCG	+ +	Malignant germ cell tumor	Orchiectomy and BEP	Stable 3 years after the diagnosis
Lopez JI [28]	1994	Retroperitoneal (n=1)	20	aFP BhCG LDH	N + +	Choriocarcinoma	Orchiectomy, biopsy of retroperitoneal masses, BEP plus vincristine	Deceased 7 months after initial complaints
Mesa H [29]	2009	Gastric ulcers (n=1)	55	aFP BhCG	N N	Poorly differentiated adenocarcinoma- further studies revealed seminoma	Orchiectomy, vincristine, ifosfamide and cisplatin	Free of disease 1 years after the diagnosis

Onishi K [30]	2014	Para-neoplastic neurological syndrome (n=1)	41	NR		Seminoma		Orchiectomy and chemotherapy			Free of disease 15 months after the diagnosis	
Patel MD [8]	2007	Testicular (n=1)	23	aFP BhCG LDH	N N N	Mixed GCT		Orchiectomy			NR	
Perimenis P [31]	2005	Retroperitoneal (n=1)	40	aFP BhCG LDH	N N N	Seminoma		Orchiectomy, resection of retroperitoneal mass, and radiotherapy to para-aortic nodes			Free of disease 2 years after the diagnosis	
Peroux E [32]	2012	Retroperitoneal (n=1)	18	aFP BhCG	+ N	Non-seminoma NOS		Orchiectomy and chemotherapy			Full remission	
Preda O [33]	2011	Retroperitoneal (n=1)	43	aFP BhCG LDH	N N +	Seminoma		Orchiectomy and chemotherapy			Free of disease 5 months after the diagnosis	
Qureshi JM [34]	2014	Retroperitoneal and Pulmonary masses (n=1)	20	aFP BhCG LDH	N + +	Teratoma GCT		BEP followed by orchiectomy, RPLND, and hepatic mass resection			Free of disease 2 years after the diagnosis	
Rzeszutko M [35]	2015	Spermatic cord (n=1)	56	aFP BhCG	N N	Non-seminoma NOS		Resection of spermatic cord mass			Free of disease 6 months post operatively	
Sahoo PK [36]	2013	Retroperitoneal (n=1)	33	aFP BhCG LDH	N N N	Seminoma vs poorly differentiated carcinoma (seminoma confirmed on IHC)		Orchiectomy and BEP			Patient under observation at time of publication	
Suzuki K [37]	1998	Mediastinum (n=1)	27	aFP BhCG	N N	Teratoma GCT and sarcomatous elements		BEP			NR	
Tasu J [7]	2003	Retroperitoneal (n=1) Retroperitoneal (n=1) Retroperitoneal (n=1) Retroperitoneal (n=1) Supraclavicular (n=1)	23 35 50 17 33	NR		Non-seminoma NOS (n=3)	seminoma (n=2)	Non-seminoma NOS: BEP (n=3)	Metastatic seminoma: radiotherapy and RPLND (n=1)	Seminoma: orchiectomy (n=1)	Complete remission (n=3)	Free of disease after 5 year follow up (n=1) Free of disease after 7 year follow up (n=1)
Yamamoto H [38]	2007	Gastric tumor (n=1)	39	aFP BhCG LDH	N N +	Seminoma		Orchiectomy and EP			Free of disease 2 years after the diagnosis	

Yucel M [39]	2009	Retroperitoneal (n=1)	28	aFP BhCG LDH	N N +	'Burned out' testicular tumor NOS	Orchiectomy and BEP	Free of disease 5 years after the diagnosis
Yucel M [40]	2009	Prostate (n=1)	49	aFP BhCG	N N	Seminoma	Orchiectomy, BEP plus vincristine, and radiotherapy to mediastinum retroperitoneal and pelvic lymph nodes	Free of disease 7 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 (3.8%), 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].

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	9	2	21	15,1,26

	Seminoma							4		2		
	NSGCT											
Testicular		10	33, (23-56)				2			1	7	2,0,8
	Seminoma									1		
	NSGCT						2					0,0.3
Mediastinum		3	30.3 (27-32)					1			2	
	Seminoma											
	NSGCT							1				
Pulmonary		3	27.3 (20-32)						2			2,0,1
	Seminoma											
	NSGCT								2			
Gastric		3	39 (24-55)					1	2			
	Seminoma								2			
	NSGCT											
Other		19	32 (20-49)					1	3	1	8	4,0,13
	Seminoma								1	1		
	NSGCT							1	2			
Total		79	32.7 (17-67)	10	4	8	4	13	16	4	38	23,1,51
	Seminoma				0	4				4		
	NSGCT				4	2						
	Other/unknown					2						

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

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 arising 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: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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