Primary Extragonadal Germ Cell Tumors in Klinefelter Syndrome: 10-Years of Experience from a Single Institute

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Background: Approximately 8% of male patients presenting with primary mediastinal germ cell tumors (GCTs) have Klinefelter syndrome (KS), while patients diagnosed with retroperitoneal GCTs also exhibit a range of chromosomal abnormalities. The exact mechanism underlying the development of GCTs in Klinefelter syndrome is unknown, but KS frequently goes underdiagnosed as a result of its varied symptoms and a low general awareness of this condition. Thus, the Children's Oncology Group recommends screening of Klinefelter syndrome in pediatric and adolescent male subjects who present with GCTs.

Methods: We retrospectively reviewed the medical records of extragonadal germ cell tumor patients treated at Severance hospital, department of pediatrics or division of pediatric hematology-oncology over the last ten years.

Results: A total of 95 patients with extragonadal germ cell tumors were included in this study. Karyotyping was done in eight patients out of 95 patients, three patients with KS and one patient with Down syndrome. Twelve of extragonadal GCT patients presented at mediastinum, with most common histology of mature teratoma, and three patients presented with chromosomal abnormalities, two with KS and one with Down syndrome. A total of nine patients were diagnosed with retroperitoneal GCTs and only one had KS.

Conclusion: We described the characteristics of 95 cases of extragonadal GCTs. Although the mechanism of extragonadal GCTs in KS is not clear, karyotyping in pediatric and adolescent extragonadal GCT patients could be helpful in figuring out chromosomal abnormalities including KS and their roles in GCT pathophysiology, which can contribute to improve one's health.

Key Words: Klinefelter syndrome, Germ cell tumors, Mediastinal neoplasm

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Introduction

Klinefelter syndrome (KS) affects approximately 1 in 600 males [1] and has been linked to an increased risk for developing extragonadal germ cell tumors (GCTs) [2], especially malignant mediastinal germ cell tumors [3]. Approximately 8% of male patients with primary mediastinal GCTs have KS [4] and these patients having a significantly higher incidence of mediastinal tumors compared with non-KS-GCT cases [1].

The exact mechanism underlying the carcinogenesis of KS-GCTs is unknown, but several studies have found that a significant percentage of KS patients also have other

sex chromosomal disorders [5]. Nearly one-third of mediastinal GCT cases have KS and 44% of males with KS-GCTs are unaware they have KS. Thus, the Children's Oncology Group recommends KS screening for pediatric and adolescent males who present with GCTs, particularly with mediastinal GCTs, to help with their clinical management [1].

Other case reports have noted a higher prevalence of GCTs in KS patients suggesting a link between KS and the development of both mediastinal GCTs and retroperitoneal GCTs. Several cases of chromosomal abnormalities including KS and Down syndrome have been reported in patients with GCTs [6].

KS is commonly underdiagnosed because of its symptoms are highly variable that it cannot be easily detected by health professionals [7]. We evaluated patients diagnosed with extragonadal GCTs in an effort to uncover whether we had any patient with Klinefelter syndrome in these cases. Our study focused on extragonadal GCTs from Severance hospital where we found a total of three patients with KS in 8 patients who had karyotyping out of 95 patients over the last ten years. Two patients presented with mediastinal GCTs and the third presented with retroperitoneal GCT. There was also one case of a Down syndrome patient in extragonadal GCTs. Our results highlight the need for karyotyping in extragonadal GCT patients to improve clinical treatment strategies.

Materials and Methods

We retrospectively reviewed the medical records of patients diagnosed with extragonadal GCTs in Severance hospital from January 2010 to December 2019. A total of 95 patients under 19 years of age were selected for this study. Inclusion criteria included: 1) treated in the department of pediatrics or division of pediatric hematology-oncology, 2) primary site of tumor was extragonadal, 3) diagnosed with a germ cell tumor by pathology. The data are given as numbers, percentages or medians with their interquartile range.

This study was approved by the Severance Hospital's Institutional Review Board, and the requirement for informed consent was waived (IRB No. 4-2020-0141).

