



Extraskelletal Mesenchymal Chondrosarcoma in the Anterior Mediastinum- A Rare Event: Case Report and Review of the Literature

Ariel Y Gliksberg^{1*}, Kiara A Tulla², Allison Fraum³, Mohamed Hassan⁴, Steven Garzon⁴, Michael Bresler³, Thom Lobe² and Mary Lou Schmidt¹

¹Department of Pediatrics, University of Illinois at Chicago, USA

²Department of Surgery, University of Illinois at Chicago, USA

³Department of Radiology, University of Illinois at Chicago, USA

⁴Department of Pathology, University of Illinois at Chicago, USA

Abstract

Background: Mesenchymal Chondrosarcoma is a rare high-grade tumor that affects mostly young adults and is comprised of a mixture of low-grade cartilaginous tumor cells as well as a primitive mesenchymal high-grade component. Most commonly, these tumors arise from the craniofacial bones but have been reported in ribs, vertebrae and long bones. However, they may be extraskelletal and have been reported mainly in the head and neck region (cranial dura most commonly), lower extremities and many other soft tissue locations. The most common types of mediastinal tumors are thymoma, thyroid disease, lymphoma, and mixed germ cell tumor, with approximately 50% found in the anterior mediastinum and 50% in middle or posterior mediastinum. There have only been 11 cases of a primary mediastinal mesenchymal chondrosarcoma reported, and only two of these occurred in the anterior mediastinum.

Case Report: Here, we present a 17-year-old Hispanic female a primary anterior mediastinal mesenchymal chondrosarcoma. We describe pre-operative radiologic findings, the surgical techniques used to remove this large tumor, the confirmatory pathologic analysis and proposed systemic and radiation therapies.

Conclusion: Mediastinal mesenchymal chondrosarcoma has been noted in the literature with only two prior cases being in the anterior mediastinum. This diagnosis may be under diagnosed. Given the paucity of uniform treatment regimens and clinical trials outcome data, it is difficult to determine exact prognosis and treatment recommendations.

Keywords: Mesenchymal chondrosarcoma; Anterior mediastinum; Pediatric germ-cell tumors

Abbreviations

CNS: Central Nervous System; CT: Computer Tomography; PCP: Primary Care Physician

Introduction

Mesenchymal Chondrosarcoma is a rare high-grade tumor. First described in 1959 by Lichtenstein [1], mesenchymal chondrosarcomas account for around 2% to 10% of all chondrosarcomas [2-4]. Furthermore, two oncologic cooperative groups reviewed soft tissue sarcoma and osteosarcoma clinical trials and found a less than 1% incidence of mesenchymal chondrosarcoma in children and adolescents, making it a difficult disease to assess and manage [3,5]. The majority of cases are osseous in origin while only 20% to 33% are extraskelletal [6-8].

Most extraskelletal mesenchymal chondrosarcomas are found in the cranium, with the first reported case of mediastinal mesenchymal chondrosarcoma in 1990 by Chetty [9]. Anterior mediastinal tumors account for 50% of all mediastinal masses and include thymoma, thyroid disease, lymphoma, and mixed germ cell tumor (more frequently teratomas histologically, especially in children). Middle and posterior mediastinal masses are typically congenital cysts and neurogenic tumors, respectively [10]. Only a select few primary mediastinal masses demonstrating the histologic subtype of mesenchymal chondrosarcoma are reported in the literature [11,12].

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*Correspondence:

Ariel Y Gliksberg, Department of Pediatrics, Division of Pediatric Hematology and Oncology, University of Illinois at Chicago, 840 S Wood Street, 1338 CSB, MC 856, Chicago, IL 60612, USA, Tel: 847-431-4477; E-mail: agliks2@uic.edu

Received Date: 14 Apr 2021

Accepted Date: 19 May 2021

Published Date: 24 May 2021

Citation:

Gliksberg AY, Tulla KA, Fraum A, Hassan M, Garzon S, Bresler M, et al. Extraskelletal Mesenchymal Chondrosarcoma in the Anterior Mediastinum- A Rare Event: Case Report and Review of the Literature. *Oncol Case Report J.* 2021; 4(1): 1033.

