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Clinical Features Distinguish Childhood Chordoma Associated with Tuberous Sclerosis Complex (TSC) from Chordoma in the General Pediatric Population

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Abstract

Background—Chordoma, an age-dependent rare cancer, arises from notochordal remnants. Fewer than 5% of chordomas occur in children. Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome characterized by abnormal tissue growths in multiple organ systems. Reports of chordoma in patients with TSC suggest that *TSC1* and *TSC2* mutations may contribute to chordoma etiology.

Methods—To determine whether the 10 TSC-associated chordomas reported in the literature are representative of chordoma in the general pediatric population, we compared age at diagnosis, primary site and outcome in them to results from a systematic assessment of 65 pediatric chordoma cases reported to the US population-based cancer registries contributing to the SEER Program of the National Cancer Institute.

Results—TSC-associated chordomas differed from chordomas in the general pediatric population: median age at diagnosis (6.2 months, TSC vs. 12.5 years, SEER); anatomic site (40% sacral, TSC vs. 9.4% sacral, SEER); and site-specific age at diagnosis (all 4 sacral chordomas diagnosed during the fetal or neonatal period, TSC vs. all 6 sacral chordomas diagnosed at > 15 years, SEER). Finally, 3 of 4 patients with TSC-associated sacral chordoma were alive and tumor-free at 2.2, 8 and 19 years following diagnosis vs. a median survival of 36 months among pediatric sacral chordoma patients in SEER.

Conclusions—These results strengthen the association between pediatric chordoma and TSC. Future clinical and molecular studies documenting the magnitude and clinical spectrum of the joint occurrence of these two diseases should provide the basis for delineating the biological relationship between them.

Keywords

chordoma; tuberous sclerosis complex; bone cancer; pediatric; childhood cancer

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Author Contributions

D Parry and ML McMaster initiated this work and interpreted the data. ML McMaster collected the SEER data, performed the analyses and wrote the initial draft of the report. All authors read, edited, and approved the final version of the manuscript.

Competing Interests

None

INTRODUCTION

Chordoma is a rare bone cancer that is believed to arise from notochordal remnants that persist along the axial skeleton into adulthood.¹ Chordoma incidence is age-dependent and it is distinctly rare in the first decade of life.² Although most chordomas are sporadic, familial clusters have been reported,^{3–5} suggesting inherited susceptibility. Recently, a genetic basis for chordoma was confirmed in four multiple case families based on autosomal dominant inheritance of duplications of the *T*-gene (brachyury).⁶ Chordoma also occurs in association with tuberous sclerosis complex (TSC) suggesting genetic heterogeneity.⁷⁸

TSC is an autosomal dominant neurocutaneous syndrome characterized by the development of abnormal tissue growths (hamartomas) in multiple organ systems including brain, skin, heart, lungs and kidneys.⁹ The clinical manifestations of TSC exhibit variable expressivity and are age-dependent.¹⁰ More than 70% of TSC cases are estimated to be diagnosed in childhood.¹¹ TSC is caused by inactivating germline mutations in either *TSC1* or *TSC2*, tumor suppressor genes that encode hamartin and tuberin, respectively. Two-thirds of TSC patients present as sporadic cases resulting from new mutations occurring in either gene.¹² Most lesions found in TSC patients demonstrate somatic inactivation of either the wild type *TSC1* or *TSC2* allele, usually as a result of a large deletion encompassing adjacent markers (loss of heterozygosity, LOH).⁹ *TSC1* and *TSC2* are important constituents of the mTOR signaling pathway. Loss or inactivation of *TSC1* or *TSC2* function results in phosphorylation of mTOR and its downstream effector molecules, ultimately leading to enhanced cell growth and proliferation.¹³

The association of a specific cancer with a known genetic syndrome can provide clues to the cancer's underlying molecular pathogenesis.^{14–17} Consequently, reports of multiple patients with TSC and chordoma have raised interest in the possible biological relationship between the two diseases and potential role(s) of *TSC1* and *TSC2* in chordoma etiology.

