Primary Extragonadal Germ Cell Tumors in Klinefelter Syndrome:
10-Year's Experience from a Single Institute

Yura Kim¹, Won Kee Ahn², Jung Woo Han², Seung Min Hahn², Seung Yeon Kwon² and Chuhl Joo Lyu²

¹Department of Pediatrics, Severance Hospital, Yonsei University Health System, 2Department of Pediatric Hematology-Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea

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
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              |
| 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                  |

*aStomach and duodenum, cervix and vagina.*
Germ Cell Tumor with Klinefelter Syndrome

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        | 1b)                      | -                           |

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

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.

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 azoospermi. The patient was unaware of his Klinefelter syndrome status before.

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 heterogeneous 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.

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-
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.

References

1. Williams LA, Pankratz N, Lane J, et al. Klinefelter syndrome in males with germ cell tumors: a report from the Children’s Oncology Group. Cancer 2018;124:3900–8.
2. Konheim JA, Israel JA, Delacroix SE. Klinefelter syndrome with poor risk extragonadal germ cell tumor. Urol Case Rep 2017;10:1–3.
3. Aguirre D, Nieto K, Lazos M, et al. Extragonadal germ cell tumors are often associated with Klinefelter syndrome. Hum Pathol 2006;37:477–80.
4. Pradhan D, Kaman L, Dhillon J, Mohanty SK. Mediastinal mixed germ cell tumor in an infertile male with Klinefelter syndrome: a case report and literature review. J Cancer Res Ther 2015;11:1034.
5. Schneider DT, Schuster AE, Fritsch MK, et al. Genetic analysis of mediastinal nonseminomatous germ cell tumors in children and adolescents. Genes Chromosomes Cancer 2002:34:115–25.
6. De Backer A, Mader GC, Hazebroek FW. Retroperitoneal germ cell tumors: a clinical study of 12 patients. J Pediatr Surg 2005;40:1475–81.
7. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter’s syndrome. Lancet 2004;364:273–83.
8. Rescorla FJ. Pediatric germ cell tumors. Semin Pediatr Surg 2012;21:51–60.
9. Horton Z, Schlatter M, Schultz S. Pediatric germ cell tumors. Surg Oncol 2007;16:205–13.
10. Göbel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D. Germ-cell tumors in childhood and adolescence. GPOH-MAE1 and the MAHO study groups. Ann Oncol 2000;11:263–71.
11. Billmire D, Vinocur C, Rescorla F, et al. Malignant mediastinal germ cell tumors: an intergroup study. J Pediatr Surg 2001;36:18–24.
12. Billmire D, Vinocur C, Rescorla F, et al. Malignant retroperitoneal and abdominal germ cell tumors: an intergroup study. J Pediatr Surg 2003;38:315–8; discussion 315–8.
13. Palmer RD, Nicholson JC, Hale JP. Management of germ cell tumours in childhood. Current Paediatrics 2003;13:213–20.
14. Hachimi-Idrissi S, Desmyttere S, Goossens A, Desprechins B, Otten J. Retroperitoneal teratoma as first sign of Klinefelter’s syndrome. Arch Dis Child 1995;72:163-4.

15. Kawakami T, Okamoto K, Sugihara H, et al. The roles of supernumerical X chromosomes and XIST expression in testicular germ cell tumors. J Urol 2003;169:1546-52.