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Teratoma With a Malignant Somatic Component in Pediatric Patients: The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Experience

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Background. Teratoma with a malignant somatic component (TMSC) is rare but described in adults, whereas information on pediatric presentation is sparse. ***Procedure.*** The Associazione Italiana Ematologia Oncologia Pediatrica identified 14 cases of TMSC. Clinical files and pathology specimens were reviewed. ***Results.*** The series (9 female, 5 male) showed the following disease: testis (2), sacrococcygeal (3), ovary (3), retroperitoneum (3), mediastinum (2), and foot soft tissue (1). Distribution of the somatic component was: carcinoma (4), pancreatic neuroendocrine tumor (1), neuroblastoma (3), rhabdomyosarcoma (3), rhabdomyosarcoma plus liposarcoma, chondrosarcoma, neurogenic sarcoma (1), chondrosarcoma plus neuroectodermal sarcoma (1), malignant peripheral nerve sheath tumor (1). Three patients were in stage I, four in stage II, three in stage III, and four in stage IV. All but one patient underwent surgery and only females showed carcinoma components. Nine patients relapsed or progressed and eight died. Six patients are alive and disease-free. Two patients underwent complete resection and four were treated based on transformed histologies. Relapse-free and overall survival rates were 35.7% and 42.8%, respectively (median follow-up, 31 months). ***Conclusions.*** Prognosis for germ cell tumors (GCTs) containing MSC is worse than that for GCTs. The pediatric disease appears to be more heterogeneous in tumor site distribution and MSC histology than in adults. Our series suggests no effects of age, histology, or gender on outcome. Surgery has an essential role in localized disease, with complete resection highly desirable. Chemotherapy optimized for histology should include reagents directed to the somatic malignancy, if chemosensitive. Malignant GCT warrants GCT-directed chemotherapy. Pediatr Blood Cancer 2010;54:532–537. © 2010 Wiley-Liss, Inc.

Key words: childhood; germ cell tumors; malignant transformation; teratoma

INTRODUCTION

A malignant somatic component, either of epithelial (i.e., carcinoma) or mesenchymal (i.e., neuroblastoma or sarcoma) origin and indistinguishable from a somatic malignancy, is occasionally seen admixed with mature or immature teratoma [1–3]. This rare entity is called teratoma with a malignant somatic component (TMSC).

Germ cell tumors (GCTs) are the most common neoplasms in young men (15–35 years old), and TMSC is a rare condition, accounting for only 3–6% of such patients. Published series report mainly males with mediastinal or testicular tumors, in which the malignant somatic component is usually a sarcoma, whereas the prevailing somatic component in ovarian TMSC (in 80% of cases) is squamous cell carcinoma [4–7]. The malignant somatic component may be present at diagnosis or only apparent at the time of analysis of residual or recurrent disease, either with or without GCT elements. The prevalence of the presence at diagnosis or at relapse is heterogeneous in published series [4,6–8].

In adults, the prognosis for GCTs that contain TMSC is worse than for GCTs in general, and the best treatment option of this rare entity remains controversial [2,3,6,7]. Surgery is still the standard option for localized disease. In the past, chemotherapy was considered ineffective, although cases suggesting the efficacy of chemotherapy directed towards the TMSC have been reported [2,6]. GCTs in childhood are rare, globally accounting for only 2% of all pediatric malignancies, but treatable with a high rate of cure. Since pediatric TMSC is very rare, the available information is sparse, no treatment guidelines have yet been developed, and cytogenetic studies are lacking [8–10].

PATIENTS AND METHODS

A retrospective analysis of the pathological and clinical files of pediatric patients who presented to the Hospital associated with the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and who were treated in Italy between 1978 and 2007 identified 14 patients with TMSC. The records of these 14 patients were reviewed and their clinical characteristics and outcomes recorded. Two independent pathologists reviewed the histological material. Since patients had been classified under different staging methods or not classified at all over the lengthy time interval involved (29 years), the whole series was re-staged according to the Children's Oncology Group (COG) staging system for GCTs (Table I) [11]. Levels of alpha-fetoprotein (αFP) and beta-human choriogonadotropin (β-HCG), both tumor markers for GCTs, were considered elevated when they exceeded the upper normal range or, for αFP, the upper physiological levels for age in infants younger than 1 year.

A response (complete, partial, or stable) had to persist for at least 1 month. Relapse and survival times were calculated from the date of diagnosis to the date of relapse and from diagnosis date to the latest contact for follow-up or upon death. Table II lists clinical and pathological data of the series and provides details of chemotherapy and local treatments.

