Primary Somatic Transformation of Testicular Germ Cell Tumours. Pathology and Outcome.

G Scandura[1], L Beltran[2], C Alifrangis[3], A Sharma[4], J Shamash[3], D M Berney[1]

[1]Queen Mary University of London, Molecular Oncology, [2]Bartshealth NHS Trust, Department of Cellular Pathology, [3]Bartshealth NHS Trust, Department of Medical Oncology

[4]Mount Vernon Cancer Centre, Department of Oncology,

ABSTRACT

Introduction: While men with somatic transformation (ST) of testicular germ cell tumours (GCT) identified in metastases have a generally very poor prognosis, the prognosis of patients with primary somatic transformation of GCTs, when first identified within the testis, is not well understood. We here describe clinical and pathological factors of a cohort of men identified with PST to determine the optimal method of treatment of these rare cases.

Design: The database of a tertiary referral centre for testicular GCT was searched between 2003 and 2020. Pathology and clinical databases were investigated to reveal the initial and late pathology, tumour marker levels including tumour type and stage as well as any recurrences. The presenting pathology was reviewed as well as any recurrences. This was correlated with treatments given and survival data as well as cause of death.

Results: 19/1567 (1.2%) of patients were identified as having a diagnosis of primary somatic transformation. The presenting pathological GCT transformation included 7 sarcomas (4 rhabdomyoblastomas, 1 osteosarcoma, 1 chondrosarcoma and 1 sarcoma NOS), 4 carcinomas, 4 PNETs and 3 nephroblastoma and 1 angiomyxoma.
The mean age was 34.5 years (18-57); mean tumour size was 45 mm (11-110). Complete follow up was available in 17 patients. Tumour markers at presentation were available in 15/17 (88%) cases and 10/15 (67%) were normal, while the remaining 5 (33%) showed raised tumour markers. At presentation, 10/17 (59%) patients had radiologically proven metastases. 9/17 (53%) patients had chemotherapy, 6/17 (35%) underwent surveillance, 1/17 (6%) underwent RPLND, 1/17 (6%) had palliative radiotherapy. To date only 3/17 (17%) of patients have relapsed.
Overall, the mean follow up was 41 months. 13/17 (76%) patients are disease free after treatment including 1 patient with nephroblastoma who underwent multiple rounds of chemotherapy. 7/17 (41%) underwent RPLND: 3 of them showed mature teratoma, 1 seminoma; 2 confirmed the somatic transformation and 1 was a secondary transformation following chemotherapy. 2/17 (12%) patients have died because of disease (1 adenosquamous and 1 rhabdomyosarcoma).

Conclusion: When compared with somatic transformations which present after initial diagnosis in metastases, primary somatic transformations show a more favourable outcome. Metastases often show discordant and more favourable pathology. We suggest that treatment should presume these tumours to be similar to germ cell tumours without somatic transformation, unless this is proven histologically. Biopsy of metastatic deposits in this situation might assist in tailoring treatment.

OBJECTIVES

The majority of testicular germ cell tumours (GCTs) are curable, with cure rates of 90-95%. However somatic transformation (ST) of a teratoma to a secondary malignancy remains poorly understood and very challenging to diagnose.
The prognosis after ST is diagnosed varies greatly depending on the site of disease. While ST in metastases such as retroperitoneal lymph node dissections is well known to have a poor prognosis, the prognosis of primary somatic transformation of GCTs (PST) identified within the testis, is not well understood and a number of small studies suggest the prognosis is more favourable. We wished to review the pathology and clinical factors at our tertiary referral centre of a cohort of men identified with PST to determine the optimal treatment for these cases.

METHODS

The database of a tertiary referral centre for testicular GCT was searched between 2003 and 2020. Reports were collected from all patients treated at Barts Health supraregional testicular cancer centre and from external consult cases received. Pathology and clinical databases were investigated to reveal the initial and late pathology, tumour marker levels including tumour type and stage as well as any recurrences. The presenting pathology was reviewed as well as any recurrences. This was correlated with treatments given and survival data as well as cause of death.

