

Inguinal Hernia in Patients With Ewing Sarcoma: A Clue to Etiology

Judith U. Cope, MD, MPH,^{1*} Maria Tsokos, MD,² Lee J. Helman, MD,³
Gloria Gridley, MS,¹ and Margaret A. Tucker, MD¹

Background. Various congenital anomalies have been associated with childhood cancer, but as yet no anomaly has been consistently found with Ewing sarcoma (ES). Recently a large case-control study of ES patients reported a greater number of hernias in both cases and their sibling controls than in population controls. Most of these hernias were inguinal. Because these anomalies were also reported previously in two case series, we looked for inguinal hernias in a different population of ES patients. **Procedure.** We abstracted medical records for 306 pathologically confirmed ES/primitive neuroectodermal tumor (PNET) patients seen at NIH between 1960 and 1992. Epidemiological data on demographics and medical conditions were analyzed. The frequency of anomalies was compared to expected rates to calculate relative risk and con-

fidence intervals. **Results.** Anomalies were present in 67 (22%) cases. A particular anomaly, inguinal hernia, was reported for 13 (5%) NIH cases. Compared to population estimates for white children, the relative risk of inguinal hernia among white NIH cases was 13.3 (95% CI 3.60–34.1) for females and 6.67 (95% CI 2.67–13.7) for males. **Conclusions.** The findings of inguinal hernias in some patients with ES suggest that a disruption in normal embryological development occurred. This may provide an important clue to the etiology of ES. We hypothesize that these hernias may relate to an in utero exposure or indicate an underlying genetic disorder. Future studies should carefully evaluate ES families for genetic disease and explore environmental factors. *Med. Pediatr. Oncol.* 34:195–199, 2000. Published 2000 Wiley-Liss, Inc.[†]

Key words: inguinal hernia; Ewing sarcoma; etiology; congenital anomaly

INTRODUCTION

Ewing sarcoma (ES) is a rare cancer that has its peak incidence during adolescence and occurs rarely among blacks. The tumor occurs in bone and soft tissue, particularly in areas of the pelvis, arms, legs, or chest. Previous diagnostic categories of ES, such as atypical ES, extraskeletal ES, Askin tumor, and primitive neuroectodermal tumor (PNET), have recently become grouped together as a family of tumors as scientists have discovered that all these tumors share the same specific chromosomal translocation, t(11,22)(q24q12) [1–3]. Current theories of carcinogenesis support the idea that these tumors may have neural and not mesodermal origins [4].

Despite continuing efforts to identify risk factors for ES, its etiology is still unknown. Recently a large case-control study reported a higher frequency of inguinal hernias among both ES patients and their siblings than among population-based controls [5]. Although this congenital anomaly is not uncommon, it occurs less frequently in whites, females, and full-term infants [6]. Interestingly, the clinical details from the Winn *et al.* [5] study revealed that the patients and siblings with hernias were white males and females and that they had been full-term infants. Three previous studies have also noted the presence of inguinal hernias in ES cases as well as their siblings [7–9]. If such an association could be established it might give further insight into the tumor's

developmental origin. Therefore, we looked for inguinal hernias in a different population of ES patients.

MATERIALS AND METHODS

Case Series at NIH

Medical records were identified for 324 patients with diagnoses of ES, peripheral PNET, primitive sarcoma of bone, and ectomesenchymomas who had been treated on high-risk sarcoma protocols at the Pediatric Branch of the National Cancer Institute during the years 1960–1992. Pathology reports were reviewed at time of initial inclusion in treatment protocols; these reports confirmed that 306 patients had sarcomas of the Ewing/PNET family. For those with available archival tissue (n = 138; 48%), histopathology was rereviewed by an expert pa-

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

²Department of Pathology, National Cancer Institute, Bethesda, Maryland

³Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland

*Correspondence to: Judith U. Cope, MD, MPH, National Cancer Institute, 6120 Executive Blvd, EPS Room 7007, Bethesda, MD 20892-7362. E-mail address: judy_cope@nih.gov

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thologist (M.T.) to confirm the diagnoses. Among the 324 patients initially identified, 154 patients had been previously reported [10], including 2 with undescended testes (cryptorchidism) and other urogenital defects, but no inguinal hernias were reported.