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TABLE I. Staging of Testicular, Ovarian, and Extragonadal Tumors

Testicular	
I	Limited to testis, completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testis; tumor markers normal after appropriate half-life decline; patients with normal or unknown markers at diagnosis must have negative ipsilateral retroperitoneal lymph node samples to confirm stage I disease
II	Trans-scrotal orchiectomy; microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end); retroperitoneal lymph node involvement (<2 cm) and/or increased tumor markers after appropriate half-life decline
III	Tumor-positive retroperitoneal lymph node(s) >2 cm diameter: no visceral or extra-abdominal involvement
IV	Distant metastases that may include liver
Ovarian	
I	Limited to ovary, peritoneal washings negative for malignant cells; no clinical, radiologic, or histologic evidence of disease beyond the ovaries (gliomatosis peritonei did not result in upstaging); tumor markers negative after appropriate half-life decline
II	Microscopic residual tumor or positive lymph nodes (<2 cm); peritoneal washings negative for malignant cells (gliomatosis peritonei did not result in upstaging); tumor markers positive or negative
III	Gross residual tumor or only biopsy performed, tumor-positive lymph node(s) >2 cm diameter; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells
IV	Distant metastases that may include liver
Extragonadal	
I	Complete resection at any site, coccygectomy included as management for sacrococcygeal site, negative tumor margins
II	Microscopic residual; lymph nodes negative
III	Gross residual or biopsy only; regional lymph nodes negative or positive
IV	Distant metastases that may include liver

Ref. [11].

RESULTS

This series, consisting of nine females and five males with a mean age of 7.5 years at diagnosis (range 0–26 years), represents approximately the 1.4% of all extracranial pediatric GCTs observed in Italy from 1978 to 2007. Table II lists clinical and pathological data of the series and provides details of chemotherapy and local treatments.

The site of the primary tumor was: ovary (3), sacrococcygeal (3), testis (2), retroperitoneum (3), mediastinum (2), and soft tissue of the foot (1). Staging according to the COG classification system (Table I) indicated three patients in stage I, four in stage II, three in stage III, and four in stage IV. In fact, the present restaging would not have had a significant impact on the subsequent treatments and results because therapies were dictated mainly by degree of resection and type of histology. Six patients were already staged according to COG criteria, the six oldest ones were staged for the first time, and staging in two patients remained unchanged despite staging according to that in use for soft tissue sarcoma. Primary tumors were surgically resected in 11 patients at diagnosis, in 2 patients after chemotherapy, and in 1 patient, only biopsy was performed. In 11 of the 14 patients, TMSC was present at diagnosis, while the somatic component in the other 3 was detected at the time of a local relapse (# 2, 4) or in the retroperitoneal lymph node and lung metastases at the time of surgery post-chemotherapy (# 14). The reference pathologists reviewed all of the series and confirmed all diagnosis. The slides from first diagnosis and from relapse or residual tumor after chemotherapy were reviewed in four patients (# 10, 11, 13, 14), from relapse-only in two cases (# 2, 4), and from first diagnosis in the remaining eight patients. In three cases (# 2, 4, 14), the MSC was not detected at diagnosis and in two of these three, slides at diagnosis were not available. In two cases (# 8, 9), the percentage of YST component, which was not available at the time of diagnosis, was provided.

In 13 of 14 of these tumors, either a mature or immature teratomatous component as well as an MSC portion were observed. αFP was elevated at diagnosis in 4 of 14 patients, accompanied by YST histology in all 4 cases, and by elevated β-HCG in 1 of these 4. Only one male revealed chondrosarcoma and neuroectodermal sarcoma together with YST without a teratomatous component [12]. In the three cases that relapsed, there was no evidence of any increase in tumor marker levels, suggesting that the TMSC accounted for the failure of the treatment.

The TMSC was epithelial in five patients (four adenocarcinoma and one well-differentiated neuroendocrine tumor) and mesenchymal in the other nine (embryonal rhabdomyosarcoma and/or other sarcomas in five, malignant peripheral nerve sheath tumor in one, and poorly differentiated neuroblastoma in three cases). Interestingly, a carcinoma component was found in females only.

