Review Paper

A 16-year-old Adolescent With Mediastinal Seminoma: A Case Report and Literature Review

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ABSTRACT

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms that arise from the primordial germ cells of the human embryo, which are normally destined to produce reproductive cells sperm, or ova. GCTs can be present in both gonadal GCTs and extragonadal GCT sites. Pediatric GCTs are relatively rare tumors with an incidence of 2%-3%. Primary mediastinal germ cell tumors GCTs are very rare extragonadal GCTs that arise in the anterior mediastinum. In this report, we present the case of a 16-year-old boy with primary seminoma arising in the anterior mediastinum. The patient presented with the symptoms of cough, fever, and chest tightness. CT finding was in favor of a large expansive process measuring 12.4x6.7x14.2 cm in the anterior mediastinum, accompanied by a conglomeration of hilar lymph nodes in the level of brachiocephalic veins juncture. Fine needle biopsy and core biopsy were performed transthoracically, under the control of MSCT. Based on histology and immunohistochemistry, the diagnosis of mediastinal germ cell tumor with immunophenotype of seminoma was made. The patient was treated with 4 cycles of chemotherapy by BEP protocol without significant side effects and toxicities. The patient remained disease-free for 16 months. The purpose of reporting this case is to confirm that chemotherapy with cisplatin-based regimens has markedly improved the outcome of adults and children with GCTs as well.

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Introduction

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms arising from the primordial germ cells of the human embryo, which are normally destined to produce reproductive cells sperm, or ova [1]. GCTs can be present in both gonadal (GGCTs) and extragonadal (EGGCTs) sites.

The overall incidence of GCTs is 2%-3%, but in childhood, they have a bimodal distribution: The first peak is at birth and up to age 4 and then a second peak is after the onset of puberty. Extragonadal GCTs are rare tumors accounting for 1% to 5% of all GCTs [2].

Primary mediastinal germ cell tumors (PMGCTs) are very rare EGGCTs that occur in the anterior mediastinum, with an incidence of 1% to 4% of all tumors found in the anterior mediastinum [1, 2].

Seminomas occur in up to 50% of malignant mediastinal GCTs in adults, predominantly in young males, but in children, these tumors are very rare with only a few case reports in the literature.

Specific subtypes of GCTs secrete proteins α-fetoprotein and β-human chorionic gonadotropin that can be used as markers of tumor presence. The treatment for GCTs includes surgical resection, chemotherapy (CT) with cisplatin-based regimens, and Radiotherapy (RT).

Case Presentation

In this report, we present the case of a 16-year-old boy with primary seminoma arising in the anterior mediastinum. In April 2020, the patient presented with the symptoms of cough, fever, and chest tightness lasting for a couple of weeks. The teenager was otherwise healthy, with an inconspicuous family medical history, although he had similar symptoms a few months prior when he was treated with azithromycin.

The physical examination revealed diminished breathing sound over the right middle lobe. He was in good performance status (ECOG 1). Due to the aforementioned symptoms, physical findings, and elevated inflammation parameters (CRP 138.7 mg/L) as well as tissue damage markers (LDH 628 U/l), an X-ray of the lungs was performed, which showed right hilar enlargement accompanied by peribronchovascular thickening (Figure 1). Consequently, the CT finding was in favor of a large expansive process measuring 12.4x6.7x14.2 cm in the anterior mediastinum, accompanied by a conglomeration of hilar lymph nodes at the level of brachiocephalic veins juncture (Figure 2). Abdominal and pelvic CT showed normal findings.

Due to unfavorable tumor placement, complete surgical removal was delayed. Therefore, fine needle biopsy and core biopsy were performed transthoracically, under the control of MSCT, and initial tumor biopsy was referred to pathology. Microscopy revealed the tumor composed of atypical larger cells with an oval nucleus and pale cytoplasm with brisk mitotic activity, embedded into the stroma and surrounded with few lymphocytes (Figure 3A). Immunohistochemistry was performed, and the tumor showed strong octamer-binding transcription factor 4 nuclear positivity (Figure 3A), and diffuse membranous Placental Alkaline Phosphatase (PLAP) positivity was noted (Figure 3B). The tumor was negative for leukocyte common antigen (LCA) (Figure 3D). Based on histology and immunohistochemistry, the diagnosis of mediastinal GCT with immunophenotype of seminoma was made.