Results

Table 1 describes the demographics of the study population. Median age was 12 years with an interquartile range of 1 to 15.5 years. The most common location for the extragonadal GCTs was the brain, followed by lesions in the sacrococcyx. A total of twelve patients in this study had mediastinal GCTs and nine had retroperitoneal GCTs. Germinoma and yolk sac tumors were the most common pathological manifestations in this study. Karyotyping was done in only eight patients and four of them had normal karyotype.

A total of 6 out of twelve in mediastinal, and a total of 5 out of nine in retroperitoneal GCTs were mature teratomas (Table 2). For the mediastinal GCTs, yolk sac tumors were the dominant pathology with most of the remaining tumors being classified as mature teratomas or immature teratomas. For the retroperitoneal GCTs, the

Table 1. Demographics of the extragonadal germ cell tumors (N=95) treated at Severance Hospital

	Number of patients
Sex (M/F)	64/31
Tumor location	
Brain	54 (56.8%)
Sacrococcyx	18 (18.9%)
Mediastinum	12 (12.6%)
Retroperitoneum	9 (9.5%)
Other[a)]	2 (2.1%)
Pathology	
Germinoma	26 (27.4%)
Yolk sac tumor	21 (22.1%)
Mature teratoma	16 (16.8%)
Immature teratoma	8 (8.4%)
Malignant teratoma	1 (1.1%)
Choriocarcinoma	3 (3.2%)
Embryonal carcinoma	1 (1.1%)
Seminoma	1 (1.1%)
Mixed	18 (18.9%)
Karyotyping	8
Normal	4
Klinefelter syndrome	3
Down syndrome	1

[a)]Stomach and duodenum, cervix and vagina.

Table 2. Characteristics of the Mediastinal and Retroperitoneal germ cell tumor (GCT) patients

	Mediastinal GCT (N=12)	Retroperitoneal GCT (N=9)
Sex (M/F)	9/3	4/5
Age (years, median)	13 [10.5;14.5][a)]	0.66 [0.41;1.0][a)]
Pathology		
Yolk sac tumor	4 (33.3%)	1 (11.1%)
Mature teratoma	6 (50%)	5 (55.6%)
Immature teratoma	1 (8.3%)	2 (22.2%)
Embryonal carcinoma	-	1 (11.1%)
Seminoma	1 (8.3%)	-
Treatment		
Surgery only	7 (58.3%)	4 (44.4%)
Surgery with chemotherapy	5 (41.7%)	5 (55.6%)
Karyotyping	4	1
Klinefelter syndrome	2	1
Down syndrome	1[b)]	-

[a)]Age is described as median and [interquartile range]. [b)]Down syndrome was known before GCT diagnosis.

treatment was divided into two categories: surgery only or surgery followed by chemotherapy. Patients with KS accounted for two out of twelve mediastinal GCTs, and one of the nine retroperitoneal GCTs. There was also a single case from the mediastinal GCTs described in a 17 year old patient, with Down syndrome. This patient was treated with chemotherapy and has been in remission for two years.

1) Case 1

A 16-year-old male whose height was 172.3 cm (50-75%) and weight was 83 kg (90-95%) presented with right shoulder and back pain over a seven-day period. Chest magnetic resonance imaging (MRI) at an outside hospital showed a well-defined heterogeneous enhancing mass at the right anterior mediastinum (Fig. 1A). Positron emission tomography-computed tomography (PET-CT) revealed increased fludeoxyglucose (FDG) uptake in the anterior mediastinal mass (Fig. 1B). Bone marrow was then examined for staging and showed no signs of malignancy, and his karyotype was consistent with Klinefelter syndrome (47, XXY). He also did sperm banking prior to chemotherapy, which showed azoospermia. The patient was unaware of his Klinefelter syndrome status before.

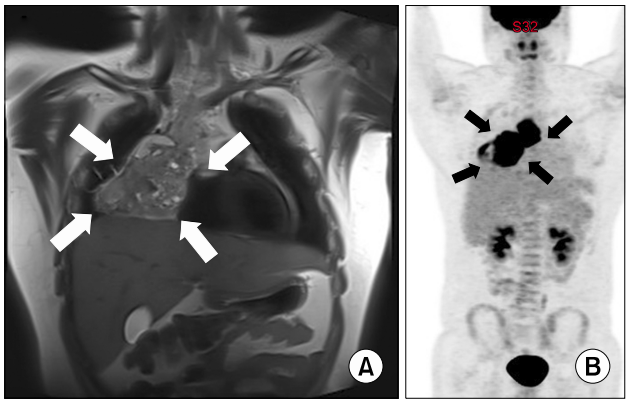

Fig. 1. Chest MRI (A) with heterogeneous enhancing mass at the Rt. anterior mediastinum (white arrow), PET-CT (B) with increased FDG uptake in the anterior mediastinal mass, suggesting malignancy (black arrow).

