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CASE REPORT

A rare presentation of giant teratoma in the mediastinum of an adolescent – a case report and treatment outcome

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ABSTRACT

Mediastinal teratoma is an unusual germ cell tumor, accounts for 1–5% of all mediastinal tumors and is the most common type of the mediastinal germ cell tumor. While mature mediastinal teratomas are infrequent, their discovery is often incidental. This case presents a 16-year-old boy with left-sided chest pain, dry cough, and decreased exercise tolerance persisting for several weeks. Imaging revealed a large mediastinal mass displacing cardiac structures and compressing the left lung. A biopsy indicated a mixed germ cell tumor, predominantly an immature teratoma with a minor yolk sac tumor component. The patient received four cycles of neoadjuvant chemotherapy, followed by complete surgical resection, with histopathology confirming a benign mature teratoma. Two months post-surgery, he developed myelodysplastic syndrome, likely related to chemotherapy, and underwent an allogeneic stem cell transplant. This case underscores the importance of multidisciplinary care and vigilant follow-up in managing large mediastinal germ cell tumors in adolescents.

KEY WORDS:
neoadjuvant chemotherapy, germ cell tumor, mediastinal teratoma, myelodysplastic syndrome.

INTRODUCTION

Thoracic neoplasms in children are uncommon, with the most frequent types being immature neuroblastomas, rhabdomyosarcomas, extragonadal germ cell tumors (GCTs), and lymphomas [1]. Teratomas, the most common histologic subtype of childhood GCT, are classified according to their histologic composition as mature, containing well-differentiated tissues; immature, containing varying degrees of immature fetal tissue, most often neuroectodermal; or malignant, containing at least one of the malignant germ cell elements [2]. While immature teratomas are initially benign, they can undergo malignant transformation, which underscores the importance of early surgical removal to prevent progression to malignant GCTs [3].

These tumors tend to secrete specific markers, such as α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG). However, it should be borne in mind that AFP levels can be elevated in newborns and infants. Therefore, only significantly elevated values may be associated with teratoma in this age group [4]. Germ cell tumors have two incidence peaks: one before the age of 3, typically located in the sacrococcygeal region and testes, and another after the age of 12, when ovarian tumors, such as dysgerminomas, become more common in females [3]. The most frequent locations of GCTs in children under 15 years are the ovaries, coccyx, testes, and brain, with extragonadal GCTs are often found in the mediastinum [4]. Primary mediastinal GCTs represent approximately 5% of all extragonadal GCTs and ac-

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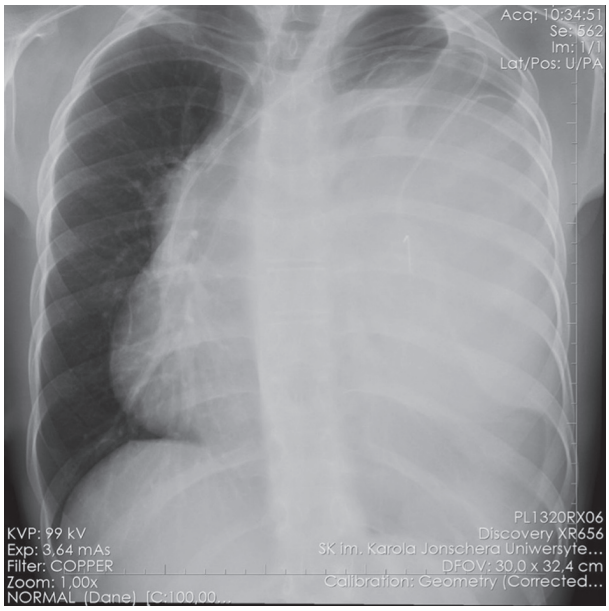

FIGURE 1. Chest X-ray demonstrating complete opacification of the left lung

count for about 25% of mediastinal tumors in pediatric patients. These tumors are predominantly classified into 60% mature mononuclear tumors, 20% mixed GCTs, and 20% germ cell carcinomas [5]. Most of these tumors are mature and benign, originating from embryonal tissues [1]. They are most frequently located in the anterior mediastinum [6]. These tumors pose a diagnostic challenge as they may remain asymptomatic for an extended period, without causing noticeable symptoms such as pain or respiratory distress. As a result, they are often identified incidentally due to an enlarging tumor mass [7]. Imaging techniques such as chest X-rays, computed tomography (CT) scans, magnetic resonance imaging, and ultrasound are utilized for diagnosis, with CT being the gold standard due to its detailed visualization of tumor characteristics. Surgical intervention remains the primary treatment, particularly for benign teratomas, with complete resection significantly improving prognosis. In contrast, malignant teratomas often require a combination of chemotherapy and surgery. Complications, such as tumor rupture, can lead to severe conditions like cardiac tamponade, necessitating urgent intervention [8, 9]. This article discusses the case of a boy diagnosed with a giant teratoma, a tumor originating from primordial germ cells.