Blood tests for GCTs tumor markers were elevated, showing alpha-fetoprotein (AFP) of 16.1 ug/L, (normal range of <7.0 ug/L) and β-hCG as well, with a pronouncedly increased level of 142.0 IU/L, (normal range of <0.2 IU/L). Considering the increased β-hCG level in correlation with the histopathological finding for extragonadal seminoma, the examination of testicles was performed to detect an occult primary testicular tumor. Ultrasound showed no solitary tumor, only discrete microlithiasis, mostly on the edges of the testes.

After the tumor staging, we started the neoadjuvant CT by BEP CT regimen with bleomycin 30 U intravenous days 1, 8, and 16, etoposide 100 mg/m^2 intravenous days 1–5, and cisplatin 20 mg/m^2 intravenous days 1–5 in 21-day cycles. The BEP protocols were realized without significant side effects. At one point, the patient presented mild eyelid swelling and erythema; so, desloratadine was introduced 30 minutes before cisplatin treatment.

Before the start of CT, sperm cryopreservation was attempted two times, rather unsuccessfully with a spermiogram showing hypospermia and azoospermia. We also did the baseline measurements of the glomerular filtration rate, pulmonary function tests, and baseline audiometry of the patient. In the period from May to July 2020, four cycles of CT were realized without significant side effects or toxicities.

Following 4 cycles of CT by BEP protocol, the levels of β-HCG and AFP were normalized. The PET CT scan has revealed partial morphological regression of the tumor with no signs of metabolic activity compared to the previous CT findings in May.

On October 2020, after CT, the thoracoscopic complete extirpation of the tumor was done, followed by pathohistological analysis. On gross examination, the tumor was sharply demarcated from the adjacent lung parenchyma, measuring 6.5 cm in the largest diameter. On cut sections, the tumor was friable, whitish-yellow with calcifications. Microscopic analysis showed necrotic mass without viable cells, fibrosis, and calcifications (Figure 4).

FISH analysis of the tumor specimen proved the additional copy of the ETV6 gene, which could be iso12p, duplication 12p, or trisomy 12p (Figures 5). The patient has not received any further treatment after finishing 4 cycles of CT.

During the regular follow-ups, the tumor markers were in the normal range as well as CT and MRI scans. From October 2020 to October 2021, a total of two control PET CT scans and two MRI scans were performed. Analysis showed substantial metabolic activity in the infiltration of the anterior mediastinum, without any changes in the aforementioned period. All things considered, the above findings will primarily be in favor of metabolic activation of the residual thymus. The scans showed no other metabolic or morphological signs of residual or disseminated disease. The last follow-up examination with PET-CT was performed in October 2021 and the patient remained disease-free for 16 months.

Discussion

GCTs are a heterogenous group of neoplasms arising from the primordial germ cells of the human embryo, which are normally destined to produce reproductive cells sperm, or ova [1]. GCTs can be present in GGCT and EGGCT sites.

Primordial germ cells are derived from the yolk sac endoderm and migrate around the hindgut to the genital ridge on the posterior abdominal wall, where they become part of the developing gonad. A vast majority of GCTs are gonadal in location and it is thought they could arise from germ cells that remain incompletely determined into germline [1-3].

Gunnar Teilum first proposed a theory known as the "germ cell theory," suggesting that EGGCTs originate from stray primordial germ cells that fail to undergo apoptosis but malignantly transform during embryonic development [4].

Viable germ cells arrested along their path of migration may form extragonadal neoplasia in common midline sites such as the pineal region (6%), mediastinum (7%), retroperitoneal area (4%), and sacrococcygeal region (42%) [1-4].

GCTs are histologically classified according to World Health Organisation (WHO 2016) into the following subtypes: Seminoma/germinoma, embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), choriocarcinoma, teratoma (mature, immature, and with secondary malignancy), and mixed tumors.

The overall incidence of GCTs is 2%-3%, but in childhood, they have a bimodal distribution: The first peak is at birth and up to age 4 and then a second peak is after the onset of puberty.

Therefore GCTs represent 3.5% of all tumors in children younger than 15 years, but between ages 15 and 19 years GCTs represent 16% of the total cancer burden. [1-3]. Our patient was a 16-years-old adolescent. Extragonadal GCTs are rare tumors accounting for 1%-5% of all GCTs [2].