To date, all but one of the chordomas reported in TSC patients have been diagnosed in individuals ≤ 16 years of age. This observation is highly unusual; in the general population, fewer than 5% of all chordomas occur in children and adolescents. To clarify the epidemiologic patterns of pediatric chordoma in the US, we performed a systematic assessment of pediatric cases reported within the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. SEER collects and publishes cancer incidence and survival data from population-based cancer registries selected to broadly represent the US population. We then compared the TSC-associated chordomas reported in the medical literature to the results from SEER to determine whether the TSC-associated tumors were representative of chordoma in the general pediatric population.

METHODS

We used the SEER program to derive frequency and survival data for all histologically confirmed cases of chordoma diagnosed in patients at or before age 18 years that were reported to 17 cancer registries during the period 1973 – 2007.¹⁸ These 17 population-based registries together represent approximately 26% of the US population. The SEER database does not record information related to diagnoses other than cancer. Cases were identified using the World Health Organization's International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology code for chordoma (9370/3).¹⁹ We calculated frequencies and analyzed them by age, gender, anatomical site of presentation, and cause-specific survival (a measure of net survival estimating the proportion of deaths due to a specific cancer diagnosis) using the SEER*Stat software public use program

version 6.6.2.¹⁸ Data were classified by median and range when a variable was continuous and by absolute and relative frequencies when a variable was categorical. Five- and ten-year chordoma-specific survival rates were calculated for the 34-year study period using actuarial and Kaplan-Meier methods. Standard SEER exclusion criteria for the survival analyses included diagnosis of other cancer prior to diagnosis of chordoma and patients for whom survival information was not available.

We identified 10 patients reported to be diagnosed with both chordoma and TSC through electronic searches of multiple electronic databases including PubMed, Scopus, Web of Science, and Google Scholar using a combination of the search terms: *chordoma*, *tuberous sclerosis*, *tuberous sclerosis complex*. In each instance in which a relevant article was identified we reviewed all the citations within the article to identify further references. The patients were described in nine reports and two abstracts published between 1975 and 2008. We reviewed each case report to determine the extent to which the putative TSC case conformed to current diagnostic criteria for TSC.²⁰ However, we did not exclude patients who did not fully meet diagnostic criteria, since most patients were very young and additional features of TSC have been shown to emerge with time.¹⁰

RESULTS

Pediatric chordoma in SEER

Sixty-five cases of histologically confirmed chordoma were reported to the SEER program during the study period (Table 1). The median age at diagnosis was 12.0 years (range 0 – 18 years), and the number of cases increased with age (Figure 1) with more than 50% being diagnosed between the ages of 12 and 18 years. Among the 64 chordomas for which primary site could be determined, 41 (64.1%) were intracranial, while 17 (26.6%) and 6 (9.4%) arose in the mobile spine and sacrum, respectively. The distribution of primary site varied with age (Figure 1): chordomas were exclusively skull-based in the youngest age tertile, while sacral chordomas were confined to patients in the oldest tertile.

Sixty-four patients had follow-up data. Twenty-one patients had died by the end of the study period. With a median follow-up of 51 months, actuarial cause-specific survival was 68.2% at 5 years following diagnosis, with 53.1% of patients surviving at 20 years. Long-term survival was similar for patients with chordoma of the skull base (56.9%; 95%CI=34.0–74.4) or mobile spine (55.1%; 95%CI=21.5–79.4) at 15 years following diagnosis. Based on small numbers (n=5), patients with sacral chordoma had a worse outcome, with a median survival of 36 months and no long-term survivors (Figure 2).

Pediatric chordoma in association with TSC

Chordoma in the 10 patients diagnosed with TSC (Table 2)^{7821–28} differed from that arising in the general pediatric population (Table 1). Median age at diagnosis of TSC-associated chordoma was 6.2 months (range 0 – 16 years) versus 12.0 years for chordoma in the general pediatric population; only a single TSC patient was diagnosed with chordoma after 5 years of age. The distribution of primary site also differed for chordomas associated with TSC compared to chordomas reported in SEER. While the majority of TSC-associated chordomas were skull-based (n=5, 50%), four (40%) arose in the sacrum. In contrast, only six sacral chordomas (9.4%) were reported in SEER. Moreover, all four TSC-associated sacral chordomas were diagnosed during the fetal or neonatal period (Table 2).

