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Case Report Open Access

22 Year Old Female with Worsening Dyspnea

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Abstract

The differential diagnosis for mediastinal tumors is broad and includes neurogenic tumor, germ cell tumor, thymoma, lymphoma, sarcoma, metastasis and more. We report a patient with a dramatic presentation of neuroblastoma in the mediastinal, a relatively uncommon location for this tumor in patient of any age and particularly in the age group of our patient. The considerable worst prognosis for older patients with neuroblastoma, a high index of suspicion is necessary to avoid unnecessary delays in the diagnosis. Here we describe the imaging and laboratory findings of mediastinal neuroblastoma.

Keywords: Neuroblastoma; Thoracic tumors; MRI; CT; MIBG; Adult; Mediastinum; Metastasis; Lymphoma

Case Report

A 22-year-old woman presented with shortness of breath that began 6 months ago along with right chest pain and back pain which progressively worsened the last 2 months. Patient was found to be hypoxemic (O_2 saturation 89% on room air), hypotensive (89/54) and tachycardic (104) in addition to moderate respiratory distress. Patient was immediately resuscitated with fluids and placed on 100% NR mask. On physical exam, the vitals were within normal limits after resuscitation except for a 95% O_2 saturation on 100% NR. There was swelling in the right supraclavicular, right arm and right facial swelling compared to the left side with signs of venous collateral on chest wall. The right hemithorax was devoid of lung sounds and was tender to palpation along with tenderness in the right upper back. The rest of the physical exam was within normal limits.

Initial portal AP chest radiograph (Figure 1) was obtained showed diffuse opacification of the right hemithorax with associated contralateral cardiomediastinal deviation. In addition, there is a suggestion of and slight splaying of the upper right posterior ribs. A follow up IV contrast enhanced Computed Tomography (CT) scan of the chest abdomen and pelvis ensued (Figure 2) to further evaluate findings on the chest radiograph and clinical findings. There was a large, heterogeneous mass with lobulated margins which appeared to be centered in the upper right posterior mediastinum. There was a large associated right pleural effusion and significant mediastinal adenopathy. As suggested on the preceding chest radiograph, there was mass effect with contralateral deviation, compression of the heart and great vessels, tension physiology, and SVC syndrome. Numerous collaterals were seen within the upper anterior and posterior thoracic walls extending to the right supraclavicular region. There was adjacent focal skin and muscle thickening below the axilla near the peripheral aspect of the tumor, which likely represented extrathoracic tumor extension.

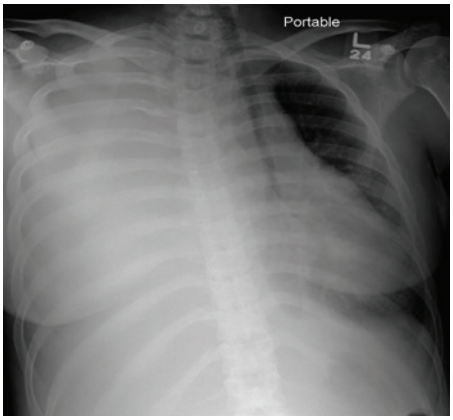

Figure 1: Initial portable AP Chest Radiograph shows a large right hemithorax opacity with associated leftward deviation of the cardiomediastinal silhouette.

After initial stabilization, laboratory findings revealed slight microcytic anemia with hemoglobin ranging 10.6-12.0 g/dL (normal range, 12.0-16.0 g/dL) with mean corpuscular volume 77.1 fL (normal range, 79-98 fL), leukocytosis with a white blood cell count of $14.5 \times 10^3/\mu L$ (normal range, $4.3\text{-}11.0 \times 10^3/\mu L$) and high neutrophil differential of 90.7% (normal range, 39-77%), and thrombocytosis with platelet count of $953 \times 10^3/\mu L$ (normal range, $140\text{-}440 \times 10^3/\mu L$). Liver enzyme levels were elevated with aspartate aminotransferase level of 91 U/L (normal range, 15-46 U/L) and an alkaline phosphatase level of 177 U/L (normal range, 38-126 U/L). Coagulation studies were abnormal with increased prothrombin time 16.6 secs (normal range, 10.1-12.6 secs). Other abnormal laboratory values include low prealbumin 9 mg/dL (normal range, 20-40 mg/dL), low albumin 2.6 g/dL (normal range, 3.9-5.0 g/dL), elevated lactate dehydrogenase level greater than 2150 U/L (normal range, 313-618 U/L), elevated homovanillic acid 7.7 mg/g creatinine (normal range, 1.4-5.3 mg/g creatinine) and elevated vanillylmandelic acid 4.9 mg/g creatinine (normal range, 1.1-4.1 mg/g creatinine).