PMGCTs are very rare EGGCTs that occur in the anterior mediastinum, which represents the second most common site of the origin [1, 2]. These rare neoplasms were first reported by Woolner et al. in 1955 [3].

Primary mediastinal germ cell tumors (PMGCTs) comprise only 1% to 4% of all tumors found in the anterior mediastinum. They include mature and immature teratomas, seminomas, and non-seminomatous GCTs.

Seminomas occur in up to 50% of malignant mediastinal GCTs in adults, predominantly in young males, but in children, these tumors are very rare with only a few case reports in the literature.

Extragonadal GCTs are described as having a different biologic behavior and less favorable prognosis (particularly mediastinal) than those with gonadal disease [1, 2, 5-11].

Primary mediastinal seminomas are typically slow growing. These tumors infiltrate surrounding organs ear-

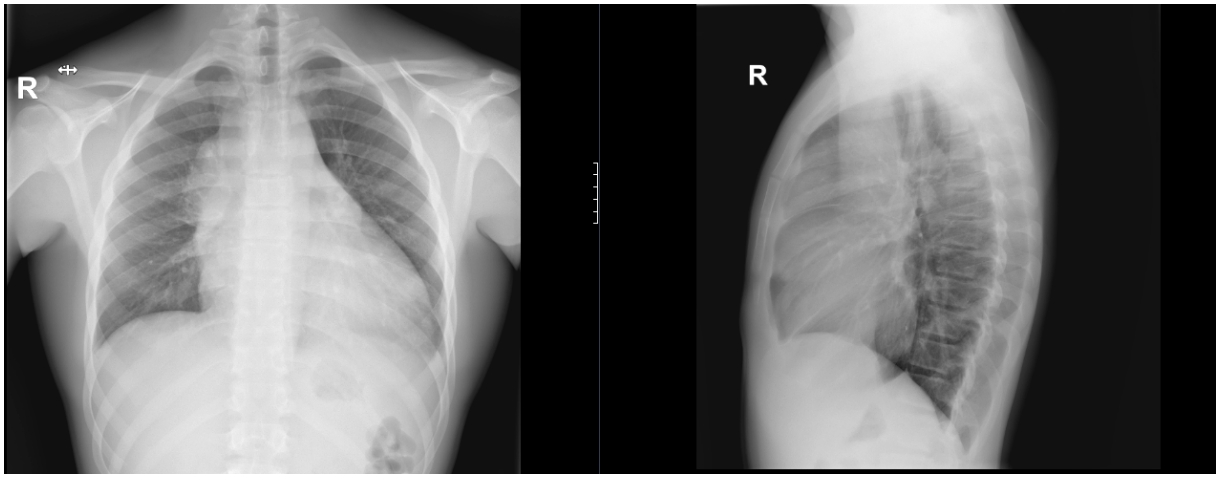

Figure 1. The posteroanterior and latero-lateral chest X-ray
The right hilar enlargement is accompanied by peribronchovascular thickening.

ly on in their growth process, with symptoms secondary to compression of the surrounding organs, such as the heart and lungs, and can be very bulky by the time they cause discomfort. Hence the majority of these tumors (75%) are symptomatic at the time of diagnosis, presenting with chest pain, dyspnea, cough, weight loss, superior vena cava syndrome, fever, and nausea. Likewise, our patient presented with a cough, fever, and chest tightness lasting for a couple of weeks [1, 2, 3, 11-14].

Specific subtypes of GCTs secrete proteins AFP and β-HCG. They can be used as markers of tumor presence, for further diagnostic and therapeutic strategy as well as follow-up for recurrence. Elevated AFP and or β-hCG at diagnosis is seen in 70%–80% of the patients. AFP is mostly not expressed in cases of pure seminomas; therefore, a significant elevation of AFP indicates mixed GCT with components of Yolk sac tumor or choriocarcinoma. β-hCG is only secreted in a third of mediastinal GCTs. Napieralska et al. in a cohort study in 2018 found a raised β-hCG in 38% of their cases [2]. In conclusion, all AFP- or β -HCG–positive mediastinal tumors in children are malignant EGGCTs. Therefore, they should always be performed when an anterior mediastinal mass is diagnosed and may guide treatment, especially important in patients requiring urgent therapy for a severe mediastinal syndrome [2, 3, 13, 14]. Blood tests for GCTs tumor markers of our patient revealed elevated AFP of 16.1 ug/L (normal range of <7.0 ug/L) and β-hCG as well, with a pronounced increased level of 142.0 IU/L, (normal range of <0.2 IU/L). Following the first cycle of chemotherapy by BEP protocol, the patient normalized the levels of the aforementioned tumor markers [2, 3, 11-14].