ISSN: 2641-9173

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This case report will describe the presentation of an adolescent female with an anterior mediastinal mesenchymal chondrosarcoma, and the discussion will help frame the therapeutic options for these patients. This case also provides the opportunity to review the related literature as well as the intricate management questions that arise.

Case Presentation

Preoperative assessment

A 17-year-old Hispanic female with no significant past medical history was referred to the Pediatric Oncology Service for evaluation of a neck mass after her Primary Care Physician (PCP) noted asymmetric neck swelling with possible supraclavicular lymphadenopathy. The patient reported no systemic symptoms, however she did recall noting prominent neck veins seven months prior to presentation. Family history was noncontributory.

On physical exam, she had mild left ptosis and a firm, immobile mass which arose from the tracheal notch and extended to the left supraclavicular and mid-cervical region. There were small hard nodules palpable within the mass. This was suspicious for left cervical adenopathy, but it was difficult to assess whether this finding instead represented extension of thyroid tissue. No other abnormalities were noted on physical exam.

Laboratory data including complete blood count, comprehensive metabolic panel, Lactic Dehydrogenase (LDH), C-reactive protein, uric acid, and thyroid function tests were all within normal limits. Chest X-ray revealed a widened upper mediastinum with associated rightward tracheal deviation most consistent with a differential diagnosis that favored lymphoma or a thyroid derived lesion.

The patient was admitted for advanced imaging and close monitoring for hypoxia during sleep. A non-contrast Computed Tomography (CT) examination performed for pre-operative work up and staging (Figures 1a-1f), demonstrated a 9.29 cm solid mediastinal mass anterior to the ascending aorta with extra-thoracic extension into the neck. The mass demonstrated many calcifications, abutted

the aortic arch and great vessels, and caused rightward mass effect on the trachea. No lymphadenopathy was noted on imaging. The mass was delineated from the thyroid on CT examination, and the primary pre-operative differential diagnosis was a germ cell tumor (such as teratoma) vs. thymoma. Pediatric surgery was consulted for biopsy or resection of the tumor. Additional tumor marks, including beta-human chorionic gonadotropin, Carcinoembryonic Antigen (CEA), alpha-fetal protein, CA125, and CA19-9, were obtained which were within normal limits. Patient had no events during sleep and patient was discharged home until date of surgery.

Surgical approach and perioperative course

Thoracoscopic mobilization of the mass was aborted due to the fixed nature of the mass to the superior and posterior edges of the mediastinum, but median sternotomy exposed the mass. Anterior exposure was complicated by left innominate vein adherence and involvement, requiring suture ligation and division. Capsular rupture occurred, and the contents were sent for pathologic evaluation. The frozen section evaluation noted a small blue cell tumor, thymoma and lymphoma were considered but further work up was needed. Findings prompted complete resection.

During circumferential mobilization, it was noted that the mass eroded through the left common carotid artery. To preserve cerebral perfusion, the decision was made to perform a proximal to distal left common carotid bypass with polytetrafluoroethylene. The proximal left common carotid artery was dissected free, and the patient was systemically heparinized to allow for clamping and resection of the involved artery. An attempt was made to resect the mass en bloc; however, to restore cerebral perfusion, the decision was made to remove only the anterior surface of the tumor prior to performing the left common carotid artery bypass. After reperfusion, the posterior and lateral portions of the mass were dissected free from the vagus nerve, and the remaining mass was excised. No gross evidence of tumor was left behind. A mediastinal and a left thoracic chest tube were placed, and the sternum was closed in the usual fashion. The