A contrast-enhanced MRI of the thoracic spine was obtained due to the patients corresponding neurological abnormalities referable to the right upper extremity as well as backpain. (15 ml Multihance was used). This showed that the mass was invading the right upper thoracic neural foramina at the levels of T3-T4 with insinuation along the right dorsolateral epidural space. There was minimal impression on the thecal sac and abnormal marrow signal, which

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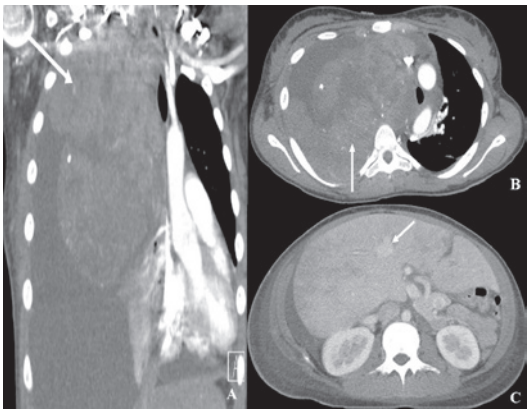

Figure 2: A 22-year-old female with a posterior mediastinal neuroblastoma.

A. CT Chest (KVP-120, mAs-170) after120 ml Optiray IV contrast demonstrates a large, lobulated, and heterogenously enhancing mass with scattered calcifications, which is centered in the superior mediastinum and the right upper chest. (White Arrow) There is associated leftward shift of the great vessels and cardiomediastinum. Note the erosion of the adjacent right posterior rib with minimal extraosseous soft tissue component posteriorly, suggesting tumor infiltration of the posterior chest wall.

B. Coronal MIP reconstruction (KVP-120, mAs-170) after120 ml Optiray IV contrast) demonstrates the bulky, heterogeneously enhancing upper mediastinal mass occupying the right superior and mid hemithorax, large effusion and collapse of the right lung. (White Arrow)

C. Axial CT image through upper abdomen. (KVP-120, mAs-170) after120 ml Optiray IV contrast) There is a focal enhancing hepatic lesion (White Arrow) and diffuse heterogeneity of the liver corresponding with focal and infiltrative metastatic disease.

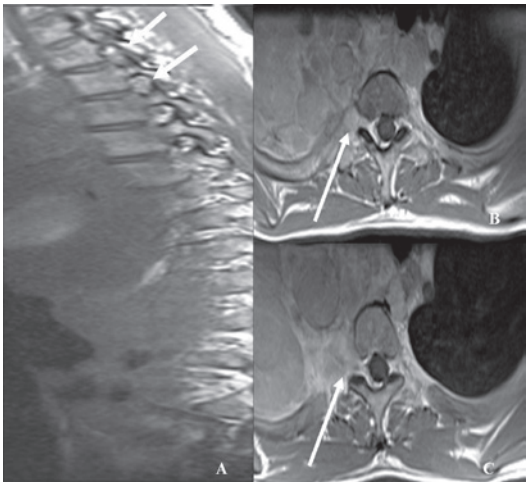

Figure 3: Selected MRI Images of the Thoracic Spine.

A. Sagittal T1-weighted MRI image (TE-7.7, TR-592, Multihance) through the right upper thoracic spine demonstrates infiltration of several upper thoracic vertebral bodies and soft tissue extension into the neural foramina with encroachment of the exiting nerves, most notably at the T2-T4 levels. (White Arrows)

B-C. Axial T1 weighted post contrast images (TE-11, TR-713, Multihance) show tumor infiltration of the right T2-T3 neural foramen and encroachment of the exiting nerve. (White Arrows) Other Axial images showed similar involvement of adjacent levels.(Not Shown)

was suspicious for osseous extension of the tumor (Figure 3). Meta-iodobenzylguanidine (mIBG) scan (Figure 4) was performed due to the elevated homovanillic and vanillymandelic acid and revealed