Stage I Disease

One female with mediastinal immature teratoma and well-differentiated pancreatic neuroendocrine tumor (# 1) had no further therapy after surgery and is disease free 18 months after diagnosis. A second 10-year-old female with retroperitoneal immature teratoma (# 2) had no further therapy after surgery but relapsed locally 6 months later with an immature teratoma plus poorly differentiated neuroblastoma component. She was treated according to the neuroblastoma protocol with vincristine, cyclophosphamide, doxorubicin, and dactinomycin but died of disease 3 years after diagnosis. A third stage I patient (# 3), who had an ovarian mature teratoma plus adenocarcinoma, received adjuvant chemotherapy with vincristine, dactynomicin, and cyclophosphamide (VAC regimen) according to the Italian protocol for GCTs of that time and remains disease-free 28 years after diagnosis.

Stage II Disease

A female infant (# 4) with sacrococcygeal mature teratoma received no further treatment after surgery until the tumor recurred

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TABLE II. Clinical, Pathological Data and Treatments of the 14 Patients

Patients	Gender	Stage	Age	Primary site	Histology of primary tumor at diagnosis	Histology after CT or at relapse	Surgery at diagnosis	Treatment at diagnosis	Treatment at relapse	Outcome	RFS (mos)	Duration of response (mos)
1	F	I	3 yrs	Mediastinum	IT + well-differentiated pancreatic neuroendocrine tumor of uncertain biological behavior		S (complete resection)			NED	18	18
2	F	I	10 yrs	Retroperitoneum	IT	At local relapse: IT + poorly differentiated neuroblastoma	S (complete resection)		Biopsy → VCR, CPM, Dox, Act D, 6 cycles	DOD	6	30
3	F	I	3 yrs	Ovary	MT + adenocarcinoma		S (complete resection)	Adjuvant VAC, 4 cycles		NED	336	336
4	F	II	4 mos	Sacrococcygeal	MT	At local relapse: MT + papillary adenocarcinoma	S (partial resection)		S (partial resection) VAC, 2 cycles	DOD	18	2
5	M	II	0 mos	Sacrococcygeal	10% MT + 90% poorly differentiated neuroblastoma		S (partial resection)	VP16 + CBDCA, 4 cycles		NED	45	45
6	M	II	18 mos	Retroperitoneum	IT + rhabdomyosarcoma, liposarcoma, chondrosarcoma, neurogenic sarcoma		S (partial resection)	IVA, 9 cycles	CBDCA, VP16, epirubicin, 3 cycles	DOD	23	15
7	F	II	17 yrs	Retroperitoneum	IT + rhabdomyosarcoma botryoid type		S (partial resection)	PEB, 4 cycles	CEVAIE regimen 9 cycles → RT on whole abdomen	NED	30	93
8	M	III	12 mos	Soft tissue of the foot	αFP: 232 IU/ml 10% YST + chondrosarcoma and neuroectodermal sarcoma		Biopsy	PEI, 3 cycles		DOD	6	6
9	F	III	13 yrs	Ovary	αFP: 190 IU/ml 10% YST + MT + adenocarcinoma		S (partial resection)		CDDP, CPM, epirubicin, 6 cycles	DOD	18	11
10	F	III	13 yrs	Mediastinum	MT + embryonal rhabdomyosarcoma	After CT and at relapse: MT + embryonal rhabdomyosarcoma	Biopsy	VAIA, 9 cycles, S post-CT (partial resection), post-surgical RT	IFM, VCR, HD-CPM, S on bone metastasis, ASCT with L-Pam and busulfan	DOD	21	12
11	F	IV	4 yrs	Sacrococcygeal with lung metastases	MT and IT + foci of adenocarcinoma	After CT and at relapse: MT and IT + foci of adenocarcinoma	Biopsy	CBDCA, IFM, VP16, VCR, ACT D, epirubicin, S post-CT (partial resection)	S on liver metastases	DOD	16	8
12	F	IV	26 yrs	Ovary with retroperitoneal lymph nodes, bone, bone marrow metastases	10% IT + 90% poorly differentiated neuroblastoma		Oopherectomy	VCR, CDDP, IFM, VP16, epirubicin × 6 cycles; HD-VP16, HD-CPM, ASCT with DHAD + L-Pam		NED	45	45
13	M	IV	17 yrs	Testis with retroperitoneal lymph nodes, lung metastases	αFP: 383 IU/ml foci of YST + IT + undifferentiated sarcoma NOS + rhabdomyosarcoma	After CT and at relapse: MT and IT + foci of adenocarcinoma	Orchiectomy	PEB, 4 cycles	ICE, 4 cycles, RPLND	DOD	10	7
14	M	IV	16 yrs	Testis with retroperitoneal lymph nodes, lung metastases	αFP: 61 IU/ml, β-HCG 570 mIU/ml, 50% YST + 10% EC + IT 40%	After CT: IT + malignant peripheral nerve sheath tumor	Orchiectomy	PEB, 4 cycles, RPLND, IFM + Dox 2 cycles, thoracotomies		NED	28	28