Pathology of the mediastinal mass revealed a yolk sac tumor with elevated alpha-fetoprotein (AFP) (8,170 ng/mL, normal range 0-9.0 ng/mL) levels. He was treated with four cycles of ifosfamide-carboplatin-etoposide (ICE) and bleomycin-cisplatin-etoposide (BEP) chemotherapy alternatively followed by mediastinal mass excision and then, followed up with another three cycles of chemotherapy using the same alternative chemotherapy regimen. Hormone tests were also done and showed that the patient's sex hormones were within normal range. The patient has been tumor free for two years.

2) Case 2

A male baby who was born at full-term without any perinatal problems was diagnosed with Klinefelter syndrome (47, XXY) one month after birth by G-scanning, a test used to detect genetic or chromosomal abnormalities using serum samples. There were no known chromosomal abnormalities in his family. However, at seven months of age, a palpable abdominal mass was noted by chance, and abdomen pelvic CT completed at our hospital showed a large and lobulated mass, 15.3×8.7×13.6 cm (Fig. 2) in this abdomen. His height was 71.6 cm (50-75%) and weight was 10.4 kg (90-95%). His AFP level was 22.87 ng/mL at diagnosis. He underwent excision of the intra-abdominal mass, and its pathology revealed it to be a mature teratoma. He stayed normal in ultrasonography

for 16 months after excision.

3) Case 3

A 16-year-old male had chest pain for 15 days, and underwent a chest CT, which showed a large heterogenous mass in the anterior mediastinum (Fig. 3A) and his PET-CT revealed intense FDG uptake in the anterior mediastinum (Fig 3B). Pathologic diagnosis in biopsy specimen was yolk sac tumor and initial AFP level at diagnosis was 26,663 ng/mL. He did not undergo bone marrow examination. He was referred to the urology department for sperm preservation prior to treatment. His height was 186 cm (>97%) and weight was 68 kg (50-75%). His examination revealed small testis volume and azoospermia resulting in diagnosis of Klinefelter syndrome, which was confirmed by chromosomal analysis. After four cycle of ifosfamide-cisplatin-etoposide chemotherapy, he had an operation to excise the tumor. For his follow up PET-CT revealed no evidence of recurrence or metastasis, he didn't undergo adjuvant chemotherapy and has been tumor free for four years.

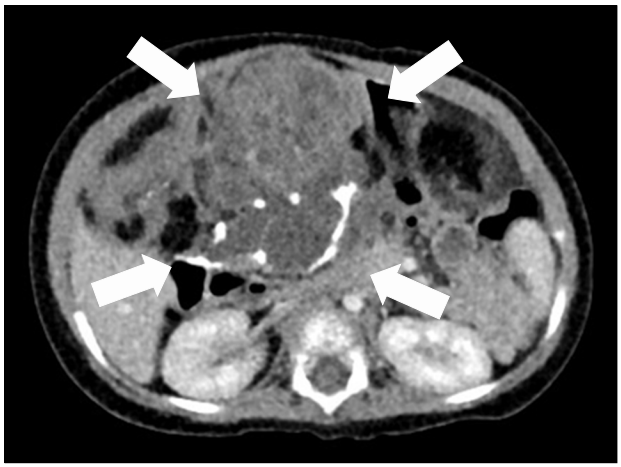

Fig. 2. Abdomen-pelvic CT showing a large lobulated mass with internal fat and calcification in the abdomen and pelvis (white arrow).

Discussion

Pediatric germ cell tumors are a heterogeneous group of tumors identified based on histology, age at presentation, tumor location and outcome [8]. It is known that GCTs represent approximately 3% of all pediatric cancers [9] and extragonadal sites account for 50% of GCTs, with sacroccygeal tumors being the most common [8].