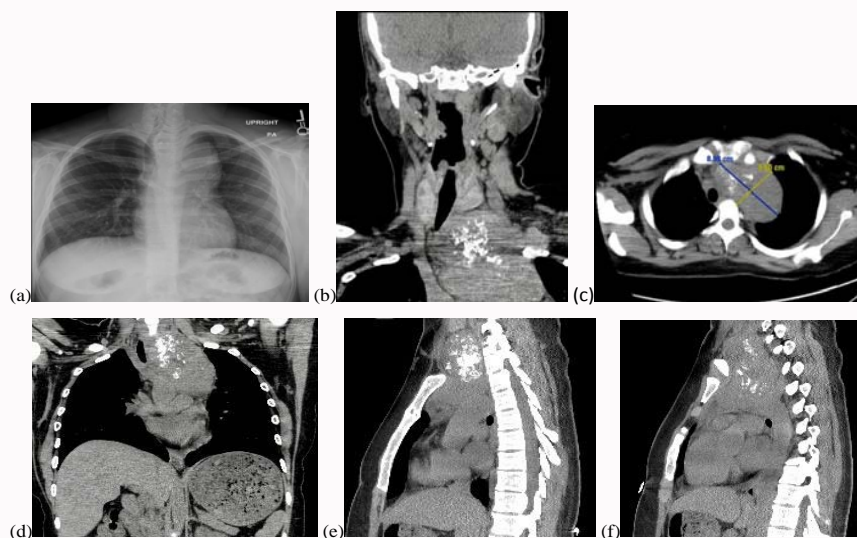


Figure 1: Pre-operative imaging. Initial chest radiograph demonstrates marked upper mediastinal widening with rightward tracheal deviation and narrowing (a). Initial non-contrast CT examination shows a large solid isoattenuating mass anterior to the ascending aorta (b-f). There is extrathoracic extension into the neck with this component demonstrating extensive calcification and causing superior displacement of the left lobe of the thyroid (b, e). Note the preserved fat plane between this mass and the left thyroid, confirming the mass is not of thyroid origin (b, e). The mass directly abuts and displaces the aortic arch and great vessels posteriorly, with the left subclavian artery visualized adjacent to the thoracic spine (c, f). The left common carotid artery is inseparable from the mass. The left brachiocephalic, common carotid, and subclavian veins are also inseparable from the mass.

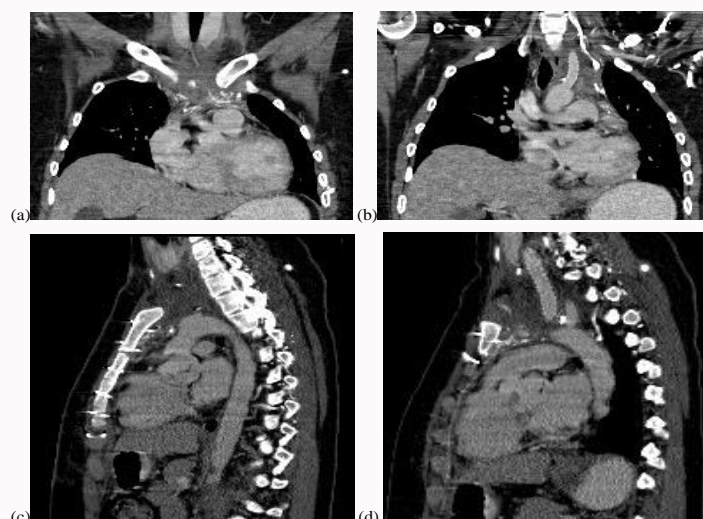


Figure 2: Post-operative contrast-enhanced CT examination after resection of the large mediastinal mass with extrathoracic extension into the neck. There is normal positioning of the left lobe of the thyroid (a). The trachea is near midline (b). There is normal contrast opacification of the aortic arch and left common carotid and subclavian arteries, which are no longer displaced posteriorly (c, d). Note the left common carotid artery bypass graft (b, d). However, also note the abnormal ill-defined isoattenuating soft tissue surrounding the great vessels in the upper mediastinum (a-d).