CT, chemotherapy; RT, radiotherapy; DOD, died of disease; NED, no evidence of disease; YST, yolk sac tumor; EC, embryonal carcinoma; IT, immature teratoma; MT, mature teratoma; S, surgery; RPLND, retroperitoneal lymph node dissection; VAC, vincristine, dactinomycin, cyclophosphamide; IVA, ifosfamide, vincristine, dactinomycin; VAIA, ifosfamide, vincristine, dactinomycin, doxorubicin; PEI, cisplatin, etoposide, ifosfamide; PEB, cisplatin, etoposide, bleomycin; CEVAIE, carboplatin, etoposide, vincristine, dactinomycin, ifosfamide, epirubicin; ICE, carboplatin, etoposide, ifosfamide; VCR, vincristine; ACT D, dactinomicyn; CPM, cyclophosphamide; IFM, ifosfamide; Dox, doxorubicin; DHAD, mitoxantrone; VP16, etoposide; CBDCA, carboplatin; CDDP, cisplatin; L-Pam, melphalan; HD, high-dose; ASCT, autologous stem cell transplantation; yrs, years; mos, months.

as a papillary adenocarcinoma 18 months later, when she again underwent surgery and received VAC chemotherapy; she died at 20 months after diagnosis. The other three patients (# 5–7) received systemic treatments after surgery. One male (# 5) with congenital sacrococcygeal mature teratoma and poorly differentiated neuroblastoma received chemotherapy with carboplatin and etoposide according to the protocol for infant neuroblastoma, and remains disease-free 3.7 years after diagnosis. Patient # 6 with retroperitoneal immature teratoma plus rhabdomyosarcoma, liposarcoma, chondrosarcoma, and neurogenic sarcoma was treated according to the rhabdomyosacroma protocol, i.e., ifosfamide, vincristine, and dactinomycin. He achieved a complete remission but relapsed locally 23 months after diagnosis and died of disease. Patient # 7 was an adolescent with retroperitoneal immature teratoma and rhabdomyosarcoma of the botryoid type, which recurred locally 2.6 years after four cycles of cisplatin, bleomycin, and etoposide (PEB) chemotherapy. The rhabdomyosarcoma protocol was adopted as a second-line strategy, with a six-drug regimen including ifosfamide, and radiotherapy of the whole abdomen. The patient is disease-free 7.7 years after the recurrence.

Stage III Disease

A 1-year-old male (# 8) with YST plus chondrosarcoma and neuroectodermal sarcoma in the soft tissue of the left foot underwent biopsy and chemotherapy with cisplatin, etoposide, and ifosfamide. Based on minimal shrinkage of the primary tumor, as revealed by magnetic resonance imaging, and on slow decline of αFP levels after three cycles of chemotherapy, amputation was recommended; the parents refused the amputation and the child died of metastatic disease 12 months after diagnosis. A second patient was a 13-year-old female (# 9) with a surgically resected ovarian cystoadenoma characterized by ascites and peritoneal implants. Given the benign histology, no further treatments were administered; however, lung, pleural, and bone metastases were detected 18 months later. At the time of relapse, a central review of histological specimens at diagnosis changed the diagnosis to YST with mature teratoma and adenocarcinoma, and the patient was therefore treated with cisplatin, epirubicin, and cyclophsphamide; however, she died of disease 11 months after relapse. The third patient (# 10) had a mediastinal mature teratoma and embryonal rhabdomyosarcoma, which was treated according to the rhabdomyosarcoma protocol (vincristine, ifosfamide, dactinomycin, and doxorubicin), followed by surgery (with microscopic evidence of residual disease) and radiotherapy. The same histological features present at diagnosis were detected at relapse. She relapsed in the bone and, despite high-dose chemotherapy, and autologous hematopoietic stem cell transplantation, died of disease 2.9 years after diagnosis.