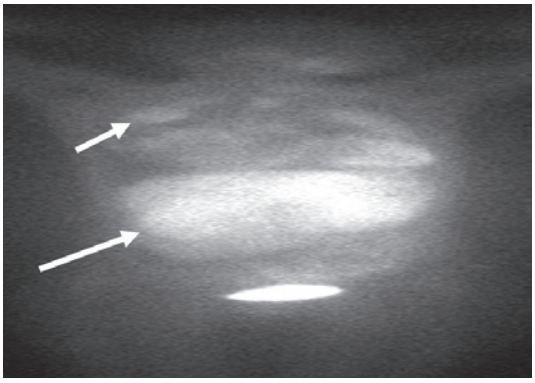

Figure 4: Whole body planar MIBG Scan obtained in anterior projection, 24 hours after intravenous injection of 9.8 mCi I-123 Metaiodobenzylguanidine. Findings are notable for increased uptake in the right medial hemithorax in the area of the mediastinal tumor (Short Arrow), and also diffusely in the liver, consistent with diffuse tumor infiltration.
(Long Arrow).

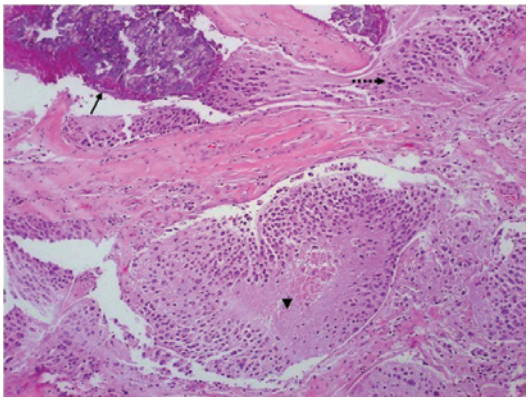

Figure 5: A 22-year-old female with a posterior mediastinal neuroblastoma. Low power view of the thoracic mass with changes consistent with treatment effect. There is necrosis (arrowhead), focal calcification (arrow) and hyalinization of the stroma. The tumoral cells are still viable (dashed arrow). 10X, Hematoxylin and eosin stain.

bilateral lung involvement; right much more than left and also liver and bilateral posterior abdomen involvement. Biopsy of the mass was performed and neuroblastoma confirmed at pathology with neuroblastoma antigen staining (Figures 5-7).

Discussion

Neuroblastoma, malignant embryonal tumor of the neural crest arising from any part of the sympathetic nervous system, remains the third most common childhood malignancy, after leukemia and CNS tumors. It represents 8-10% of childhood cancers with an incidence per year of 10.5 million children who are less than 15 years of age, and causing 15% of all childhood cancer deaths [1-3]. The median age of presentation overall is 23 months and 40% occur during infancy, 89% by age 5, and 98% by age 10 [4]. It can uncommonly present in adolescence with less than 0.3 cases diagnosed per million people per year, and rarely even well into adulthood, with cases reported even up to 75 years of age [4-6]. The gender ratio of 1:1 in most studies with some showing boys with slightly more frequent than girls at 1.2:1 [1,4,7]. Some risk factors that have been described include maternal alcohol consumption, paternal exposure to nonvolatile and

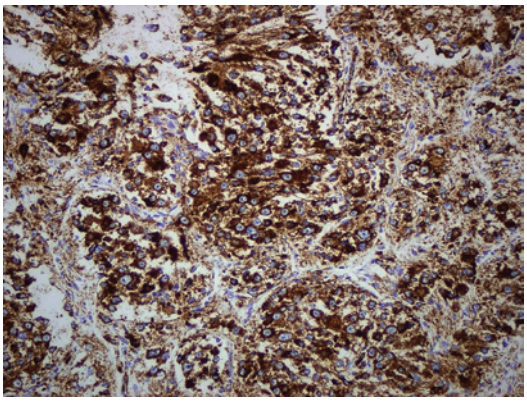

Figure 6: A 22-year-old female with a posterior mediastinal neuroblastoma. Medium power view (20X) of immunohistochemistry for Neuroblastoma antigen (NB), a highly specific marker for neuroblastoma. Note the intense cytoplasmic staining.