CASE REPORTS

A 16-year-old male presented with a chief complaint of left-sided chest pain, a history of decreased exercise tolerance, and a recent history of fever and night sweats persisting for three weeks. He also reported a dry cough. The patient was born at term as the first child in an uncomplicated pregnancy, with an Apgar score of 10. His medical and family history was unremarkable. Upon examination, auscultation revealed muffled breath sounds in the left lung, except for the apex, and dullness on percussion. His heart rate was elevated (130 beats per minute), and he exhibited acne on his back, though no other abnormalities were observed.

The initial chest X-ray showed complete opacification of the left lung (Figure 1) and subsequent CT identified a large, hypodense mass measuring 10.5 × 14.9 × 15.5 cm, occupying the left thoracic cavity and partially extending into the anterior mediastinum. The tumor displaced cardiac structures and exerted compression on the left pulmonary artery. The patient was transferred to a tertiary hospital for further management, where echocardiography revealed the presence of pericardial fluid and compression of the right ventricular outflow tract.

A biopsy was performed, and the results revealed fragments of an immature triploblastic teratoma, without neuroepithelial clusters, and with scattered glandular tissue suggesting a primitive endodermal component, typical of a yolk sac tumor. Immunohistochemical (IHC) analysis showed CK AE1/AE3 (+), EMA (+/– in AFP-expressing tubes), AFP (+ focal), WT1 (+/–), Glipican3 (+ focal), CD30 (–), Synaptophysin (–/+ in glandular tubes with intestinal differentiation), and Myogenin (–/+ in isolated stromal cells). The findings indicated that the tumor was primarily an immature teratoma (~95%) with a small component of yolk sac tumor (~5%).

In laboratory tests, lactate dehydrogenase (LDH) was markedly elevated at 486 U/l (N: 105–235 U/l), accompanied by increased levels of C-reactive protein at 23.19 mg/dl (N: < 5 mg/dl), white blood count at 11.08 G/l (N: < 10 G/l), international normalized ratio at 1.84 (N: 0.8–1.2), and fibrinogen at 814 mg/dl (N: 200–400 mg/dl). Hemoglobin was decreased to 11.2 g/dl (N: 13–18 g/dl), while ferritin remained within normal limits at 90 µg/l (N: 20–200 µg/l). Tumor markers showed heterogeneous results, with β-HCG significantly elevated at 385.09 mIU/ml (N: < 5.0 mIU/ml) and AFP at 7,848.65 ng/ml (N: < 8.78 ng/ml) on April 7, 2022. In contrast, other tumor markers remained within normal limits, including carcinoembryonic antigen (CEA) at 2.5 ng/ml (N: < 5 ng/ml) and neuron-specific enolase at 8.7 ng/ml (N: 0–12.5 ng/ml). In addition, hormonal abnormalities were noted, with testosterone elevated at 43.00 nmol/l (N: 8.2–34.6 nmol/l) and estradiol at 145 pg/ml (N: 11–44 pg/ml).

Given the clinical and diagnostic findings, a vascular port was placed, and chemotherapy was initiated using the etoposide, ifosfamide, and cisplatin (VIP) regimen. Over the course of four chemotherapy cycles, computed tomography scans monitored tumor progression, with the tumor growing to 18.1 × 16.6 × 18.3 cm by July 2022 (Figure 2). This growth caused compression of the left bronchus and atelectasis in the left lower lobe. Despite chemotherapy, the tumor continued to grow, leading to a decision for surgical intervention. In August 2022, the tumor was excised *via* bilateral thoracosternotomy, successfully separated from surrounding structures and