Stage IV Disease

A young female (# 11) with sacrococcygeal mature and immature teratoma plus adenocarcinoma with associated lung metastases received a six-drug chemotherapeutic regimen, including carboplatin, etoposide, and ifosfamide, for 10 months and achieved disease stabilization. She underwent coccygectomy, but liver metastases were detected 1 month later. Surgical resection of these metastases was attempted, but only a partial excision was feasible and she died 24 months after diagnosis. Both histology specimens showed the same features as at diagnosis. A second patient (# 12) was a young woman with immature teratoma plus poorly differentiated neuroblastoma and bone, bone marrow, and retroperitoneal lymph node metastases. She was treated with the protocol for stage IV neuroblastoma, including cisplatin, ifosfamide, etoposide, and epirubicin, in sequential high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. The patient is alive and disease-free 3.7 years after diagnosis.

Two other cases (# 13 and 14) were adolescent males with testicular tumors associated with retroperitoneal lymph node and lung metastases. Patient # 13 had YST, immature teratoma, undifferentiated sarcoma, and rhabdomyosarcoma, all components already present in the primary site. Despite a normalization of αFP after four cycles of PEB, progression of lung and retroperitoneal disease together with bone metastases were detected 1 month later. He died of disease 17 months after diagnosis. The second (# 14) was a 16-year-old male with malignant non-seminomatous GCT of the testis without TMSC at diagnosis and with both tumor markers elevated. After four cycles of PEB, tumor marker levels returned to within normal range, and surgical excision of residual disease (lymph node and lung metastases) was planned. He underwent retroperitoneal lymph node dissection (RPLND), but histology revealed teratoma and malignant peripheral nerve sheath tumor (MPNST). After two cycles of ifosfamide and doxorubicin, the lung metastases remained stable and two subsequent thoracotomies were performed. The same histological features were detected in the resected lung metastases as in the retroperitoneal lymph nodes. The patient is disease-free 2.4 years after diagnosis.

In our series, two patients received inappropriate or incomplete treatment, with stage III patient # 8 refusing local therapy and stage III patient # 9 receiving no treatment except for surgery because of misdiagnosis. At the time of this report, the relapse-free and overall survival rates after a median follow-up of 31 months (range 12–336) were 35.7% and 42.8%, respectively. Nine of the 14 patients relapsed or progressed, and 8 of them soon died of their disease. The median time from diagnosis to relapse was 18 months (range 6–30 months).

Six patients (two males and four females) are alive and disease-free, with a median survival of 45 months (range 18–336 months). One female with a completely resected mediastinal tumor had received no further therapy, and only one patient who relapsed with TMSC was salvaged; the other five were cured with first-line therapy. Of the five survivors who received chemotherapy, one received adjuvant treatment directed toward GCTs, two were treated according to the neuroblastoma component, and the remaining two were treated according to GCT disease and the malignant mesenchymal component, sequentially or at relapse.

DISCUSSION

Our series of 14 patients with TMSC is representative of the disease as a whole, including all sites of presentation (gonadal and extragonadal), both genders, and different histologies (epithelial and mesenchymal), age and stage. As first-line therapy, 9 of the 14 patients were treated with surgery and chemotherapy, 4 underwent surgery as unique treatment, and 1 received chemotherapy only. Nine patients relapsed and eight died of disease. Six patients are currently alive and disease-free. In the whole series and particularly among these six survivors, neither age, gender, site of disease nor histology appeared to correlate with outcome. We find that the

prognosis for pediatric GCTs containing TMSC is generally worse than that for GCTs alone. We also find that surgery plays an essential role in localized disease, with complete resection desirable. Chemotherapy chosen based on the histology of the malignant transformed component and on a clearly malignant GCT component, if present, is also valuable.

The role of surgery for localized disease in our series, especially with respect to patients # 1, 3, and 5, is consistent with the conclusions of Biskup et al. [8] who studied a pediatric series of nine females (seven ovarian and two sacrococcygeal tumors). In that study, TMSC was always detected at diagnosis, no sarcomatous component was ever identified, while carcinoma was found in five cases. Six patients underwent surgery as a unique treatment (one sacrococcygeal and five ovarian tumors), and four of these patients are alive and disease-free without further therapies.