Table 1: Demographic and clinical characteristics of the 17 cases with primary somatic transformation

Patient	Age	Tumour markers at presentation	Diagnosis (date)	Clinical stage	Initial Treatment	Relapse	Further Surgery	Last follow up (date)
13	18	Normal	10% teratoma with 90% somatic transformation to a PNET (Jul 2016).	1	Surveillance	No	No	Disease free (Sep 2016)
16	25	Raised AFP and β-hCG	15% embryonal carcinoma, 5% yolk sac tumour, teratoma with 55% nephroblastomatous elements (Dec 2020	1	Surveillance	No	No	Disease free (Dec 2020)
14	28	Normal	Post-pubertal type teratoma with 95% PST and 5% teratomatous elements (Mar 2017)	1	Surveillance	No	No	Disease free (Sep 2019)
10	30	Normal	Somatic transformation within a teratoma to a basaloid variant of squamous cell carcinoma (Oct 2010)	1	Surveillance	No	No	Disease free (Jul 2017)
1	36	Normal	25% seminoma, 5% embryonal carcinoma and 75% teratoma components with somatic transformation of a GCT to sarcoma (Jan 2010)	1	Surveillance	Yes	RPLND (metastatic seminoma)	Disease free – discharged (Nov 2015)
7	42	Normal	Somatic transformation to PNET from teratoma (Nov 2007).	1a	Chemotherapy (GAMEC)	No	No	Disease free (Sep 2018)
17	57	Normal	10% seminoma and teratoma with somatic transformation to PNET (90%) (Aug 2020)	1	Chemotherapy (BOP followed by VIP)	No	Yes (secondary somatic transformation followed by chemotherapy)	Ongoing treatment (Jan 2021)
8	21	Normal	PNET arising on a background of teratoma pT1 (Oct 2012).	2	Chemotherapy (BEP)	No	No	Disease free (Jan 2021)
12	26	Normal	Somatic transformation to adenocarcinoma of a 30% postpubertal-type teratoma (Jul 2016).	2	Surveillance	No	RPLND (mature teratoma)	Disease free (Mar 2017)
15	27	Normal	95% low grade angiomyxomatous tumour, 5% focal seminoma (Jan 2020)	2b	Chemotherapy (BEP)	No	RPLND (teratoma and angiomyxoma transformation)	Disease free (Nov 2020)
2	28	Normal	Teratoma, postpubertal-type, showing overgrowth of cartilage suggesting somatic transformation as well as focal ganglioneuronal tissue (Sep 2016)	2	RPLND (metastatic postpubertal-type teratoma with only a well-differentiated neuroectodermal glial component	No	No	Disease free (Jun 2017)
11	38	Raised AFP and LDH	Somatic transformation of a 40% teratoma to an embryonal rhabdomyosarcoma (Aug 2016)	2	Chemotherapy (1 cycle POMB, stopped for worsening side effects and then Gem-TIP)	Yes	No	Disease free (Jun 2019)
9	45	Raised LDH	Somatic transformation to Adenocarcinoma arising in a NSGCT (Dec 2012)	2	Chemotherapy (BEP)	No	RPLND (mature teratoma)	Disease free (Jan 2016)
3	29	Not Available	Rhabdomyosarcoma arising in a GCT (Jun 2003)	3	Chemotherapy (BEP)	No	No	DoD (Apr 2005)
6	35	Raised AFP and LDH	10% teratoma, 90% secondary malignant somatic transformation into rhabdomyosarcoma (Mar 2015)	3	Chemotherapy (cisplatin, ifosfomide and doxorubicin)	No	RPLND (mature teratoma)	Stable disease (Sep 2020)
4	47	Not Available	somatic transformation to adenosquamous carcinoma in a primary combined mixed GCT (Apr 2014)	3c	Palliative RT to bone	No	No	DoD (Aug 2014)
5	51	Raised AFP, β-hCG and LDH	- Extensive disease at diagnosis (Aug 2014); - patient treated initially on the basis of tumour markers; - post-chemotherapy orchidectomy showed nephroblastomatous somatic transformation within a 20% post-chemotherapy teratoma; patient relapsed multiple times.	3c	Chemotherapy (BEP) at diagnosis; Chemotherapy (GAMMA) at first relapse; Chemotherapy: Cisplatin and Epirubicin followed by high dose chemotherapy (Carboplatin, Etoposide, Epirubicin and Melphalan), followed by RT	Yes (x 3)	- Neck mass biopsy at first relapse (metastatic GCT with nephroblastomatous somatic transformation); - Metastatic brain resection at second relapse (metastatic mixed NSGCT with 20% embryonal carcinoma, 80% teratoma includes substantial amounts of nephroblastoma elements and 1% yolk sac tumour); - Neck mass dissection: GCT with nephroblastomatous somatic transformation.	Disease free (Dec 2020)