Outcome data were available for 7 of the patients with TSC-associated chordoma, including 3 of 4 patients with sacral chordoma (Table 2). Four of the patients treated with surgery alone were reported to be alive from 1 to 19 years later²⁹ without evidence of disease, while the fifth patient died 2 years following diagnosis. The patient who received post-operative

proton beam radiotherapy was reportedly alive and disease-free at 5 years following diagnosis. One patient with metastatic chordoma treated with chemotherapy was reported to be alive without evidence of disease at 5 years following diagnosis; no outcome information was available for the other patient with metastatic disease. Although numbers are small and data reporting is incomplete, the estimated 5-year survival for these patients was 83%, with a median follow-up of 5 years.

Only 1 patient, a 16-year old female, had been diagnosed with TSC prior to presenting with chordoma (Table 2). Eight of the other patients were discovered to have TSC either during (5 cases) or after (3 cases) evaluation for chordoma, including one who was diagnosed with TSC 12.5 years after presenting with chordoma. TSC was diagnosed posthumously in the tenth patient when DNA from his archived chordoma tissue demonstrated the same *TSC1* mutation identified previously in his father who had clinical stigmata of TSC. Germline *TSC* mutations were sought and identified in two other patients: one had a *TSC1* mutation and the other had a *TSC2* mutation. No information on *TSC1/TSC2* mutation status was provided for the seven other patients. Family history of TSC was queried for the three patients whose *TSC* mutation status was reported and four of the other patients; it was positive for the patient found posthumously to have a *TSC1* mutation and for two of the patients whose *TSC1/TSC2* mutation status was not reported.

DISCUSSION

To gain insight into the potential biological relationship between pediatric chordoma and TSC, we compared information on TSC-associated chordomas reported in the literature to data from a systematic population-based assessment of chordomas diagnosed in the US pediatric population up to age 18 years. The results demonstrated that age at diagnosis, primary site of presentation, and possibly outcome differed between chordomas reported in these two populations.

Incidence data in the general US population²¹⁸ suggest that chordoma may be diagnosed annually in fewer than 1 in 10,000,000 children under age 10 years. Therefore, the development of chordoma by age 16 in all 10 reported patients with TSC is very unusual. More striking, chordoma was diagnosed prior to age 5 in nine of these patients and by age two in seven of them. One possible explanation is that chordoma was diagnosed at a young age in some of them as a consequence of an evaluation for suspected TSC. However, chordoma presented or was diagnosed prior to recognition of TSC in all 9 patients who developed signs or symptoms from this tumor before age 5 suggesting that TSC-associated chordoma may have unusually early onset and/or extremely rapid growth.

In all patients with chordoma, the site of presentation is age dependent.² Among children with chordoma reported to SEER, over 60% presented with intracranial chordoma, whereas only 9.4% had sacral chordoma. This pattern is in accord with reported clinical series of pediatric chordomas.^{30–32} In SEER, chordomas in the very young were limited exclusively to the skull base while sacral chordomas were seen only in adolescents. The anatomic location of a chordoma may affect the age at which it is diagnosed, since a slow-growing tumor would be more likely to produce symptoms earlier in the closed intracranial space compared to a tumor originating in the sacrum, regardless of the presence or absence of TSC. However, the site distribution reported thus far for TSC-associated chordoma contrasts sharply with that observed for chordoma in children reported to SEER. In the children with TSC, sacral chordomas accounted for 40% of all tumors, and all four sacral chordomas were diagnosed during the fetal or neonatal period. The early ages at diagnosis of the four TSC-associated sacral chordomas were not necessarily a consequence of increased clinical scrutiny because of suspected TSC: although sacral chordoma was diagnosed within the

same time frame as TSC in three of the reported patients, it was diagnosed more than 12 years earlier than TSC in the fourth patient.