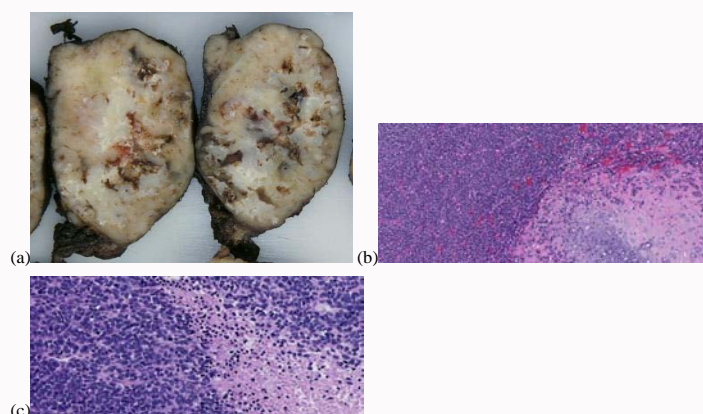


Figure 3: Pathology slides. (a) Gray-white cut surface with cartilaginous center and foci of calcification, (b) Biomorphic pattern of small rounded blue cells and island of hyaline cartilage (staining, haematoxylin and eosin; magnification, x200), (c) Area of small blue cells and necrosis (staining, haematoxylin and eosin; magnification, x200).

patient was brought to the intensive care unit for recovery, did not have any neurologic deficits post-operatively, and was successfully extubated on post-operative day one. The patient had a length of stay of seven days due to chest tube management and optimal pain control.

During follow-up visits, the patient developed new onset loss of proprioceptive sensation along the chest wall and headaches, which prompted repeat imaging. A contrast-enhanced CT examination of the chest demonstrated normal positioning of the left lobe of the thyroid, a midline trachea, normal contrast-opacification of the aortic arch as well as the left common carotid and left subclavian arteries, and a patent left common carotid bypass graft (Figures 2a-2d). This CT examination also demonstrated abnormal isoattenuating soft tissue in the superior mediastinum surrounding the great vessels, measuring approximately 4.5 cm × 3.4 cm × 4.7 cm (Figures 2a-2d). It was unclear if the tumor bed was showing regrowth or evolutionary scarring, but prompts clinical re-evaluation and oncologic treatment planning ensued.

Pathology

Grossly, the mass was multilobed and 12 cm in the largest dimension. Cut surface showed firm, gray-white tissue with hemorrhagic, calcified and cartilaginous center (Figure 3a). Microscopically, the tumor showed biphasic pattern of small blue cell like areas and cartilaginous areas composed of mature hyaline cartilage with foci of calcification (Figure 3b). The tumor had a mitotic rate of 13/10 High-Power Fields (HPF), with 20% necrosis ultimately making the tumor a pathologic T3 and grade 3 (Figure 3c).

Immunohistochemical staining revealed that the tumor cells were positive for CD99, Pax-8, vimentin and glypican 3, focally positive for MyoD1 and negative for SALL4, OCT 3/4, FLI1, AR, b-HCG, AFP, PLAP, synaptophysin, chromogranin, desmin, EMA, AE1/AE3, S100, CD20, CD34, CD45, CD3, Tdt, SOX10, CD117, thyroglobulin, and CAM5.2.

Molecular cytogenetic testing showed hallmark characteristic fusion between HEY1 and NCAO2 and negative for rearrangement of the EWSR1 (22q12) locus matching mesenchymal chondrosarcoma

[13]. Genotype sequencing revealed missense substitutions in ATM, BRCA1, and PMS2. As well as splice region variations in ATM and FGFR2. CCND2 and CDK4 amplification on chromosome 12 were considered to be pathogenic.

Final diagnosis

Mesenchymal chondrosarcoma-anterior mediastinum, resected with capsular disruption and spillage but gross total resection. No evidence for metastatic disease.