Data on race, sex, birth place and residence, age at diagnosis, tumor site, pattern of tumor spread and metastasis, preexisting medical conditions, past surgical procedures, and family history of disease and cancer were abstracted from the medical records. Information on birth and medical history of the cases and medical disorders in first-degree relatives was abstracted when available. Clinical findings were obtained from NIH admission history, physical examinations, laboratory, X-ray reports, and medical consultations. Although the medical chart format was not fully uniform, it has been relatively similar over the past 30 years. Charts were fairly standardized and contained high-quality medical information, though data varied by physician. As part of their treatment protocol, patients had usually undergone biopsy or major surgical procedures at NIH, so most charts included a standard anesthesia record form that included information regarding any previous surgeries. Autopsy reports were included for 49 (24%) of 206 patients who died.

The number of observed congenital anomalies and birth defects was compared to the expected population rates of congenital anomalies obtained from the Collaborative Perinatal Project 1966 [11]. This large longitudinal study with extensive follow-up of congenital malformations provided rates of anomalies per 10,000 white children who were examined at ages 1 and 7 years. Because published population estimates of childhood inguinal hernia rates vary considerably, inguinal hernia rates for both genders were also obtained from the Centers for Disease Control and Prevention in Atlanta, Georgia, and were found to be concordant with the above rates (personal communication from Dr. L.J. Paulozzi, with rates from the Metropolitan Atlanta Congenital Defects Program, a population-based surveillance system). The observed associations were tested for significance by the calculation of relative risk (observed/expected) and 95% confidence intervals under the assumption that the observed numbers of anomalies follow a Poisson distribution for rare events [12]. For sex-specific malformations (e.g., cryptorchidism) the denominators were adjusted to include only children of the appropriate sex. Recorded height measurements were compared to standardized measurements for age and gender according to the national NCHS standards [13].

RESULTS

Demographics

Among the 306 NIH ES patients 196 were males and 110 females (m:f ratio, 1.8:1). Two hundred ninety-four

(96%) of the cases were of white race. Age at diagnosis for 306 cases ranged from 2 to 46 years (mean 17.7, median 16). Tumor sites for 303 of the cases for whom primary site data were available revealed 95 (31%) in the lower extremity, 84 (28%) in the pelvis, 48 (16%) in the chest, 35 (12%) in the upper extremity, 29 (9%) in the back or spine, 7 (2%) in the head and neck, and 5 (2%) in other areas.

Pregnancy and Birth History

Birth history was reported for only 31 (10%) of the NIH cases. Among these cases, all but one were full-term or normal birth weight. Two patients had received blood transfusions during the neonatal period. Three mothers reported viral illnesses during the case pregnancies; one had a bad chest cold and had a premature birth, one had mumps, and one had German measles.

Anomalies

Overall, 67(22%) of NIH patients had anomalies, 22% of males and 21% of females (Table I). A history of inguinal hernia was reported for 13 NIH patients (4 females, 9 males). One patient was excluded from our analysis because he had surgical correction at age 20 years and there was insufficient detail to determine whether he had a congenital type of inguinal hernia. Some of the observed and expected numbers of hernias and genitourinary anomalies are given in Table II. Only whites were included in the analyses because comparisons were made using white rates. Inguinal hernias were in excess for both females (RR = 13.3, 95% CI 3.60–34.1) and males (RR = 6.67, 95% CI 2.67–13.7). All patients except one with inguinal hernias had a history of surgical repair in early childhood, and the median time interval between surgery for inguinal hernia and diagnosis of ES was 14 years (range 3.5–25 years). Eleven of the thirteen patients with inguinal hernias had presented with the tumor originating from a near-inguinal site (the pubis, ilium, or proximal femur bone). Among the 13 inguinal hernia cases, 3 had neurological problems years before their cancer diagnosis, including 2 cases with sensorineural hearing loss and one with facial asymmetry. Only one had been born prematurely. Two cases with inguinal hernia were tall (>99% in height). One other case had all three characteristics: inguinal hernia, sensorineural hearing loss, and >99% in height. Other types of hernias were reported for two patients, one umbilical and one of the chest wall.

