

Mediastinal Germ-cell Tumors Relapse in a Male With Klinefelter Syndrome. Is Longer Surveillance Needed?

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Summary: Germ cell tumors (GCTs) are a heterogeneous group of pediatric cancers. In up to one-third of male patients, a primary mediastinal location is associated with the presence of Klinefelter syndrome (KS). We describe a case of mediastinal GCT in a patient, with unacknowledged KS, that presented a relapse 7 years from diagnosis, that is, 2 years after the end of the follow-up program usually recommended for patients with GCT. There are no recommendations for screening for KS in patients with mediastinal GCT and there are no specific guidelines for surveillance of GCT in KS patients. Our experience suggests that KS should be suspected in patients with mediastinal GCT, and a longer follow-up plan should be implemented when GCT occurs in patients with KS.

Key Words: Klinefelter syndrome, germ-cell tumor, teratoma, children

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Germ cell tumors (GCTs) represent 3% of pediatric cancers and more than 10% of tumors in adolescents.¹ In the pediatric population, more than half of GCT occurs in the extra-gonadal site (eGCT), more commonly in the sacrococcygeal region in younger children and in the central nervous system during and after puberty.^{2,3}

With modern multidisciplinary approaches, the GCT overall survival is above 90%. Age of older than 11 years, extra-gonadal site, and the presence of metastasis are described as poor prognostic factors.¹ Most patients achieve tumor complete remission by the end of treatment. The first 2 years from diagnosis are the period at higher risk of relapse⁴ but late events are described and a 5 years follow-up is recommended in all patients.⁵

GCT may be associated with genetic disorders including Klinefelter syndrome (KS), Turner syndrome, Swyer syndrome, and others.¹ Patients with KS present an increased

risk of eGCT in comparison to the general population.⁶ In these patients, the mediastinum is the most frequent primary location and teratoma is the most frequent histology.⁷

We describe a late relapse of a mediastinal teratoma that occurred in a patient with KS 7 years after the first complete remission, to discuss the follow-up program in syndromic patients.

Patient-informed and written consent was obtained for this report. Authors have no conflicts of interest to declare.

CASE REPORT

An 11-year-old male patient presented with chest pain, fatigue, and fevers. Chest radiograph and CT scan revealed an expansive 11 × 9 × 15 cm mediastinal mass occupying the left hemithorax with radiologic features consistent with a teratoma.

Alpha-fetoprotein was moderately increased (49 ng/dL) and β-human chorionic gonadotropin was normal.

The patient underwent surgery, which resulted in microscopically complete resection of the lesion. Histologic analysis confirmed a mixed GCT tumor with 95% mature teratoma and a small and isolated component of immature neuroectodermal tissue, with seminoma foci and necrotic areas. After surgery, the AFP levels went down to normal. Investigations performed after surgery (CT scan and AFP) remained negative for the 5-year follow-up.

Seven years after the initial diagnosis, the patient started to complain of cough and chest pain. The chest radiograph revealed a mediastinal enlargement and the subsequent CT scans revealed the presence of a new 128 × 54 × 87 mm mass in the mediastinum. APF was 713 ng/mL.

A new surgery was performed, and the histologic analysis demonstrated a GCT composed of mature teratoma (90%) with multiple foci of immature teratoma with neuroectodermal differentiation and a single focus of seminoma. As no yolk sac element was recognized; the increase in AFP should be linked to the immature teratoma components.⁸ Surgical margins in the pericaval region resulted in positive for teratoma tissue. The patient started a new follow-up program and remains without evidence of disease 1 year after surgery.

When he was 16 years old, a testicular volume low for his age was detected and genetic advice was requested. The karyotype demonstrated a diagnosis of KS.

DISCUSSION

KS has an incidence of 1 in 600 males, it is characterized by a 47XXY karyotype and an abnormal sex differentiation with hypergonadotropic hypogonadism, small testes, and infertility. In childhood, KS may be undiagnosed because the phenotypic features appear during puberty.⁹

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FIGURE 1. Axial contrast-enhanced chest CT performed at diagnosis showing a large (11 × 9 × 15 cm) left-side well-demarcated inhomogeneous soft-tissue density mass (yellow arrow) with calcification (blue arrow) displacing the adjacent structures. Radiologic features were consistent with teratoma.