Mediastinal GCTs are occasionally reported by case and malignant type represents only 4% of the mediastinal GCTs [10]. Yolk sac tumors and mixed histology are the predominant pathology for this type of tumor [11]. Cisplatin-based chemotherapy followed by surgical resection of residual disease is the first line treatment for GCTs in adults and children [9].

Nearly one-third of mediastinal tumors are diagnosed in males with KS and a majority of these cases occur in adolescents. Our first and third cases showed similar characteristics, as they were both adolescents, with mediastinal yolk sac tumors who were diagnosed with KS after the mass was found. This supports the hypothesis that KS screening in pediatric and adolescent males with mediastinal GCTs is important for proper clinical intervention [1].

Primary retroperitoneal germ cell tumors are also rare, accounting for approximately four percent of all GCTs [12]. Mature and immature teratomas are the most com-

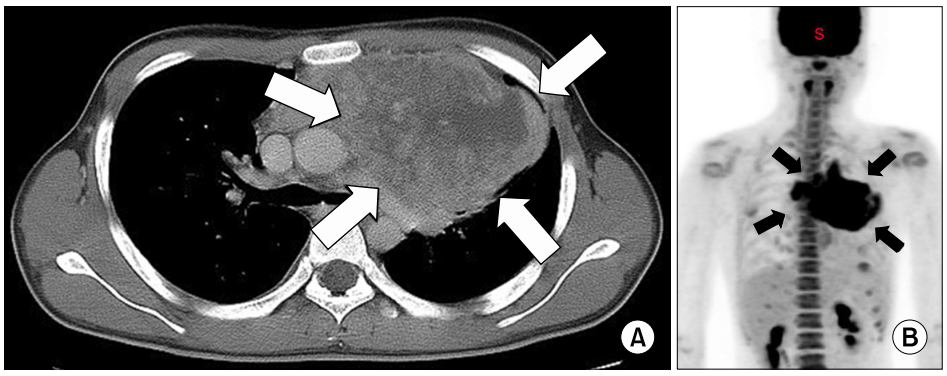

Fig. 3. Chest CT (A) showing a large heterogeneous mass in the anterior mediastinum (white arrow), PET-CT (B) with intense FDG uptake in the anterior mediastinum, consistent with malignancy (black arrow).

mon histopathology for this type of tumor, however malignant retroperitoneal GCTs tend to be yolk sac tumors [12]. Primary resection is preferred, but depending on the extent of disease, chemotherapy can be done before complete resection [8,12].

There have been occasional reports linking chromosomal abnormalities with retroperitoneal GCTs [13,14]. Among the twelve cases in this report, chromosomal abnormalities were observed in three cases: two with Down syndrome and one with KS. The majority of retroperitoneal GCTs are benign mature and immature teratomas, and ten of the twelve cases were diagnosed in the first year of life [6]. Our second case showed similar characteristics to these in terms of age at diagnosis, histology type and chromosomal anomaly.

Severance hospital had twelve cases of mediastinal GCTs and nine retroperitoneal patients within the last ten years (from January 2010 to December 2019). There were four patients in the mediastinal GCTs who did karyotyping and among them, three patients with chromosomal abnormalities: two with KS and one with Down syndrome. For the retroperitoneal GCTs, only one patient underwent karyotyping and was diagnosed with KS.

This is not a representation of the incidence of chromosomal abnormalities in the extragonadal GCT cases from this hospital as most patients did not perform karyotyping, for only eight out of 95 patients did karyotyping in this study. Though, they might be less likely to have chromosomal abnormalities because patients have been followed up for several years, some patients with the department of pediatric endocrinology, which makes it enable to detect signs and symptoms of chromosomal abnormalities.

The carcinogenic mechanism of GCTs is unknown, but genes on the extra X chromosome which escape inactivation may contribute to the KS phenotype and increase the risk of GCT development [1] as testicular tumors in patients with an additional X chromosome have been shown to have an increased expression of several oncogenes [15]. However, it will require further study to understand why extragonadal GCTs show a preference for the mediastinum [4].

Although the relationship between KS and extragonadal GCTs and its underlying pathological mechanisms are not yet clear, karyotyping for pediatric and adolescent extragonadal GCT patients, especially those in the mediastinum, could be helpful in identifying the chromosomal abnormalities in these patients and could help in the management of any comorbidities they may present with.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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