Five (3%) NIH male patients had a history of unilateral cryptorchidism (RR = 2.66, 95% CI, 0.86–6.21); one had clinical features suggestive of a prune-belly like syndrome and a second patient had a Zollinger-Ellison syndrome with tall stature (6 feet, 8 inches). There were 14 patients with bony anomalies, including 2 hyperplastic clavicles, 9 rib or vertebral anomalies (mostly fusion

TABLE I. Characteristics of 306 NIH Patients

Demographics	
Gender (M/F)	196/110
Age (mean/median)	17.7 (16)
Age range	2–46 years
Race	
White	294
Black	5
Hispanic	5
Asian	2
Tumor site	
Pelvis	84
Leg	95
Arm	35
Back & spine	29
Chest	48
Skull & neck	7
Other	5
Total sites	303 (3 missing)
Anomalies	
Bone	14
Cardiac	2
Eye	
Muscle problems	9
Cataract	1
Face/neck	
Cleft lip/or palate	2
Torticollis	2
GI	
Esophageal stenosis	1
Hernias	
Umbilical	1
Inguinal	13
Absent rectus abdominis	1
Omphalocele	1
Genitourinary	
Undescended testis	5
Urethral stenosis/stricture	3
Hypospadias	1
Duplication of system	6
Abnormal kidney	4
Cysts	
Pilonidal	1
Thyroglossal duct cyst	1
CNS	
Hydrocephalus	1
Other	
Polydactyly	1
Arteriovenous malformation	1
Total No. anomalies (no. persons)	71 (67)
Syndromes	3 (1 each of prune-belly, Zollinger-Ellison, and restless leg syndrome)

defects), 2 skull deformities, and 1 osteoid osteoma. Among these 4 were located near the tumor site. Two patients had heart disease, one aortic stenosis and one Ebstein anomaly (with tricuspid valve anomaly). Eight patients had strabismus, four with history of surgical correction. An additional patient had ‘optokinetic nystagmus’ and had a history of multiple surgeries for congenital microphthalmus and cataract. Fifteen other patients had kidney and genitourinary anomalies, including 4 pa-

tients with kidneys of abnormal size and shape and fetal lobulation, 1 with hypospadias, 3 with urethral stenosis, and 6 with duplication anomalies of the urinary tract. Two patients had congenital torticollis, one who had had three prior surgical corrections. Other anomalies included one each of pilonidal cyst, thyroglossal duct cyst, esophageal stenosis, polydactyly, arteriovenous (AV) malformation, omphalocele, and absent rectus abdominis.

Medical records of NIH patients had little information for relating anomalies to possible in utero exposures. However, two patients with heights 99% and bony abnormalities had mothers with thyroid disease.

History of Medical Conditions and Family Disorders

Few patients had preceding medical conditions. Two patients had been diagnosed with juvenile diabetes and another with cystic fibrosis several years prior to their cancer diagnosis. Five patients had a history of sensorineural hearing loss (including the 3 mentioned earlier).

Family history of disease revealed that in four families the case and two or more different family members were each affected with the medical conditions: gout, vertebral anomalies and restless leg syndrome (autosomal inherited myoclonus), and sensorineural hearing loss. One other patient’s mother had had Addison disease and uterine cancer diagnosed in her twenties. One case family had probable multiple endocrine neoplasia (MEN), one had Li-Fraumeni syndrome (LFS), and another had an excess number of family members with varying types of cancer.

DISCUSSION

We found an excess number of inguinal hernias in both female and male ES patients compared to normal population rates. Our findings are consistent with the large case-control study by Winn *et al.*[5]. Three other investigations have also reported inguinal hernia anomalies in ES patients. An Italian case series of 424 ES patients reported 40 patients with anomalies, 6 with inguinal hernias [9]. In a childhood cancer questionnaire study, Li *et al.*[7] reported that, among 59 children with bone cancer, 3 ES patients had inguinal hernias, another ES patient had a strong family history of inguinal hernias, and another had a sibling with both inguinal hernia and cryptorchidism. In a hospital case series of 146 ES patients, Glass and Fraumeni [8] reported 2 cases with inguinal hernias, 1 case with cryptorchidism, and 1 case with a number of anomalies, including cryptorchidism and inguinal hernia. Recently, Holly *et al.*[14] found a nonsignificant excess of hernias overall in 43 patients with ES compared to controls. The number of cases in her study was small and the types of hernias were unspecified. Epidemiologically it is known that nearly all

TABLE II. Hernia and Genitourinary Anomalies in NIH Ewing Sarcoma Patients (104 White Females, 190 White Males)

Type of anomaly	No. observed	Percentage	No. expected	Percentage ^a	RR (CI) ^b
Inguinal hernia					
Females	4	3.85	0.30	0.29	13.3 (3.60–34.1)
Males ^c	7	3.68	1.05	0.55	6.67 (2.67–13.7)
Umbilical hernia (male)	1	0.53	0.27	0.14	3.70 (0.09–20.6)
Undescended testis, unilateral	5	2.63	1.82	0.96	2.74 (0.88–6.41)
Urethral stenosis (males)	3	1.58	1.01	0.53	2.97 (0.60–8.68)

^aChildhood rates for white race from Myrianthopoulos and Chung [11].