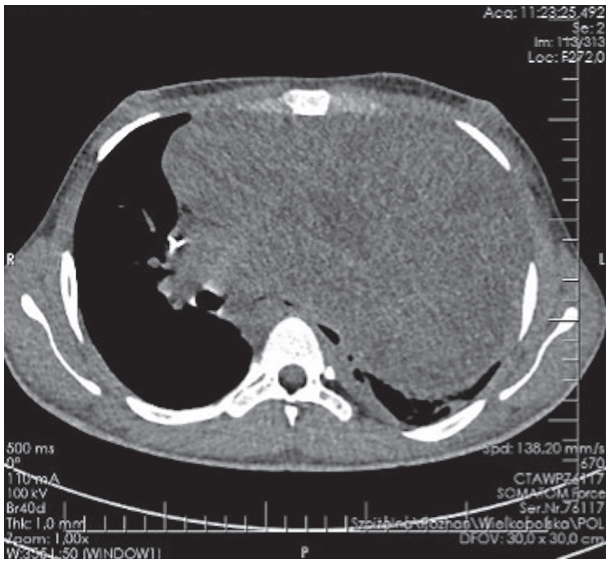

FIGURE 2. Preoperative chest computed tomography from July 2022 showing a large, low-density mass measuring 18.1 × 16.6 × 18.3 cm, occupying the left thoracic cavity and extending into the anterior mediastinum

The tumor's growth led to compression of the left bronchus and caused atelectasis in the left lower lobe.

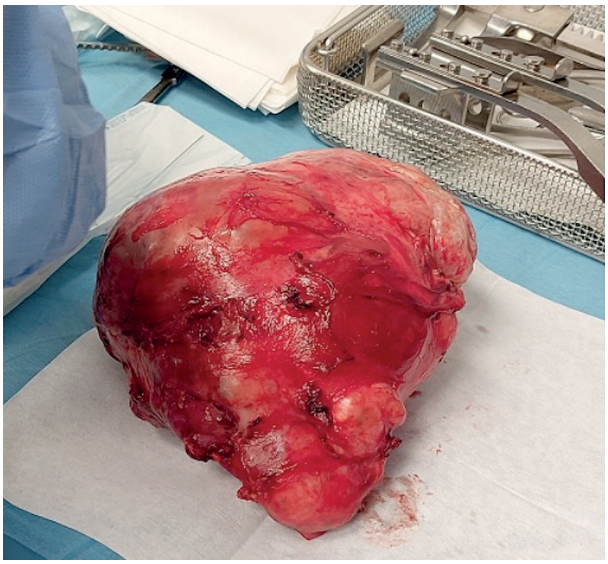

FIGURE 3. Completely excised tumor following bilateral transverse thoracosternotomy in August 2022

The mass was successfully removed after dissection from surrounding structures, including the anterior thoracic wall, left brachiocephalic vein, superior vena cava, and pericardial sac.

entirely removed (Figure 3). Post-surgery, an air leak from the left lung required sutures and tissue glue for closure, and two chest drains were placed. The patient initially required inotropic support, but their condition improved, and they were extubated six days after surgery. The patient was discharged in good condition in September 2022.

Biochemically, following the first two chemotherapy cycles in April and May 2022, AFP levels showed significant reduction, decreasing to 132.12 ng/ml (N: < 8.78 ng/ml) by June 13, 2022, with undetectable β-HCG (N: < 5.0 mIU/ml). After the third and fourth cycles in June and July 2022, AFP levels normalized at 5.41 ng/ml (N: < 8.78 ng/ml) by August 23, 2022, with β-HCG consistently negative, indicating a strong biochemical response to treatment.

Microscopic histopathological examination revealed that the surgical specimen consisted of a mature three-layered cystic teratoma characterized by focal necrosis, which represented 20% of the sample examined. No malignant or neuroepithelial components were identified, and the resection margins were free of tumor, confirming an R0 resection. Immunohistochemical analysis showed the following results CKAW1/AE3 (+), EMA (+/–), S100 (+/–), CD99 (+/–), synaptophysin (–/+) and Ki67 (–/+).

In October 2022, the patient was readmitted to the hospital after experiencing a tonic-clonic seizure postoperatively. The initial laboratory findings indicated leukopenia, thrombocytopenia, and mild anemia. After discontinuing anticonvulsant therapy, platelet counts improved, but leukopenia persisted, prompting trepanobiopsies in November 2022 and February 2023. The bone marrow biopsies revealed dysplastic changes, indicating the presence of a hypoplastic myelodysplastic syndrome (MDS) or post-chemotherapy dysplasia.

