Management of Germ Cell Tumors with Somatic Type Malignancy: Pathological Features, Prognostic Factors and Survival Outcomes

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Purpose: Germ cell tumors with somatic type malignancy are rare, occurring in approximately 2.7% to 8.6% of germ cell tumor cases. Prognostic factors and optimal management remain poorly defined.

Materials and Methods: The Indiana University testis cancer database was queried from 1979 to 2011 for patients demonstrating germ cell tumor with somatic type malignancy at orchiectomy or subsequent resection. Patients with transformation to primitive neuroectodermal tumor only were excluded from study due to distinct management. Chart review, pathological review and survival analysis were performed.

Results: A total of 121 patients met the study inclusion criteria. The most common somatic type malignancy histologies were sarcoma (59), carcinoma (31) and sarcomatoid yolk sac tumor (17). Of these patients 32 demonstrated somatic type malignancy at germ cell tumor diagnosis. For those with delayed identification, median time from germ cell tumor to somatic type malignancy diagnosis was 33 months. This interval was longest for carcinomas (108 months). At a median followup of 71 months, 5-year cancer specific survival was 64%. Predictors of poorer cancer specific survival included somatic type malignancy diagnosed at late relapse ($p = 0.017$), referral to Indiana University for reoperative retroperitoneal lymph node dissection ($p = 0.026$) and grade ($p = 0.026$). None of these factors maintained prognostic significance on multivariate analysis. Somatic type malignancy histology subtype, stage, risk category and number of resections were not predictive of cancer specific survival.

Conclusions: Germ cell tumor with somatic type malignancy is associated with poorer cancer specific survival than traditional germ cell tumor. Established prognostic factors for germ cell tumor lose predictive value in the setting of somatic type malignancy. Aggressive and serial resections are often necessary to optimize cancer specific survival. Tumor grade is an important prognostic factor in sarcomas and sarcomatoid yolk sac tumors.

Key Words: testicular neoplasms, retroperitoneal space, sarcoma, teratoma, drug therapy

Abbreviations and Acronyms

CR = complete response
CSM = cancer specific mortality
CSS = cancer specific survival
GCT = germ cell tumor
IGCCCG = International Germ Cell Cancer Collaborative Group
IU = Indiana University
LR = late relapse
NSGCT = nonseminomatous germ cell tumor
PC-RPLND = post-chemotherapy retroperitoneal lymph node dissection
PNET = primitive neuroectodermal tumor
RPLND = retroperitoneal lymph node dissection
SM = somatic type malignancy

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THE presence of malignant nongerm cell histologies admixed with germ cell tumors has been referred to as malignant transformation as well as GCT with somatic type malignancy. This phenomenon is rare, reported to

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occur in 2.7% to 8.6% of nonseminomas treated at referral centers.[1–3] Germ cell tumor with SM is characterized by chemoresistance of SM elements. Thus, surgical resection remains the only potentially curative modality in the majority of cases. Primitive neuroectodermal tumor represents a notable exception in that PNET specific chemotherapy has demonstrated efficacy in treating GCT with this histology.[4] Despite aggressive resection performed at referral centers, cancer specific survival rates for patients with SM have been reported to range from 50% to 60%.[1–3]

Reports on this topic have failed to reveal consistent prognostic factors. Review of SM pathology shows common histologies to be sarcomas and PNET, although a variety of carcinomas and even hematologic malignancies have been reported (the latter having only been reported to occur with mediastinal primary GCT).[1,3,5] Interestingly, specific SM histology has not been shown to affect survival outcomes.

Given its rarity, the pathogenesis, prognostic factors and optimal management of GCT with SM remain poorly defined. This is most likely due to small study populations as well as inconsistencies in study inclusion criteria. To address these issues we reviewed a large, single center experience consisting only of male patients with nonPNET, nonmediastinal primary GCTs with somatic type malignancy.

PATIENTS AND METHODS

After institutional review board approval had been obtained the Indiana University database was queried for all patients demonstrating GCT with SM and undergoing RPLND from 1979 to 2011, yielding 246 patients. There were 94 patients with transformation to PNET only who were excluded from analysis as these patients were managed distinctly from other transformations and this experience has been reported separately.[4] Pathological review led to reclassification of transformed histology to immature teratoma in 11 patients and to GCT in 2. Ten patients with cystic trophoblastic tumors as well as 1 with ganglioneuroma were excluded from study as these histologies have been shown to exhibit a natural history similar to that of teratoma. Seven patients with insufficient clinical and pathological data on chart review were also excluded from analysis, leaving a study group of 121 patients.

While all pathology specimens containing malignant transformation had been previously reviewed at Indiana University, repeat pathology review was performed on specimens from 86 (70%) patients for whom slides were available. Sarcomas were graded using the criteria of the French Federation of Cancer Centers with those qualifying as grade 1 considered low grade, and those qualifying as grade 2 and 3 considered high grade.[6] Carcinomas were subjectively graded as low or high grade based on the degree of nuclear pleomorphism, mitotic rate and necrosis. With the use of antibodies directed against glypican 3, cytokeratin AE1/AE3 and the general germ cell tumor marker SALL4, 12 spindle cell tumors that had been classified as sarcomas were reclassified as sarcomatoid yolk sac tumors based on strongly positive reactions for the first 2 antigens with variable reactivity for SALL4. These neoplasms were included in the analysis of SMs because they no longer resembled any of the usual histological types of germ cell tumor. They were also graded using the sarcoma criteria.

Survival outcomes were calculated from the time of SM diagnosis rather than the time of GCT diagnosis. The interval to SM diagnosis was defined as the time elapsed from histological diagnosis of GCT to the date of histological diagnosis of SM. Late relapse was defined as recurrent disease 24 months or more after complete clinical remission to primary treatment. In addition to traditional staging and risk stratification, patients were categorized by extent of SM defined as 1) limited to testis, 2) spread to retroperitoneal nodes or 3) visceral/nonregional nodal metastases.

Frequencies and proportions are reported for categorical patient features, and measures of central tendency and dispersion are reported for continuous patient features. Kaplan-Meier unadjusted survival analysis curves were used to determine CSS for the entire study group. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine independent predictors of cancer specific mortality.

RESULTS

A total of 121 patients met the study inclusion criteria. Demographic and baseline disease characteristics are listed in table 1. Interestingly 5 of the patients with pure testicular seminoma demonstrated nonseminomatous elements in extragonadal resections and/or increased alpha-fetoprotein. Thus, all cases but 1 were nonsemimomas (99.2%). There were 93 patients (77%) with teratoma in

Table 1. *Characteristics at GCT diagnosis*

Mean pt age (range)	28.36 (15—54)
No. location of primary:	
Testis	112
Retroperitoneum	7
Pineal gland*	1
Groin	1
No. primary histology:	
NSGCT	116
Seminoma	5
No. stage:	
I	24
II	45
III	43
Missing	9
No. IGCCCG risk category:	
Good	29
Intermediate	13
Poor	18
Missing	17

*Peritoneal seeding from ventriculoperitoneal shunt.