An increased incidence of different malignancies is well documented in KS patients, especially breast cancer,¹⁰ leukemia, lymphomas,¹¹ and GCT.

Concerning GCT there is a 50-fold increased risk over the general population. This caused discussion on the opportunity to recommend a screening program for patients with KS, but as of now, it is not suggested.^{7,12,13} The reason for this higher incidence is not known but there are different hypotheses such as the germ cell proliferation due to hypergonadotropic hypogonadism or the escape of X inactivation of the genes in the additional chromosome.^{7,14}

In KS children up to 80% of eCGT is located in the mediastinum and typically affects children 10 to 14 years old, with prevalence of mixed-type-nonseminomateus histology in adolescence and teratoma in prepubertal age.^{7,12,15} It is not clear if GCT has a different outcome when occurs in patients with KS, but some reports described a poor prognosis and the risk of postsurgery relapse, even in case of favorable histology.^{16,17}

In pediatric population, the mediastinal GCT represents only 2% to 4% of all pediatric GCT. The authors estimated that one-third of male patients with mediastinal GCT have KS.^{15,18} Consequently, it is suggested to investigate the presence of KS in pediatric patients with mediastinal GCT.^{7,15,19}

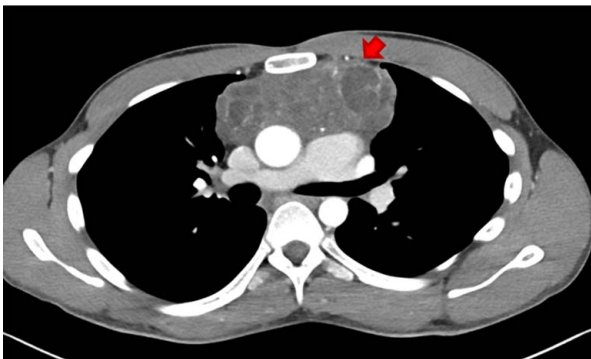


FIGURE 2. Contrast-enhanced chest CT demonstrating an inhomogeneous soft-tissue density mass (red arrow) located in anterior mediastinum. This finding is referable to recurrence of teratoma.

There is only one case report in the literature that describes GCT relapse in KS. As in our case, it was a mature teratoma with a small portion of the neuroepithelium, with serum markers increasing at diagnosis. In this case, the relapse occurred 7 months after surgery and was treated with surgery and chemotherapy, with a good short-term prognosis.¹⁶

In this article, we describe the occurrence of a late relapse of a mediastinal GCT in a patient with KS. We may also hypothesize this is a new malignancy in a predisposed subject. In both cases, the report highlights the importance of surveillance and suggests that in patients with GCT and KS, the follow-up should be longer than the 5 years planned for non-KS patients.

In our patient, the KS was diagnosed after the end of the planned follow-up. This information should have changed our approach leading to a prolongation of the follow-up plan and possibly to an earlier detection of the second mediastinal lesion. An earlier diagnosis may have allowed a complete surgical tumor resection, unfeasible in our case due to the mass extension.

Another challenge is how to extend the surveillance without significantly affecting the patient's life and avoiding unnecessary investigations. Recent studies demonstrated that serum tumor markers are an effective and safe relapse detection method for malignant GCT, with the ability to identify more than 95% of recurrence in patients with increased markers at diagnosis.²⁰ This may be true for all secreting GCT, as it was in our case. Surveillance with serum markers and infrequent chest radiographs may allow a longer follow-up reducing the biologic risk of radiologic examinations²¹ and may be recommended in patients with cancer predisposition syndromes, such as KS.

CONCLUSIONS

With the limitations of a single case experience, our report confirms the importance of investigating the presence of KS in males with a diagnosis of primary mediastinal GCT and suggests the need for a personalized and longer follow-up strategy in syndromic patients with GCT (Figs. 1 and 2).

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