The patient was qualified for allogenic hematopoietic stem cell transplant (allo-HSCT), which he underwent in August 2023. He received marrow from a matched unrelated donor compatible with main blood groups and 10/10 regarding HLA. Before the procedure, he had been conditioned with treosulfan, fludarabine, thiotepa and thymoglobulin. Cyclosporin A and methotrexate were administered to prevent graft vs. host disease. After the treatment, patient's laboratory parameters improved including the count of platelets, reticulocytes and granulocytes. The boy experienced some adverse effects after the allo-HSCT, which included parenteral feeding for 35 days, toxic lesions on oral mucosa, HSV infection, decreased diuresis and a high level of fear and anxiety. Nevertheless, his condition gradually improved and 40 days after the allo-HSCT he was discharged home in good general condition. Importance of further monitoring was stressed and the patient was advised to have regular follow-up visits.

DISCUSSION

GCTs are neoplasms developing from primordial germ cells [10]. They can be classified into three main groups: teratomas, seminomas and nonseminomatous GCTs [11]. Teratomas are derived from 2 or 3 germinal layers (endoderm, ectoderm, mesoderm). They are built of multiple types of mature or immature somatic tissues [12]. Teratomas can be further divided into three main groups: mature teratomas, immature teratomas and teratomas with malignant transformation [13]. Mature teratomas are usually benign and contain only fully developed, adult-type tissues [12, 14]. Immature teratomas are composed of fetal or embryonic tissues and have more

aggressive potential [12, 14]. Teratomas with malignant transformation may contain other malignant components including sarcoma, malignant GCTs or carcinoma [14]. Mature teratoma was diagnosed in our patient.

Mature teratomas same as GCTs in general are most commonly found in ovaries and testes [15–17]. Extragonadal locations are much rarer. Mediastinal location of the tumor is present in 27% of teratoma cases in adults and in 4–13% of cases in children [12]. Our patient presented with this unusual mediastinal location of the tumor, a finding that is particularly rare in the pediatric and adolescent population.

Clinically, mediastinal teratomas are asymptomatic in about 60% of cases and often discovered incidentally during chest imaging for unrelated reasons [13, 18]. When symptomatic, patients may experience chest or back pain, cough, dyspnea, fever from chronic pneumonia, or other rare symptoms like Horner syndrome, superior vena cava syndrome, tumor rupture, pneumothorax, or even the expectoration of hair or other materials due to tumor erosion into adjacent structures [12, 13, 18]. A study from Taiwan found that among 57 patients diagnosed with anterior mediastinal teratoma, 49.1% were asymptomatic, and symptoms in the remaining cases included chest pain (31.6%), tightness (14%), cough (7%), and fever (7%), with fever more common in patients younger than 12 [19]. Our patient, presenting with chest pain, nonproductive cough, and reduced exertional tolerance, showed nonspecific symptoms that can be observed in various pulmonary or cardiac conditions.

Adolescents and postpubertal children, like our 16-year-old patient, represent a high-risk group for primary mediastinal GCTs, which further underscores the complexity of diagnosis and management in such patients [14].

In most cases of mediastinal GCTs, the initial diagnosis is based on small needle core biopsies followed by IHC valuation [20]. However, in certain situations, clinical findings combined with imaging may be sufficient to initiate treatment without the need for a biopsy [21]. For instance, in young male patients with a prevascular mediastinal mass and elevated levels of AFP or β-HCG (> 100 IU/l), a diagnosis of nonseminomatous GCT can be made, and treatment can begin without biopsy confirmation [21]. Blood tests, including complete blood count, biochemistry, and tumor markers such as AFP, β-HCG, and LDH, should be performed in all cases [20]. In our patient, tumor markers were markedly elevated, with AFP at 7,848.65 ng/ml (N: < 8.78 ng/ml) and β-HCG at 385.09 mIU/ml (N: < 5.0 mIU/ml), which strongly indicated a germ cell tumor. Imaging, particularly computed tomography (CT), plays a crucial role in diagnosing mediastinal GCTs, revealing characteristic features such as soft tissue, multi-lobulated, heterogeneous masses with areas of fluid and calcifications. Calcifications are present in approximately 20–40% of benign mediastinal teratomas [13]. In our case, CT findings demonstrated these typical characteristics, along with atelectasis, likely caused by lung compression from the tumor mass [12, 22].