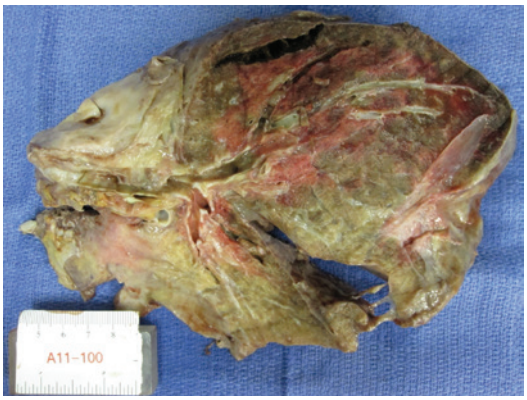

Figure 7: Gross specimen from the autopsy showing right lung parenchyma showing a combination of post-treatment changes and sequelae from prior tumor involvement.

volatile hydrocarbons, diuretic use, pain medications or codeine, low birth weight, and ALK and PHOX2B mutation in familial neuroblastomacases [4,8,9]. These tumors are of ganglion cell origin and are derived from primordial neural crest cells. Consequently, the tumors are found along the typical distribution of sympathetic ganglia, most commonly in the adrenal medulla (35%), but can also be found in the extra-adrenal paraspinal ganglia (30%-35%), followed by the posterior mediastinum in 20%. Interestingly, the disease distribution in younger patients (<1 year) compared to older (>1 year) patients in a previous investigation, found that the mediastinum was an even less common site of presentation in older patients. Other more uncommon sites include the pelvis (2%-3%) and the neck (1%-5%) [2].

The imaging findings of Neuroblastoma are variable, but often well characterized on CT and MRI versus other imaging modalities [10]. Ultrasound shows an echogenic mass with shadowing if calcifications are present [11]. CT is the most commonly used imaging modality for initial assessment and preliminary diagnosis of Neuroblastomas, most often with examination of the chest, abdomen, and pelvis. However, MRI is superior with respect to organ of origin, and regional invasion due to its superior tissue discrimination. Importantly, CT demonstrates the size and extent of the tumor, as well as enhancement characteristics, calcifications, invasion or encasement of vessels and other organs, as well as metastatic lesions [12]. The tumors are often large, lobulated, and heterogeneous in appearance, with variable calcifications and mild, if any enhancement after contrast administration [12]. There may also be hypoattenuating areas of necrosis, or areas of hemorrhage with variable attenuation. Involvement or compression of adjacent structures is common. Invasion of the neural foramina and extension to the epidural space is also common, and can be seen to an extent on CT, but is optimally characterized on MRI. Liver metastases may be diffusely infiltrative, causing global hyperattenuation, or can be in the form of focal hypo enhancing lesions, as in our patient.

On MRI, the tumors are heterogenous enhancing masses, with a iso- or hypointense to surrounding tissue on T1 and a hyperintense on T2-weighted fat-suppressed images [12,13]. Signal voids can be seen in areas of calcification. In addition to being the superior modality for organ of origin, it is also the preferred modality for evaluation of neural foraminal and nerve root invasion or displacement, which occurs in 10% of cases, including that of our patient. Bone marrow disease appears as confluent high T2 and low T1 signal within marrow.

Another imaging modality used utilizes the function of the neuroendocrine nature of these tumors. Meta-iodobenzylguanidine (mIBG), an analog of norepinephrine, is taken up by catecholamine producing cells and neuroendocrine tumors making radiolabeled mIBG uptake quite specific for neuroblastoma, taken up by 90% to 95% of all neuroblastomas, especially in the pediatric population [12,14,15].

Prognosis is determined by stratification of patients into low-,

Etiology	Malignant embryonal tumour of the neural crest cells and can arise from any part of the sympathetic nervous system.
Incidence	It represents 8-10% of childhood cancers with incidence of 10.5 million children less than 15 years of age per year.
Gender ratio	1:1 in most studies with some showing boys slightly higher than girls 1.2:1.
Age predilection	40% in infancy, 89% by age 5, and 98% by age 10. In adults, less than 0.3 cases diagnosed per million people per year.
Risk factors	Maternal alcohol consumption, paternal exposure to nonvolatile and volatile hydrocarbons, diuretic use, pain medications or codeine, low birthweight . ALK and PHOX2B mutation in familial neuroblastoma cases.
Treatment	Treatment includes surgical excision, radiotherapy and chemotherapy depending on risk group classification from the the Children Oncology Group studies. Adult cases are rare and are often treated with pediatric guidelines.
Prognosis	Prognosis is based on strafication of patients into low-, intermediate-, or high-risk categories based on the Children Oncology Group studies which includes age at diagnosis, INSS stage, tumor histopathology, DNA index (ploidy), and MYCN amplification status. Another prognostic factor is Evan's stage.
Computer Tomography	Heterogenous with areas of hemorrhage, necrosis interposed between areas of enhancing mass with scattered calcifications.
Ultrasound	Echogenic mass with shadowing if calcifications are present.
Magnetic Resonance Imaging	On T1-weighted spin-echo images, usually mass will be iso- or hypo-intense to surrounding soft tissues and hyperintense on fat-suppressed T2-weighted or short tau inversion recovery sequences. There is some enhancement after administration of intravenousgadolinium chelate agents.
Nuclear Medicine	Radiolabeled metaiodobenzylguanidine, a norepinephrine analog, is concentrated selectively in sympathetic nervous tissue and neuroblastoma.