Once diagnosed, chordoma appeared to behave differently in TSC patients compared to general pediatric patients. In SEER, median actuarial survival differed by site of presentation. Based on small numbers, patients with sacral chordoma had a median survival of 36 months compared to chordoma at other sites, for which the median had not been reached at study cutoff (> 15 years). Atypical and poorly differentiated chordomas are associated with a poor prognosis in a subset of pediatric patients;^{32,33} however, we were unable to assess the impact of variant histologies on outcome because these are not recorded in the SEER database. Follow-up was comparatively short for TSC patients with chordoma; however, of the four patients with sacral tumors, two were reportedly alive and free of disease at 8 and 19 years following diagnosis, respectively. Although based on very small numbers, these data suggest that sacral chordoma may have a better clinical outcome in TSC patients than in general pediatric patients.

Our results are based on the assumption that all of the patients reported with TSC and chordoma had both diseases. Five patients (Cases 2, 5, 6, 7 and 8) with two major features²⁰ meet diagnostic criteria for definite TSC; Case 9, with one major feature and one minor feature, fulfills criteria for probable TSC; and Case 4, with one major feature, meets criteria for possible TSC. In addition, the diagnosis of TSC was confirmed in Cases 4 and 5 by the presence in each of a constitutional *TSC* mutation, and Case 3 had the same *TSC* mutation as his affected father. No specific clinical information was provided for Cases 1 and 10: the former was reported to have “classical clinical features (of TSC)”, and the latter patient was said to have epilepsy and a family history of TSC, in particular, a half sibling with a subependymal giant cell astrocytoma. Epilepsy was not the basis for the diagnosis of TSC in Case 10 but its occurrence initiated the evaluation that led to the diagnosis. The fact that clinical features consistent with definite TSC were not reported for every patient is not surprising because most patients were very young at the time of evaluation and may not have yet developed the full clinical phenotype.¹⁰ In addition, the case reports varied widely in both the quality and quantity of clinical details and on whether the focus was on TSC or chordoma. However, we believe that further clinical follow-up would have confirmed TSC in all of the patients and that, if mutation analysis had been routinely available and conducted, the probability of detecting *TSC1* or *TSC2* mutations would have been high.³⁴

Chordoma was reported to be diagnosed on the basis of resection or biopsy of the primary tumor (9 cases) or a metastasis (1 case). No additional information was given for three patients (Cases 1, 3 and 6). Images of tumor histopathology and detailed descriptions of tumor morphology were provided for four patients (Cases 4, 5, 7, 8) and supplemented by immunohistochemistry for three patients (Cases 5, 7, 8). Radiographic characteristics of the tumors were described for five patients (Cases 2, 7, 8, 9, 10) and augmented by magnetic resonance (MR) and/or computed tomographic (CT) images in four (Cases 2, 7, 8, 9).

This study is limited by the small number of reported cases of TSC-associated chordoma, potential biases in ascertainment and reporting of these cases, and the lack of systematically collected data on them. Consequently, we do not know whether the reported cases are representative of TSC-associated chordoma in general. If they are not, then our comparisons with the SEER data on pediatric chordoma and interpretation of the results may not be accurate. In addition, the SEER database is subject to certain well-known constraints,³⁵ although it continues to represent the largest available population-based dataset on chordoma in the US. Despite these substantial limitations, the results suggest that chordoma in the reported children with TSC differs in some important aspects from chordoma in children in the general US population. Germline *TSC1/TSC2* mutations were identified

directly in two of the 10 reported patients with TSC-associated chordoma and confirmed posthumously in a third patient. Molecular and immunohistochemical studies of the chordomas from the first two patients with identified mutations demonstrated that one tumor exhibited reduced signal from the wild type *TSC1* allele suggestive of LOH as well as absence of staining for hamartin, while the other tumor had clear LOH for the wild-type *TSC2* allele and focal very weak staining for tuberlin.⁸ These results support a pathogenetic role for the *TSC1/TSC2* genes in these TSC-associated chordomas.