Oncologic treatment plan

The patient is recommended to receive therapy as per Children's Oncology Group protocol ARST0332: A risk-based treatment strategy for non-rhabdomyosarcoma soft tissue sarcomas in patients younger than 30 years [14]. This regimen consists of: Ifosfamide 3 gm/m² over 3 h IV on days 1, 2, and 3 (for 6 cycles) and Doxorubicin 37.5 mg/m² over 24 h days 1 and 2 (for 5 cycles). Chemotherapy will be repeated every 3 weeks during weeks 1 to 19. Radiation (55.8Gy) is divided into 31 treatment sessions delivered from weeks 4 to 10.

Discussion and Conclusion

Chondrosarcoma is one of the most common malignant tumors of bone. Multiple subtypes of chondrosarcoma have been described. The conventional intramedullary subtype is most common, typically seen in long bones and the pelvis. Extraskeletal chondrosarcomas, or those arising in soft tissue, are far less common. Myxoid chondrosarcoma is the most frequent extraskeletal subtype and is an intermediate-grade tumor usually found in the extremities, typically the thigh [15]. Mesenchymal chondrosarcoma is a high-grade, sometimes extraskeletal subtype which contains a mixture of low-grade cartilaginous tumor cells as well as a primitive mesenchymal high-grade component that is akin to Ewing sarcoma [16].

Anterior mediastinal tumors are often large at presentation. As there is more space to grow in the anterior mediastinum compared to the posterior mediastinum, these tumors are presumed to grow over months before patients develop symptoms or come to medical attention. In the present case, the patient presented with suspected cervical lymphadenopathy secondary to extra-thoracic tumor extension. The patient previously noted prominent neck veins likely related to central venous compression by the mass. The mean tumor size of the two previously reported cases and this case is 10.2 cm, which is 81% larger than the 4 cases of posterior mediastinal masses presented in our literature review [12]. This large size highlights the importance of a multidisciplinary approach to treatment with an experienced surgical team.

The radiographic findings of chondrosarcomas as a whole and the rare subtype discussed here correlate with their histologic descriptions. Chondrosarcomas produce lobules of well-formed hyaline cartilage. The high-water content of these lobules results in their low-attenuating appearance on CT examination as well as their hyperintensity on T2-weighted Magnetic Resonance (MR) imaging. Endochondral ossification occurs within the periphery of these lobules, resulting in a characteristic ring-in-arc calcification pattern seen on radiograph and CT examination as well as signal loss on all MR sequences. Post-contrast CT and MR imaging of chondrosarcomas is characterized by thin peripheral and septal enhancement secondary to central water-dominant contents [15].

In contrast to conventional chondrosarcomas, the rare mesenchymal subtype is composed of primitive mesenchymal cells

in addition to well-differentiated cartilaginous tissue, which alters its imaging appearance. Mesenchymal chondrosarcoma (both the osseous and extraskeletal types) presents as a well-delineated lobular soft tissue mass usually measuring at least 5 cm to 8 cm in size at presentation [17,18]. They typically demonstrate dense, granular calcifications like the ring-in-arc calcifications of conventional chondrosarcoma, although the calcification pattern may differ between tumors as well as within a single lesion [18]. Calcifications may be diffuse throughout a lesion or more focal. In the present case, the calcifications were clustered predominantly in the superior and extra-thoracic components of the mass. The CT attenuation of mesenchymal chondrosarcoma is increased compared to the conventional type due to increased cellularity contributed by mesenchymal cells. This increased cellularity also results in intermediate signal on T2-weighted MR imaging (as opposed to hyperintense signal of the fluid-rich conventional type). In tumors that have relatively sharp demarcation of their calcified and unmineralized components, T2-weighted images may show a characteristic division of signal, or two-component configuration, with the highly mineralized component demonstrating homogenous signal loss adjacent to an unmineralized region showing intermediate signal [18]. Contrast-enhanced CT and MR imaging demonstrate diffuse heterogeneous enhancement of both calcified and unmineralized regions, while necrotic areas (if present) will not enhance.