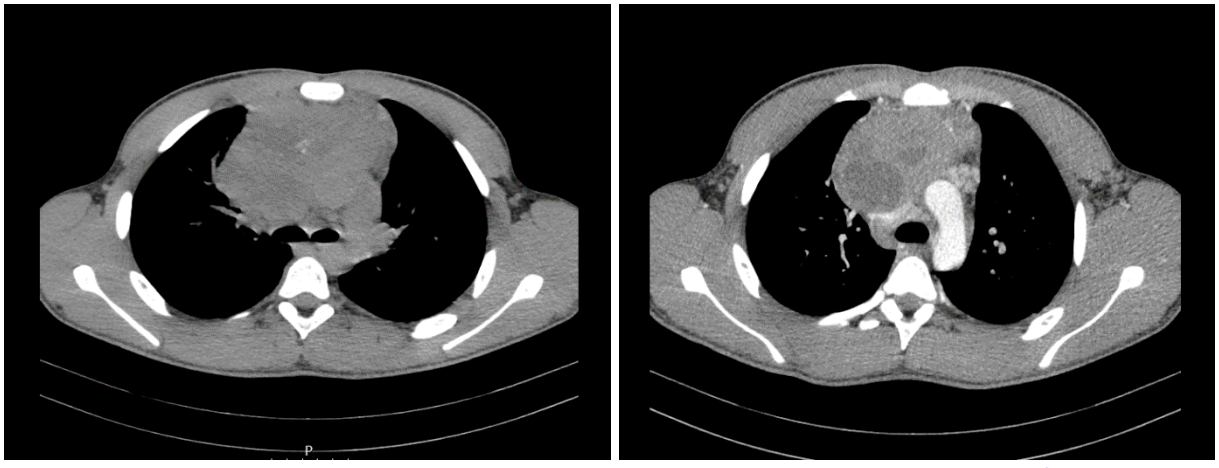

Figure 2. Large expansive process measuring 12.4x6.7x14.2 cm in the anterior mediastinum, accompanied by conglomeration of hilar lymph nodes in the level of brachiocephalic veins juncture