Immunohistochemistry is particularly useful for characterizing immature tissues, though it is often unnecessary in diagnosing mature teratomas as was the case with our patient [12, 23]. Microscopic examination confirmed the presence of mature cells from all three germ layers, with no malignant features, consistent with a benign mature teratoma. The World Health Organization classification of GCTs distinguishes between mature and immature teratomas, as well as teratomas with malignant transformation. According to the grading system, the tumor was classified as a mature teratoma [24, 25].

In considering differential diagnoses, various mediastinal masses should be included, such as thymic diseases, lymphomas, lymphangiomas, neurogenic tumors, mesenchymal tumors, other GCTs, pulmonary neoplasms, hydatid cysts, fungal balls, and lung abscesses [13, 20, 26].

Treatment of primary mediastinal GCTs generally requires a multidisciplinary approach. In cases of nonseminomatous GCTs, cisplatin-based chemotherapy is followed by surgical resection to remove residual tumor tissue [19, 23]. For seminomas, chemotherapy alone is often sufficient, while for nonseminomatous GCTs, a combination of chemotherapy and surgery is typically employed [11]. In our patient's case, four cycles of neoadjuvant chemotherapy using VIP were administered prior to surgery. The etoposide, ifosfamide, and cisplatin regimen was preferred over BEP (bleomycin, etoposide, and cisplatin) due to the potential risk of bleomycin-induced lung injury, which can result in interstitial pneumonitis and postoperative fibrosis [23].

Despite the significant reduction in tumor markers resulting from chemotherapy, the tumor itself did not respond as expected. Specifically, the levels of AFP decreased from 132.12 ng/ml (N: < 8.78 ng/ml) after the first cycle to 5.41 ng/ml by the third cycle (June 2022) and 3.34 ng/ml after the fourth cycle (July 2022), with undetectable β-HCG. Instead, its dimensions increased from 10.5 × 14.9 × 15.5 cm to 18.1 × 16.6 × 18.3 cm. This unanticipated growth, despite the normalization of tumor markers, is indicative of growing teratoma syndrome (GTS), a rare occurrence in nonseminomatous germ cell tumors. Growing teratoma syndrome is characterized by the progressive growth of mature teratoma tissue that does not respond to chemotherapy due to the absence of malignant components [27, 28].

In the present case, chemotherapy was initially administered as a rescue strategy to reduce the tumor burden and minimize surgical risks. Despite the reduction in tumor markers, follow-up imaging demonstrated tumor growth, leading to the realization that the lack of response was not indicative of chemotherapy failure, but rather consistent with GTS. This underscores the importance of distinguishing GTS from true chemotherapy resistance

as misinterpretation of the findings can lead to unnecessary treatment delays.

The diagnosis of GTS remains challenging, primarily due to its rarity. According to Logothetis' diagnostic criteria, GTS is defined by the normalization of tumor markers, an increase in tumor size or new lesions during or after chemotherapy, and the presence of mature teratoma tissue in the resected tumor [27]. In our case, imaging confirmed that surgical resection was required as the only viable treatment option. Radical surgical intervention remains the cornerstone of GTS management as chemotherapy and radiotherapy have proven ineffective against this benign yet growing tissue [28].

Although GTS is a rare condition, it is imperative to recognize it in order to avoid the administration of unnecessary chemotherapy or radiation therapy and to expedite the appropriate surgical intervention. The prognosis following complete surgical resection is generally favorable, with a 5-year survival rate of 89–90% [27]. However, there remains a 10% risk of mortality, largely due to postoperative complications or the potential development of secondary malignancies. Early diagnosis and timely surgical intervention are critical to improving outcomes and reducing complications [28].

Primary mature mediastinal teratomas may be treated with surgery alone [23, 26]. When immature component, somatic transformation or elevated tumor markers are present chemotherapy is added [20, 26]. Surgical excision of teratomas can be performed through open surgery or video-assisted thoracoscopic surgery (VATS) [29]. Open surgery is advised when dense adhesions are present in the preoperative CT scan, when the tumor is large in size or malignant [6, 29]. Otherwise VATS is a recommended method of choice due to smaller number of required blood transfusions, shorter postoperative recovery time and shorter hospital stay [6, 29]. Dense adhesions and existing symptoms increase the risk of complications [26]. In our case, the tumor adhered to the thoracic wall. It infiltrated the left brachiocephalic vein, superior vena cava and pericardial sac. The left lung was significantly compressed posteriorly by the mass. The tumor resection was performed through open access. The choice of incision in open surgeries is based on the tumor size and location in regard of neighboring anatomical structures [26]. Our patient's tumor was large in size (18.3 cm in the biggest dimension) and adjoined vital anatomical structures. Bilateral transverse thoracosternotomy was decided to be the best surgical approach. No adjuvant, postoperative chemotherapy was administered. Long-term observation and regular follow-up visits were indicated as the correct course.