In adults, surgery remains the mainstay of treatment for TMSC in localized disease. Motzer et al. [3] report that the prognosis is more related to extent of disease and operability than to histological type, with complete resection of TMSC impacting favorably on survival. Donadio et al. [6] recommend surgery as the first choice of treatment in cases with a single tumor site. In the series of 14 adult males described by the French group [7], 3 of the patients where treated and cured with surgery only. Thus, in adults, it has been suggested that the surgeon be prepared to resect even adjacent organs or large vessels to ensure complete excision of the tumor [13]. In women, radical surgery, such as total hysterectomy, bilateral salpingo-oopherectomy, and lymphadenectomy, is associated with a better outcome [14].

In GCTs with TMCS, there are no typical clinical or radiological signs to predict malignant transformation of GCTs, which is one reason that surgery is advocated for patients with post-chemotherapy residual tumors or relapses, especially without evidence of elevated tumor markers [15–17]. Complete resection of residual masses after systemic therapy for GCTs might not only allow diagnosis of TMSC, but also prevent malignant transformation of residual teratoma. Note that there is no evidence that mature versus immature teratomas have more risk of malignant transformation [8]. The presentation of TMSC differs in different series, with 43% of adult cases identified within the primary tumor [3,7] and the remaining at the time of relapse [7] or in metastatic sites. By contrast, in the study by Biskup et al. [8], TMSC was already present at diagnosis in 100% of cases and in our series, in 78.5% of patients. In adults, it has been claimed that the transformation into adenocarcinoma takes longer than the other histologies [6,18]. In our series, all recurrences occurred within 2 years from diagnosis, including the case of adenocarcinoma. However, the carcinoma component is prevalent in females in the published series [5,8] and in ours as well.

In advanced disease, survival may be improved by combining systemic therapy with loco- regional treatments. Surgery has been recommended for metastatic disease, depending also on the type of MSC detected, since a favorable impact on survival has been observed in all major published series [5–7,18]. It is worth nothing that the male (# 14) with an MPNST component in retroperitoneal lymph node and lung metastases is disease-free after three surgical procedures involving the complete removal of the retroperitoneal lymph nodes and two subsequent thoracotomies.

Radiotherapy should be considered in addition to surgery, particularly when a sarcomatous component is identified. Although a clear-cut benefit has yet to be reported in adult with TMSC, radiotherapy has had a relevant clinical impact in selected cases of pediatric soft tissue sarcoma [19]. Of the nine patients in the present series who relapsed, only the patient (# 7) given chemotherapy and radiotherapy focused on the rhabdomyosarcoma component is still alive and free of disease.

TMSC has been thought to be unresponsive to chemotherapy or less responsive to cisplatin-containing chemotherapy, but it is now known that the efficacy of chemotherapy depends on the histological type. In the presence of a malignant GCT type, cisplatin-based chemotherapy should be initiated to eradicate that part. Overall, GCT-directed chemotherapy is reasonable only if there is a clearly malignant GCT component (i.e.,YST, embryonal carcinoma, or choriocarcinoma). Donadio et al. [6] suggest that systemic therapy has a role in selected patients and that the expected response is based on histology, always requiring a multimodality approach to attempt eradication of all residual disease. In the 10 patients in our series who received chemotherapy at diagnosis, prognosis was improved when the chemotherapy was oriented to the transformed histology, consistent with reports in adults [6,7]. In fact, four patients still alive and disease-free (# 5, 7, 12, and 14) received chemotherapy according to tumor cell type. Most exemplary of the benefit of this approach is patient # 12 with stage IV neuroblastoma, who is alive after aggressive chemotherapy directed toward the somatic malignancy.

In published series and in ours as well, a few patients with complete resection underwent adjuvant chemotherapy; however, the total number of these cases is too small to draw conclusion about the usefulness of adjuvant therapy. It has been suggested that this choice should be dictated by type of transformed histology and whether adjuvant treatment has proven benefit in stage I disease of that histology [6].

Although conclusions from our retrospective study are limited by the small sample size, the heterogeneity of the patient series, and the lengthy time interval involved (29 years), we find a poor prognosis for GCTs associated with TMSC, consistent with reports in adults [3,6,7]. We also find that the optimal treatment was complete surgical resection of the tumor or resection of residual disease after systemic therapy. The role of adjuvant chemotherapy remains unclear. First-line therapy is helpful in advanced stages and should be optimized for histology. Chemotherapy should include reagents directed towards the somatic malignancy, if it is known to be chemosensitive disease. GCT-directed chemotherapy should be chosen only if there is a malignant GCT. Radiotherapy should be considered when TMSC is a sarcoma. Further large-scale cooperative efforts are warranted to enable clinical data collection and to perform biological studies.

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