Table 1: Summary table for Neuroblastoma.

Mediastinal Mass	MRI T1 W	MRI T2 W	CT	US	MIBG
Neuroblastoma	iso- or hypo-intense to surrounding soft tissues	hyperintense on fat-suppressed	Heterogenous with areas of hemorrhage, necrosis interposed between areas of enhancing mass with scattered calcifications	Echogenic mass with shadowing if calcifications are present	Diffuse uptake of the radiotracer evident.
Lymphoma	Low intensity with enhancement post contrast	Hyperintense with mild heterogeneity	Lobulated heterogeneous mass with mild to moderate enhancement, rare calcification, no invasion of chest wall	Lobulated, hypoechoic and hypervascular masses, possibly with septations.	Not applicable
Osteosarcoma	Isointense to hypointense relative to skeletal muscle	Predominantly hyperintense relative skeletal muscle	Well-circumscribed soft tissue mass with variable mineralization, necrosis, hemorrhage.	Not applicable	Not applicable
Metastasis	Variable, often with enhancement on post contrast imaging.	Variable, often hyperintense on T2	Variable, depending on primary.	Often vascular, echogenic soft tissue mass, variable, depending on primary tumor.	Not applicable
Ewing Sarcoma	Low to Intermediate signal, hypointense to bone marrow	Intermediate to High signal intensity	Heterogeneous enhancement, central necrosis is common	Not applicable	Not applicable
Germ Cell Tumor	Well-circumscribed lesion with variable signal, reflecting fat, soft tissue, or calcium	Variable, often hyperintense on T2 if contains fluid	Variable, but will often be a well circumscribed mass containing fat if a Teratoma, but may be heterogenous and aggressive with invasion of adjacent structures if NSGCT or Seminoma. Mild heterogeneous enhancement	Not applicable	Not applicable

Abbreviations
CT=Computed tomography
DWI=Diffusion weighted images
H & E=Hematoxylin and Eosin
INSS=International Neuroblastoma Staging System
mAs=Milli ampere second
mm=Millimeter
MRI=Magnetic resonance imaging
T1W=T1 weighted
T2W=T2 weighted
TE: Echo Time
TR: Repetition Time

Table 2: Differential diagnosis table for neuroblastoma.

intermediate-, or high-risk categories based on the Children Oncology Group studies which includes age at diagnosis, INSS stage [1,16], tumor hisopathology, DNA index (ploidy), and MYCN amplification status [17]. Evan's stage is another prognostic factor. Generally, older ages of presentation, advanced stages (3-4), and presence of cytogenetic abnormalities such as MYCN amplification (25-35%), DNA ploidy, and loss of chromosome 1 p (30-40%) are associated with a poorer prognosis. Neuroblastoma in adolescents and adults appears to differ from that seen in early childhood in several important aspects, as suggested in recent studies. For example, the overall survival appears to be significantly worse and the disease course more indolent. Franks et al. studied a group of 16 such patients over a 27 year period. Overall survival of this group was only 30% at 5 years, whereas the typical overall survival of younger children <1 year is often >70% and can be well into the 90% range with favorable histopathology and single copy MYCN profile [6].

Interestingly, NMYC amplification, a cytogenetic characteristic which is known to be associated with a more aggressive phenotype, was not observed in any of the six patients who were tested. Yet, relapses were observed in all but one, and all but two went on to succumb to their disease. Also, only 40% of those studied had elevations of urinary catecholamines, compared with that expected in this disease, 90-95%. Other studies have also shown poorer survival, more indolent course, and higher morbidity in older patients [7]. Thus, there likely are important biochemical and histopathological differences between Neuroblastomas seen in this population. Treatment includes surgical excision, radiotherapy and chemotherapy depending on risk group classification from the Children Oncology Group studies. Adult cases are rare and are often treated with pediatric guidelines [5].