The pathogenetic mechanism(s) underlying the etiology of sporadic chordoma remain unclear. However, reports of TSC-associated chordomas have generated interest in the role of the mTOR signaling pathway in the development of sporadic chordoma. If the mTOR pathway is involved in sporadic chordoma etiology, development of therapeutic inhibitors of molecules associated with the pathway could potentially provide effective treatments for chordoma. Treatment with one mTOR inhibitor has been associated with regression of astrocytomas in patients with TSC.³⁶ Inactivation of *TSC1/2* function leads to phosphorylation of mTOR and its downstream effectors, ultimately resulting in initiation of translation, cell growth and proliferation. Mutations in several other components of the mTOR pathway, including *Akt*, *P13K*, *S6K*, *LKB1*, *NF1*, *PTEN*, or *VHL*, can also result in aberrant mTOR activation and are characteristic of several hamartoma syndromes and some cancers.³⁷ In a recent study of 50 'typical' sporadic adult (mostly sacral) chordomas³⁸ the mTOR pathway was activated in 65% of the tumors. Because *TSC2* was phosphorylated in 96% of the studied tumors in the absence of LOH for either *TSC1* or *TSC2*, mTOR activation may have occurred as a result of post-translational inactivation of *TSC1/TSC2* mediated by *Akt*. Alternatively, *TSC2* has been shown to be a phosphorylation target of Ras-Erk signaling, with the result that direct phosphorylation of *TSC2* by *Erk* leads to inhibition of its tumor-suppressor function.³⁹ No molecular studies of sporadic pediatric chordomas have been reported, so whether activation of the mTOR pathway plays a significant role in the development of these tumors is unknown.

In summary, the reported chordomas in children with TSC were diagnosed at earlier ages and had a different site distribution than sporadic chordomas in the general US pediatric population. Previous work demonstrated somatic inactivation of the *TSC* genes in the chordomas from two of the TSC patients reported here. These results suggest that chordoma is a rare pediatric manifestation of TSC. Whether chordoma can also be an adult manifestation of TSC is not known. However, a case of chordoma with unusual clinical and anatomical presentation has recently been reported in an adult with TSC.⁴⁰ Before the relationship between TSC and chordoma can be fully explored, it will be necessary to carefully document the magnitude and clinical spectrum of their joint occurrence. This effort requires that consecutive patients diagnosed with chordoma at any age and site in a defined population be evaluated for TSC, and that the chordomas of those who meet TSC diagnostic criteria or have germline *TSC1/TSC2* mutations be examined for *TSC1/2* LOH. Meanwhile, future reports of chordoma diagnosed at any age in patients with TSC should provide detailed reporting of the features of both conditions, including the chronology of disease presentation and diagnosis, chordoma immunohistopathology and treatment outcome, and symptoms and signs attributable to TSC. Finally, clinicians who evaluate very young patients with chordoma, especially those with a sacral tumor, should maintain a high index of suspicion for the possibility of undiagnosed TSC.

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Figure 1. Distribution of primary chordoma sites by age in SEER

Each site-by-age segment is depicted as a proportion of all chordomas in the pediatric age group. The frequency of chordoma overall increases with age. In this study population, chordoma site appears to be age dependent. While chordoma was diagnosed at intracranial sites in all age groups, chordoma of the mobile spine appeared in the second tertile, and sacral chordoma was diagnosed only in adolescents (third tertile).

Figure 2. Survival of pediatric chordoma by primary site in SEER

Kaplan-Meier plot of cause-specific survival of patients aged 0 – 18 years diagnosed with chordoma affecting intracranial sites, the mobile spine, or the sacrum and reported to SEER. Median follow-up for the entire cohort was 48.5 months. Median survival was 36 months for patients with sacral chordoma. The median survival has not been reached for chordoma at other sites.

Table 1

Characteristics of pediatric chordoma occurring in association with tuberous sclerosis complex (TSC) and in SEER.

Feature	TSC-Associated			SEER		
	No. (%)	Median Age at Diagnosis	Age Range	No. (%)	Median Age at Diagnosis	Age Range
Males	6 (60)	6.2 months	0 – 4 years	38 (58.5)	13 years	0 – 18 years
Females	4 (40)	2.3 years	0 – 16 years	27 (41.5)	11 years	2 – 17 years
Tumor Site*						
Skull base	5 (50)	1.7 years	0.3 – 4.5 years	41 (64.1)	9 years	0 – 18 years
Mobile spine	1 (10)	16 years	16 years	17 (26.6)	13 years	8 – 17 years
Sacrum	4 (40)	2 days	0 – 5 days	6 (9.4)	16 years	15 – 18 years
All tumors	10 (100)	6.2 months	0 – 16 years	65 (100)	12 years	0 – 18 years
Metastases**	2 (20)	—	—	10 (19.6)	—	—
Treatment***						
Surgery alone	5 (62.5)	—	—	33 (50.8)	—	—
Postoperative radiotherapy	1 (12.5)	—	—	26 (40.0)	—	—
Radiotherapy alone	0 (0.0)	—	—	2 (3.1)	—	—
Chemotherapy	2 (25.0)	—	—	n.a.	—	—

* Primary site could be determined for all patients with TSC-associated chordoma and 64 of 65 chordoma patients reported to SEER.