^bConfidence intervals using Poisson distribution for rare events [12].

^cOne white male case was excluded as congenital inguinal hernia, because surgical repair was at 20 years of age.

ES patients are of white race, and congenital inguinal hernias are less common in white persons. Therefore, the finding of increased numbers of inguinal hernias becomes even more important. We suggest that it may be a clue to the etiology of ES.

Abnormal Development During Embryology

Congenital inguinal hernias result from abnormalities in the descent and migration of tissues as well as the closure of the processus vaginalis during normal embryological development [15]. Current theory (the genitofemoral nerve hypothesis) [16,17] proposes that not only hormonal and mechanical processes are involved but neural tissues as well. We speculate that this may fit well with the hypothesis that ES has a neural origin [4].

Genetic and Environmental Considerations

Inguinal hernias were previously thought to be due to local weakness of tissues, but recent evidence points to a genetic cause [18]. Inguinal hernias may occur in families by an autosomal pattern of inheritance, but they are also featured in genetic disorders of collagen, such as osteogenesis imperfecta, Ehler Danlos syndrome, and Marfan syndrome. Could inherited genes causing both anomalies and cancer be involved with the etiology of ES? Although no specific collagen disorder was recognized in our cases, it is interesting that, in a study of 396 ES patients, Narod *et al.*[19] reported 2 children with osteogenesis imperfecta.

Few studies have supported a genetic predisposition for ES. In our study the number of families with excess numbers of cancers was relatively small. There was insufficient data in our review to quantify the risks of cancer in first-degree relatives. However, in a detailed family study including more than 70% of these NIH patients and their relatives, with longer person-years of follow-up, Novakovic *et al.*[20] reported an increased risk of neuroectodermal and stomach cancers.

Alternatively, environmental exposures might be considered. Inguinal hernia and cryptorchidism have been linked either to elevated maternal estrogen levels during pregnancy [21,22] or conversely to low testosterone levels [23] during pregnancy, but no common exposures

have been identified for patients with ES. Also, in utero viral infections might cause damage to fetal tissue and result in anomalies, with subsequent development of malignancy in later years. Congenital infections have been associated with some of the uncommon anomalies seen in our NIH patients, such as cataract and hydrocephalus. Interestingly, Narod *et al.*[19] also reported 2 cases with cataracts in their series, and Hartley *et al.*[24] reported a significantly lower birth weight for patients with ES.

Strengths and Weaknesses

Because the NIH cases represent a select, nonrandom population that was referred for high-risk sarcoma protocols, most patients had cancer sites of the limbs and pelvis, and this may have somehow biased our findings. These protocols might have excluded patients with major organ malformations or disease. As with any unblinded retrospective study, selection bias, measurement error, and biased interpretation of medical charts may exist. Our statistically significant results may have occurred by chance. We believe that the reliability of our data was good for both inguinal hernias and cryptorchidism, because history of surgery for these anomalies came not only from the medical history records but from anesthesia and surgical reports as well. Because the inguinal hernias in the ES patients had been surgically repaired years before cancer diagnosis, we believe that there was probably underascertainment of the inguinal hernias. These hernias were not related to increased abdominal pressure from the tumor. The strength of this archival data is that it is rich in both clinical detail and pathological information.

SUMMARY

Our investigation supports a significant association of ES with inguinal hernias. Although our numbers are small, they offer a clue to the etiology of ES. Biologically it seems important and plausible that these anomalies may result from an interference or disruption in the embryological development of tissues. Attention should be focused on further understanding the distribution pattern of anomalies together with the anatomical tumor sites in

order to better answer the question of whether these anomalies are concomitant findings or cause and effect. Both environmental and genetic factors should be studied further. Focus should be on specific in utero exposures, and family studies should investigate possible genetic disorders in those patients with several or unusual types of anomalies.

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