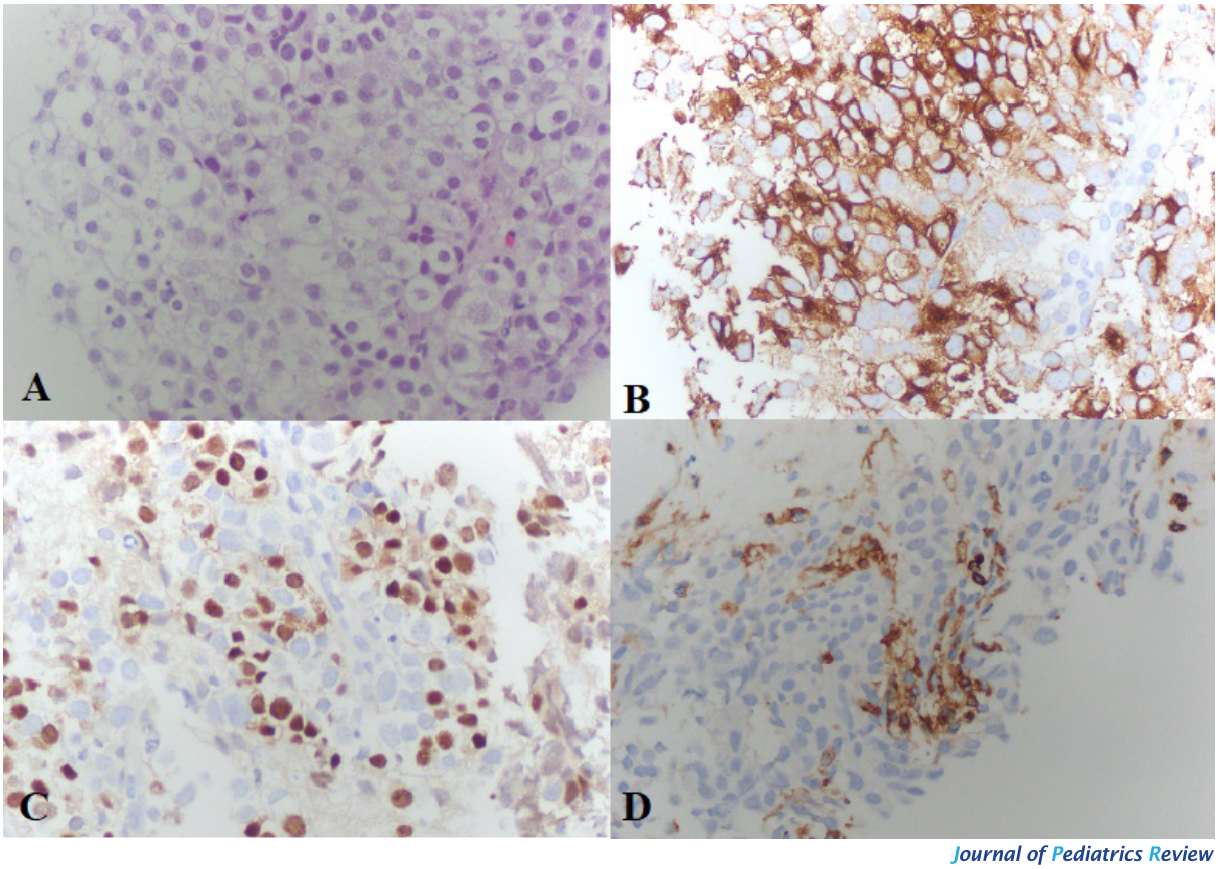

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Figure 3. A) Light microscopy of the tumor composed of atypical larger cells with oval nucleus and pale cytoplasm (H & E staining, magnification 400x). B) Diffuse membranous staining for plapp (magnification 400x). C) Strong nuclear positivity for Oct4 (magnification 400x). D) negative staining for Lca (magnification 200x.

Lactate dehydrogenase isoenzyme1 is also elevated in many GCTs as a marker of tumor mass and proliferation, but is not a specific marker [13, 14].

It is well known that GCTs are related to gonadal dysgeneses like Klinefelter's syndrome and undescended testes [15]. G-banding karyotyping in our patient ruled out the diagnosis of Klinefelter syndrome, with a report of 46 XY karyotypes. Our patient had a retractile testis in childhood, but the testis has remained in the proper position temporarily. The sperm cryopreservation was attempted two times before chemotherapy,

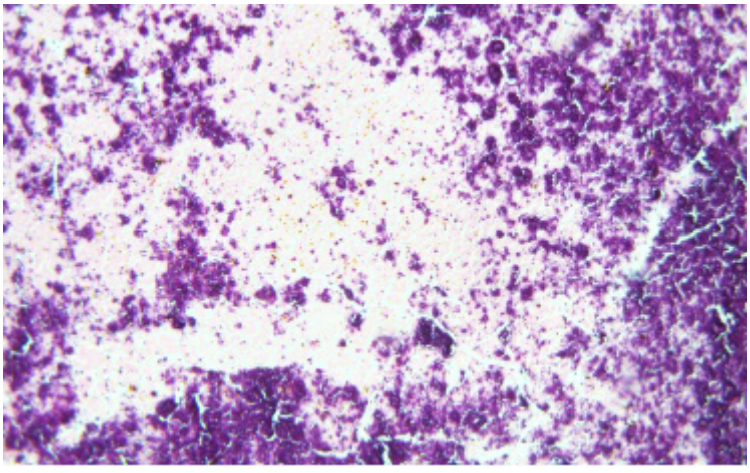

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Figure 4. Light microscopy of the mediastinal tumor upon chemotherapy, necrosis, and calcifications are presented without viable cells (H & E staining, 100x magnification)