** Staging information was available for all patients with TSC-associated chordoma and 51 of 65 chordoma patients reported to SEER.

*** Treatment data were available for 8 patients with TSC-associated chordoma and all chordoma patients reported to SEER. Among SEER patients, 3 (4.6%) received no treatment during the first year following diagnosis and 1 (1.5%) had no surgery and, though advised to receive radiotherapy, had no documentation confirming that radiotherapy was administered.

**** Because of issues related to data collection, information regarding chemotherapy is not routinely available via SEER*Stat.

Table 2
Features of chordoma and tuberous sclerosis complex (TSC) in ten patients with both disorders.

Chordoma				Tuberous sclerosis complex (TSC)					
Case No.	Sex	Age at Diagnosis	Primary Site/Metastases	Outcome and Time Since Diagnosis	Age at Diagnosis	Reported Clinical Features*	TSC mutation status	Family History	Ref.
1	M	neonate	sacrum/no	NED at 19 years	12.5 years	sclerotic changes in ribs and skull; multiple aortic aneurysms, "classical clinical features"	n.r.	n.r.	Dutton 1975 Nix 1978
2	F	4.5 years	skull base/no	n.r.	4.5 years	seizures, ash-leaf macule, calcified periventricular nodule, cortical tubers	n.r.	n.r.	Schroeder 1987
3	M	4 years	clivus/no	dead at 2 years	6 years (posthumous)	n.r.	** pos	pos	Borgel 2001
4	F	33-week fetus	sacrum/no	n.a.	33-week fetus	cardiac rhabdomyomas	*** pos	neg	Lee-Jones 2004
5	F	5 days	sacrum/no	NED at 8 years	6 years	hypomelanotic macules, shagreen patch, subependymal nodules, lipomas	**** pos	neg	Lee-Jones 2004
6	M	3 days	sacrum/no	NED at 26 months	~ 3 days	subcortical nodule, ocular hamartoma, cardiac rhabdomyoma, vitiligo, shagreen patch, descending aortic aneurysm	n.r.	neg	Kimura 2005
7	M	20 months	clivus/yes	NED at 5 years	20 months	ash-leaf macules, cortical tubers, subependymal nodules	n.r.	neg	Lountzis 2006
8	M	15 weeks	skull base/yes	n.r.	15 weeks	subependymal nodules, foci of T1-weighted high signal in both frontal lobes	n.r.	pos	Kombogiorgas 2006
9	F	16 years	mobile spine/no	NED at 1 year	< 16 years	seizures, intracranial hamartoma, cortical tubers	n.r.	n.r.	Roy 2004 Storm 2007
10	M	9 months	clivus/no	NED at 5 years	~ 1 year	seizures	n.r.	pos	Puccetti 2008

Abbreviations: M, male; F, female; NED, no evidence of disease; n.r., not reported; pos, positive; n.a., not applicable; neg, negative; RT, radiotherapy

* Cases 2, 5, 6, 7, and 8 had sufficient reported clinical features to confirm the diagnosis of TSC using current diagnostic criteria and Case 9 had features consistent with probable TSC. Cases 1, 4, and 10 were reported to have a clinical diagnosis of TSC with incomplete clinical details provided. In addition, Cases 4 and 5 each had a constitutional TSC mutation and Case 3 was diagnosed with TSC based on molecular genetics combined with family history of TSC. See Discussion.

** TSC1 nonsense mutation, G2045T, exon 15

***
TSC2 nonsense mutation, Q1010X, exon 26

****
TSC1 9-bp in-frame deletion, 402_410delCTGACCAC, exon 4