More common anterior mediastinal tumors such as lymphoma, thymoma, and teratoma, may be difficult to differentiate from mesenchymal chondrosarcoma by their imaging appearance. Lymphoma is the most common anterior mediastinal tumor seen in children and typically presents on CT examination as a well-circumscribed, solid, homogeneously enhancing mass, although additional adenopathy is usually seen elsewhere in the chest [19]. Calcifications can occur in mediastinal lymphoma but is rare, usually seen only after treatment. Necrosis may be seen in up to 50% of cases [19,20], which results in heterogeneous enhancement. Thymoma is the most common anterior mediastinal tumor in adults but is rare in children [10]. Often difficult to differentiate from lymphoma, low-stage thymoma typically presents as a well-circumscribed, homogeneously enhancing mass, with up to 25% demonstrating calcifications [20,21]. Unlike in lymphoma, additional lymphadenopathy is not typically seen in thymoma [22]. In scenarios where lymphoma and thymoma remain in the differential by imaging characteristics, the use of CT spectral imaging may show potential value by determining the iodine content of the lesion in question after contrast administration [23]. Furthermore, high-stage thymoma is associated with increased tissue heterogeneity as well as possibly increased calcification [22]. Teratomas are the most common mediastinal germ cell tumor and are composed of at least 2 primitive germ cell layers. Teratomas classically present as well-circumscribed, heterogeneously enhancing masses demonstrating both solid and cystic areas, with up to 26% containing calcifications [10,19]. Up to 50% of teratomas contain fat, which highly supports this diagnosis when visualized on CT or MR examination [19,20]. Finally, intra-thoracic extension of a thyroid goiter or thyroid malignancy may occur, although CT imaging would demonstrate continuity of the mediastinal lesion with the thyroid gland in the neck.

There is substantial overlap between the possible imaging findings of the most common anterior mediastinal tumors and extraskeletal mesenchymal chondrosarcoma. All of these tumors may present as a well-circumscribed, heterogeneously enhancing mass

Table 1: Cases reported and literature review of mesenchymal chondrosarcomas in the mediastinum.

Case	Reference	Age/Sex	Location	Size (cm)	Treatment	Outcome
1	Jeong [11]	21/F	Anterior	13	Surgery	Alive with disease 8 months after surgery
2	Li [25]	66/F	Anterior	5.6 × 3.8	Surgery + Radiation	Remission
3	Current Case	17/F	Anterior	12	Surgery + Radiation + Chemotherapy (recommended)	Not available
4	Angulo Hervias [27]	48/F	Middle	5	Radiation + Chemotherapy (vascular invasion)	*
5	Chetty [9]	25/M	Posterior	7.5	Surgery	Died of disease 6 months after surgery
6	Suster [12]	11/M	Posterior	5	Surgery	Alive 6 years after surgery
7		15/F	Posterior	5.5 × 3 × 2	Surgery	Local recurrence 7 years after surgery
8		31/M	Posterior	5 × 4 × 4	Surgery	Local recurrence 3 years after surgery
9		36/F	Posterior	7 × 5 × 5	Surgery + Radiation	Died of metastatic disease 8 years after surgery
10	Chung [28]	26/M	Posterior	8	Surgery + Radiation + Chemotherapy	Lost to follow up
11	Hwang [29]	22/M	Posterior	7	Surgery + Radiation	Remission at 26 months after surgery
12	Tsuda [30]	*	Posterior	*	*	*

*Not described in the case report or paper

with calcifications. Some imaging features, such as homogeneous enhancement and lack of calcifications, may point away from a diagnosis of extraskeletal mesenchymal chondrosarcoma while diagnoses such as thymoma and lymphoma would remain in the differential. When the diagnosis of an anterior mediastinal mass is unclear by CT examination, further evaluation with MR may prove useful. Extraskeletal mesenchymal chondrosarcoma sometimes demonstrates sharp demarcation of its calcified and unmineralized components, which is well-appreciated by MR examination as a stark division of signal on T2-weighted images [18]. When present, this division of signal may be a distinguishing feature suggestive of extraskeletal mesenchymal chondrosarcoma over other diagnoses.