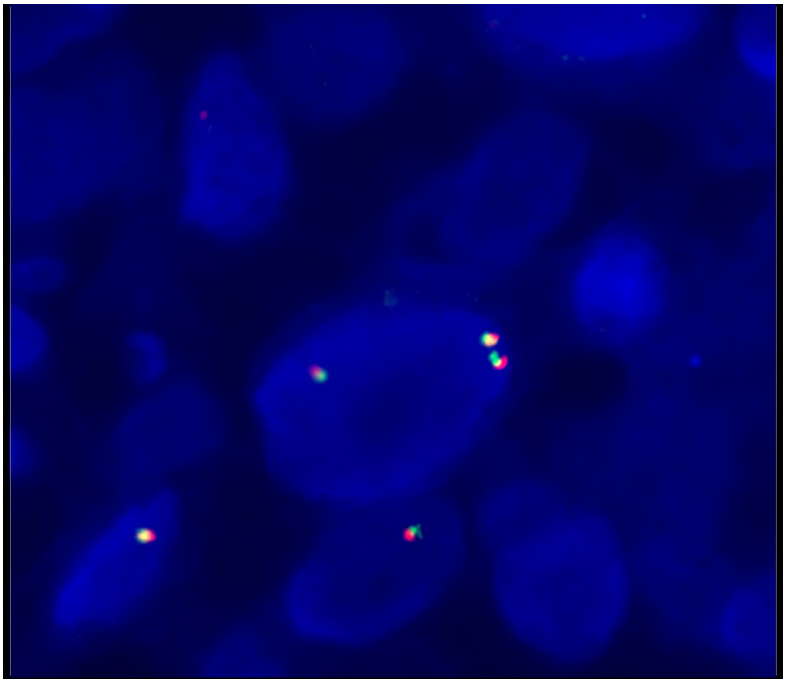

Figure 5. LSI ETV6 dual color break apart rearrangement probe

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The LSI ETV6 fluorescence in situ hybridization (FISH) probe kit detects chromosomal rearrangements involving the *ETV6* gene located at chromosome 12p13. Hybridization of this probe to interphase nuclei of normal cells is expected to produce two pairs of overlapping, or nearly overlapping, orange and green (yellow fusion signals). The anticipated signal pattern in abnormal cells having a chromosomal breakpoint within the gap between the two probe targets on one chromosome 12 is one orange, one green, and one fusion signal.

rather unsuccessfully with a spermiogram showing hypospermia and azoospermia. The Endocrinological survey has shown normal pubertal development with normal bone age assessment, normal testosterone (27.800 nmol/l), and lower gonadotropin level (LH <0.3 IU/lm FSH <0.3 IU/l). 17-hydroxyprogesterone (17-OHP) was also elevated (18.77 nmol/l), but normal prolactin and cortisol levels after adrenocorticotropic hormone administration excluded the non-classical congenital adrenal hyperplasia [15, 16].

Gonadal and mediastinal GCTs share the same histologic and biochemical features and also a common cytogenetic abnormality, that is, the gain of isochromosome 12p. For this purpose, the tumor specimen of our patient was analyzed with an LSI ETV6 Dual Color Break Apart Rearrangement Probe. This fluorescence in situ hybridization (FISH) probe kit detects chromosomal rearrangements involving the *ETV6* gene located at chromosome 12p13. So, using this probe, we have indirectly proved the additional copy of the ETV6 gene, which could be iso12p, duplication 12p, or trisomy 12p (Figures 5) [12, 15, 16].

Mediastinal seminomas are most commonly found in the anterior-superior mediastinum. A chest CT scan with contrast, MRI, or PET-CT is the most important diagnostic imaging which can identify the location and extent of involvement of the mediastinal mass. The CT scan performed on our patient has revealed a large expansive process in the anterior mediastinum with dimensions of 12.4 x 6.7 x 14.2 cm, accompanied by a conglomeration of hilar lymph nodes in the level of brachiocephalic veins juncture (Figure 2). An anterosuperior mediastinal mass can also be caused by Hodgkin and non-Hodgkin lymphoma, sarcoma, thymoma, and thymus carcinoma. Therefore, the biopsy and patohistological analysis of tumor tissue are essential for diagnosis [12, 13, 14].

The treatment for GCTs includes surgical resection, CT, and RT. Mediastinal seminomas have a good prognosis with 88%-90% overall survival. These tumors represent a unique example of solid tumors highly sensitive to chemotherapy and, in the case of seminoma, to radiotherapy, regardless of location [13, 14].