Given the imaging findings of a low attenuation, lobulated, and mildly enhancing posterior mediastinal mass with scattered calcifications in our 22 years old female, the differential diagnosis would be led by lymphoma. However, the mass in our patient appeared to be centered at the posterior mediastinum, which made lymphoma, a predominantly anterior mediastinal mass, much less likely. Moreover, Mediastinal lymphoma usually is a result of systemic lymphomas (Hodgkin and non-Hodgkin lymphoma) and rarely is the lymphoma isolated to the mediastinum. Hence patients with mediastinal lymphoma generally present with systemic manifestations most commonly the presence of constitutional or "B" symptoms, which were notably absent in our patient [18]. The laboratory findings of elevated urinary HVA and VMA in a relatively young patient also highly favor the diagnosis of Neuroblastoma rather than lymphoma.

Other entities such as Osteosarcoma, Metastases, Ewings Sarcoma, and Germ cell tumors would also need to be considered and excluded. In this case, the clinical absence of "B" symptoms and elevated urinary HVA and VMA, favors the diagnosis of Neuroblastoma rather than lymphoma. A metastatic lesion in this setting is also unlikely, in view of the patients age. Furthermore, there was no expansile, enhancing, calcified bone mass suspicious for the rare intra-thoracic osteosarcoma, nor was there a destructive chest wall mass concerning for Ewings Sarcoma. In addition, each of the above differential considerations have associated multimodality imaging findings which were not wholly demonstrated in this case, lending further confidence in the imaging diagnosis of Adult Neuroblastoma, rather than these.

The imaging findings of Neuroblastoma can be suggestive, but are not pathognomonic, with some features shared with other entities

in the differential diagnosis. Examples of these shared findings can include Low T1 signal or hyperintense signal on T2 weighted imaging, which can also be seen with Lymphoma and Ewing Sarcoma. Neuroblastoma can also be rather heterogenous on CT imaging, which can also be seen with lymphoma. Therefore, the imaging features are best considered along with clinical and laboratory data. MIBG scan is the only exception to this, as it is highly specific for Neuroblastoma. Additional multimodality imaging findings regarding the differential considerations for mediastinal Adult Neuroblastoma include: Low T1 signal intensity with enhancement post-contrast and high T2 signal, with lobulated and complex vascular appearance on ultrasound for Lymphoma, T1 iso- to hypointensity with T2 hyperintensity to skeletal muscle with well-circumscribed soft tissue mass containing variable necrosis, mineralization, and hemorrhage on CT with Osteosarcoma, Variable CT, MRI, and Ultrasound findings in the case of metastasis, and low to intermediate T1 and intermediate to high T2 signal intensity to bone marrow with heterogeneous post-contrast enhancement on CT in the case of Ewing Sarcoma [19-23].

Mediastinal germ cell tumors are rare, and represent less than 5% of all germ cell tumors and with anterior mediastinal location being the most common extragonadal site, representing 50-70% of extragonadal germ cell tumor [24]. Mature teratomas and even less commonly, seminomas are the most frequently seen germ cell tumors in the mediastinum [25]. Occasionally, a mature teratoma may appear in the posterior mediastinum, but only represents up to 8% of all cases [26]. Nonetheless, the majority of mediastinal mature teratoma and 30% of mediastinal seminomas are asymptomatic with symptoms related to the size and location of the tumor and resultant compression of adjacent anatomical structures. [25]. On imaging, they are usually cystic lesions that demonstrate a combination of fat, calcification, fluid and soft tissue attenuation values [27]. These features are absent in our patient's case. The mediastinum is an uncommon site of presentation compared to the abdomen and pelvis at any age, and is surpassed in rarity only by the cervical region in this respect.

In conclusion, our adult patient presented in dramatic fashion with a mediastinal Neuroblastoma, which is known to be a relatively uncommon location for this tumor in patients of any age, but particularly in this age group. Lymphoma would generally lead the differential in this age group from an imaging perspective, however Adult Neuroblastoma may also be considered. Given the considerably worse prognosis of Neuroblastoma in older patients, a high index of suspicion is necessary to avoid unnecessary delays in the diagnosis of this highly uncommon, yet grave variety of this tumor.

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