AFP: alpha-Fetoprotein; β-hCG: beta-Human Chorionic Gonadotropin; DoD: died of disease; GCT: germ cell tumour; LDH: Lactate Dehydrogenase; NSGCT: non seminomatous germ cell tumour; PNET: primitive neuro-ectodermal tumour; RPLND: retroperitoneal lymph node dissection; RT: radiotherapy.

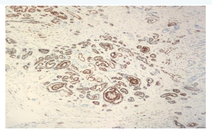

Fig 3: Immunochemistry for WT1 showing nuclear positivity in nephroblastomatous areas.

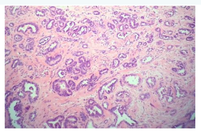

Fig 4: Somatic transformation to nephroblastoma

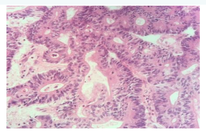

Fig 5: Adenocarcinoma somatic transformation

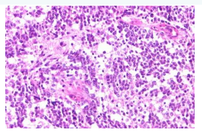

Fig 6: PNET transformation

RESULTS

Of 1597 patients reviewed and diagnosed with GCT, 19 (1.2%) were identified with primary somatic transformation. Percentage of GCTs with primary somatic transformation is showed in Fig 1. The mean age was 34.5 years with a range of 18-57. Complete follow up was available in 16 patients. Final histologies and follow ups are described in Table 1. Mean tumour size was 45 mm (11-110). On clinical review, at presentation, 10/17 (59%) patients had radiologically proven metastases, 9/17 (53%) patients had chemotherapy, 6/17 (35%) underwent surveillance and 1/17 (6%) had palliative radiotherapy.
13/17 (76%) patients are disease free after treatment, 1/17 (6%) on treatment, 1/17 (6%) has stable disease and 2/17 (12%) patients have died because of disease.

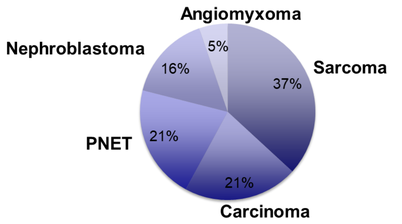

Fig 1: Histology of Germ Cell Tumours with somatic transformation

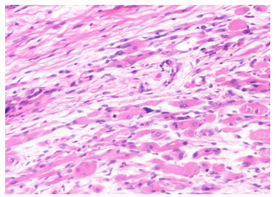

Fig 2: Rhabdomyosarcoma transformation

CONCLUSIONS

Diagnosis of PST has not resulted in disease progression in the vast majority of patients, suggesting it behaves considerably better that ST diagnosed at metastatic sites. It should be also noted that some cases of PST in the testis had discordant morphology in the resected metastasis.

We suggest that the following treatment strategies should be considered.

1. When the ST disease is stage 1, treatment and monitoring should be considered equivalent to a germ cell tumour without ST with consideration of the equivalent pathological prognostic information (size, vascular invasion, age etc)

2. When the ST disease is stage 2 or higher, biopsy or resection of the metastatic disease might be considered prior to chemotherapy to ensure that the disease is ‘malignant’ and not pure teratoma.

This work is supported by Orchid, fighting male cancer and by Bart and The London Charity