The lack of registry data specificity is another obstacle in studying extraskeletal mesenchymal chondrosarcoma. In the SEERs database, chondrosarcoma location is categorized as bone, soft tissue, skull, or “other” encompassing all these rare cases without much specificity. However, with only 6.2% of all mesenchymal chondrosarcomas being in the “other” category, the low volume of cases allows for incomplete investigation [4].

Due to the rarity of this tumor, mesenchymal chondrosarcoma was not considered in the differential diagnosis at presentation for the reported patient. When the patient first presented to the PCP and then to the Pediatric Oncology Clinic, based on age, sex, and physical exam, the most likely diagnosis was lymphoma or thyroid tumor. Following the CT examination, the differential diagnosis favored germ cell tumor, particularly teratoma, given the presence of calcification. However, subsequent tumor markers were negative, making this diagnosis less likely. The final diagnosis was not confirmed until the final pathology was reported. The tumor presented similarly both clinically and radiologically to numerous other malignancies. In the absence of abnormal labs and no constitutional symptoms, one might consider extraskeletal (and possibly mesenchymal) chondrosarcoma on evaluation of a mediastinal tumor.

The prognosis for patients with mesenchymal chondrosarcoma is difficult to assess given the rarity of this diagnosis. In a survival analysis of the SEER database which included 205 patients with mesenchymal chondrosarcoma (of which 60% were extraskeletal as in this patient), the 5-year and 10-year survival were 52% and 44%. The exact management (surgery/radiation/chemotherapy)

was not reported [24]. The results of the COG ARST0332 study for Intermediate risk disease utilizing ifosfamide and doxorubicin and involved field radiation (55.8 Gy) resulted in a 5-year event free survival of 65% and a 5-year overall survival rate of 79% [5]. According to the study investigators, a very small number of patients on ARST0332 did have mesenchymal chondrosarcoma.

While extraskeletal mesenchymal chondrosarcomas most frequently affect the head and neck, only 11 cases of mediastinal mesenchymal chondrosarcoma have been reported in the literature, and most of these have occurred in the posterior mediastinum. To date, there have only been two cases reported of primary mesenchymal chondrosarcoma within the anterior mediastinum, with this case being the third [11,25]. While extremely rare, it is clinically important as this might influence prognosis and treatment options. The first reported case declined additional treatment after surgery and was alive with residual disease at 8 months post-surgery [11]. The second case was treated with surgery and radiation, with the patient being tumor free at time of publication [25]. This will be the first known pediatric case to be treated following the ARST0332 protocol (Table 1).

Treatment decisions for the management of extraskeletal mediastinal chondrosarcoma is challenging due to the extreme rarity of these tumors. Given that this patient is only the third case of anterior mediastinal chondrosarcoma, clinical trial results are not available. The ideal management for mesenchymal chondrosarcoma is unknown but frequently includes surgery ± radiation and ± chemotherapy [26]. Given the difficult tumor resection, capsule rupture and presumed tumor spillage, post-operative chemotherapy and radiation is recommended as per COG ARST0332. Of note, patients with mediastinal mesenchymal chondrosarcoma need extended surveillance for relapse as relapses have occurred many years (3 to 8 years) after surgery and post-operative therapies [12].

Authors Contribution

AYG participated in patient’s preoperative and postoperative care, oncology plan of care, writing the manuscript, critical review of the literature. KAT participated in patient preoperative assessment, surgical case, writing the manuscript, critical review of the literature. AF participates in review of patient case, writing the manuscript,

critical review of the literature. MH participated and critically reviewed the pathology portion of the patient's case. TL participated in patient preoperative assessment, surgical case, and post-operative care, review of the manuscript, critical review of the literature. MLS participated in patient preoperative assessment, post-operative care, oncology plan, of care review of the manuscript, critical review of the literature. All authors read and approved the final manuscript.

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