Some types of primary mediastinal GCTs are associated with hematologic malignancies, Klinefelter's syndrome, and other chromosomal disorders [20, 21]. Hematologic malignancies are present in 2–3% of non-seminomatous primary mediastinal GCTs. The most common include various types of leukemia, myelodysplasia, malignant mastocytosis, essential thrombocytopenia, and malignant histiocytosis [20].

Our patient developed neutropenia and thrombocytopenia two months after the surgery. Two trepanobiopsies were performed, which confirmed the diagnosis of MDS, likely induced by the prior administration of chemotherapeutic agents. While the role of chemotherapy is clear, the possibility of shared genetic alterations between the teratoma tumor cells and the dysplastic bone marrow cells cannot be excluded. The presence of identical heterozygous genetic profiles in both the bone marrow and teratoma tissue suggests that somatic hematopoietic stem cells may give rise to the trilineage hematopoiesis observed in the bone marrow of teratomas [30]. This indicates that bone marrow cells within teratomas may originate from circulating hematopoietic precursors capable of infiltrating the tumor [30]. Genomic alterations responsible for the development of the mediastinal teratoma could have predisposed the patient to MDS. To treat the MDS, the patient underwent allo-HSCT. Long-term follow-up and regular screening will be necessary to monitor for potential long-term effects or complications arising from the treatment administered. Chemotherapy-induced myelodysplastic syndrome is a rare but serious complication, often occurring in patients with solid tumors who receive certain chemotherapeutic agents, such as alkylating agents and platinum compounds. Studies conducted on larger populations have demonstrated an elevated risk of therapy-related MDS or acute myeloid leukemia following chemotherapy for most solid tumor types [31]. In our case, the patient underwent allo-HSCT as treatment for myelodysplastic syndrome. In order to check for possible side effects of the implemented therapy, our patient will require long-term monitoring and screening.

The prognosis in primary mediastinal GCTs depends on the tumor type [11]. Seminomas respond very well to cisplatin-based chemotherapy and the 5-year survival rate exceeds 90% [11, 20]. Primary mediastinal non-seminomatous GCTs are typically more aggressive and overall 5-year survival is 45% [11]. Benign, mature teratomas have excellent prognosis after complete surgical excision [22]. In immature teratomas low recurrence rate and long-term survival depend on radical surgical resection [26]. Two studies conducted on patients with mediastinal teratomas showed 100% overall survival rate and no recurrences in the long-term observation [32, 33]. However, a high percentage of immature elements within the tumor, patient age above 15 years, and large tumor size increase the risk of the relapse [32, 33]. The patient treated in our department had no immature elements in the tumor on histopathological assessment, which is a good prognostic factor. On the other hand, he was 16 at the time of diagnosis and his tumor was large in size. These two components negatively affect the prognosis. Outpatient follow-up visits accompanied by appropriate diagnostics are critical in this case.

Considering the complexity of the mediastinal teratoma case and the extensive surgery performed, multidisciplinary collaboration was implemented in the treatment of our patient. Surgeons, oncologists, radiologists, pathologists and other specialists worked together to provide the best possible care.

CONCLUSIONS

Extragonadal teratomas in the mediastinum are rare and often discovered incidentally. Adolescents and postpubertal individuals are at increased risk and may present with nonspecific symptoms such as persistent nonproductive cough, left-sided chest pain, dyspnea, and decreased exercise tolerance. Complete surgical excision is the treatment of choice, with open surgery recommended in cases of dense adhesions, ensuring favorable postoperative outcomes. Accurate histopathologic evaluation is essential to confirm the diagnosis.

Patients require ongoing outpatient follow-up after extensive surgery for mediastinal teratoma due to the proximity of the tumor to vital structures and potential hematopoietic complications, especially if chemotherapy has been administered. Monitoring is essential for the early detection of any adverse effects of treatment, allowing for timely intervention to support the patient's long-term health.

DISCLOSURES

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3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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