Surgical resection is essential for the treatment of most GCTs. It is the first-line treatment of choice for benign teratomas, immature teratomas, and low-stage malignant GCTs.

Surgery for PMSGCT is technically demanding for these tumors are mostly bulky mediastinal masses at

presentation, infiltrating surrounding organs early on in their growth process such as the heart and lungs, lymph nodes, or great veins and phrenic nerves. So, primary surgery is not usually feasible at presentation, but as a procedure after first-line CT [14, 17-19]. As the CT scan in our patient revealed a large expansive process, we decided not to proceed to a complex surgery but to use a fine needle biopsy and core biopsy transthoracically, under the control of MSCT, to gain a tumor sample for pathohistological diagnosis (Figure 3A, B, C, D). The complete excision of the tumor mass would give us surely a more accurate diagnosis [13, 17, 18].

The most widely recommended first-line CT regimen is BEP protocol for three or four courses, depending on whether the PMGCT falls into the good or intermediate (seminoma) or poor-risk (nonseminoma) category according to the International Germ Cell Cancer Collaborative Group. Bleomycin is notorious for possible lung damage, especially in patients with bulky thoracic involvement; therefore, some groups prefer to replace bleomycin with ifosfamide [13, 14].

The introduction of Einhorn-type CT initially for malignant testicular GCTs has been the major factor in improved survival in the 1980s and 1990s [2, 3, 13, 14].

CT with cisplatin-based regimens has markedly improved the outcome of adults and children with GCTs as well. In a collaborative effort involving 11 centers in Europe and USA over 21 years, Bokemeyer et al. have described data from 635 consecutive adult patients with mediastinal and retroperitoneal EGGCTs treated with platinum-based CT. Fifty-one were mediastinal seminoma with an excellent 5-year survival of nearly 90% [13, 19].

Therefore, following the histological diagnosis, a BEP CT regimen was initiated and realized in our patient, without significant side effects. To date, he has completed four cycles, with no oncologic relapse and with laboratory values in the normal range.

Control PET-CT scan showed the partial morphologic response of the tumor by decreasing in size compared to the previous CT findings in May and with no signs of metabolic activity as FDG uptake was not observed.

After the first-line CT, the thoracoscopic complete extirpation of the tumor was done, followed by pathohistological analysis. Microscopic analysis showed necrotic mass without viable cells, fibrosis, and calcifications (Figure 4). Kesler et al. showed that complete necrosis was found in 25% of samples taken from 158 patients with PMGCT undergoing surgery after CT, in a large single-center experience. Bokemeyer et al. reported that resection of post-treatment residual mass demonstrated a high probability for necrosis which is similar to our observation. We confirmed that cisplatin-based CT for PMGCTs results in extensive tumor necrosis [17-19].

Although it is uncommon for testicular seminoma to metastasize to the mediastinum in the absence of retroperitoneal lymph node involvement, all men with mediastinal germinoma should undergo careful testicular palpation and ultrasonography [2, 3].

During the tumor staging in our patient, the testicular ultrasound showed discrete microlithiasis, mostly on the edges of the testes. According to the literature, microlithiasis presents a risk of development of testicular tumor, but its association with extragonadal GCT is rare. Anyway, regular monitoring, and clinical and sonographic check-ups, are necessary [20].

Due to the rarity of the disease, scarce studies are comparing different treatment strategies or CT schedules for primary mediastinal GCTs in children. For this reason, oncology societies recommend treating PMGCTs like other GCTs, according to general risk categories [13, 14, 19].

The case represented in this report is the first case of a child/adolescent with mediastinal seminoma treated in our institution. The last follow-up examination with PET-CT was performed in October 2021 and the patient remained disease-free for 16 months.

Conclusion

PMGCTs are very rare EGGCTs in children and adolescents that occur in the anterior mediastinum with an incidence of 7% of all GCTs. CT with BEP protocol has markedly improved the outcome of adults and children with GCTs. Due to the rarity of the disease, scarce studies are comparing different treatment strategies or CT schedules for primary mediastinal GCTs in children, as is the case for primary gonadal tumors in adults. For this reason, oncology societies recommend treating PMGCTs like other GCTs, according to general risk categories. Due to the paucity of patients with PMGCT, they should be referred to centers with experience in this rare disease [13, 14, 19].

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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