Thoracic spine fracture secondary to anterior mediastinal yolk sac germ cell tumor: A case report and a brief review

Fractura de columna torácica secundaria a tumor de células germinativas del saco vitelino del mediastino anterior: reporte de un caso y breve revisión

Fratura de coluna torácica secundária a tumor de células germinativas do saco vitelino do mediastino anterior: relato de caso e breve revisão

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Abstract

Yolk Sac Germ Cell Tumors (GCT) are rare nonseminomatous tumors. When yolk sac tumors (YST) are primarily from the anterior mediastinum, they may be asymptomatic for an extended period with a bad prognosis. Some tumor markers, such as cytokeratins, OCT 3/4, SALL-4, and alpha-fetoprotein (AFP), are essential for diagnoses. Diagnosis is based on imaging, immunohistochemistry, and the presence of tumor markers. In YST, beta-human chorionic gonadotropin hormone is negative. Treatment is adjuvant cisplatin-based chemotherapy and surgery.

The critical point of this article is to demonstrate how the evolution of a mediastinal tumor can cause an acute neurological condition, in this case, transversal myelitis, which sometimes requires support in the intensive care unit.

We described a rare clinical case of primary YST of the anterior mediastinum clinically presented as pneumonia followed by the completed medullary syndrome. We included a complete review of this tumor and discussed the medullary compromise to increase the medical knowledge and suspicion of lectors. Prompt treatment of medullary syndrome and tumor characterization is critical to definitive treatment and prognosis estimation.

Keywords: Nonseminomatous, germ cell tumors, mediastinal tumor, yolk sac tumor, vertebral fracture

Resumen

Los tumores de células germinales del saco vitelino (TCG) son tumores no seminomatosos poco frecuentes. Cuando los tumores del saco vitelino (YST) provienen principalmente del mediastino anterior, pueden ser asintomáticos durante un período prolongado con un mal pronóstico. Algunos marcadores tumorales, como las citoqueratinas, OCT 3/4, SALL-4 y la alfafetoproteína (AFP), son esenciales para el diagnóstico. El diagnóstico se basa en imágenes, inmunohistoquímica y la presencia de marcadores tumorales. En YST, la hormona gonadotropina coriónica humana beta es negativa. El tratamiento es quimioterapia y cirugía adyuvantes basadas en cisplatino.

El punto crítico de este artículo es demostrar cómo la evolución de un tumor mediastínico puede provocar una afección neurológica aguda, en este caso, mielitis transversal, que en ocasiones requiere apoyo en la unidad de cuidados intensivos.

Describimos un caso clínico raro de YST primario del mediastino anterior que se presentó clínicamente como neumonía seguida de síndrome medular completo. Incluimos una revisión completa de este tumor y discutimos el compromiso medular para aumentar el conocimiento médico y la sospecha de los lectores. El tratamiento oportuno del síndrome medular y la caracterización del tumor son fundamentales para el tratamiento definitivo y la estimación del pronóstico.

Resumo

Os tumores de células germinativas do saco vitelino (TCG) são tumores não seminomatosos raros. Quando os tumores do saco vitelino (TSV) são originários principalmente do mediastino anterior, eles podem ser assintomáticos por um período prolongado com mau prognóstico. Alguns marcadores tumorais, como citoqueratinas, OCT 3/4, SALL-4 e alfa-fetoproteína (AFP), são essenciais para o diagnóstico. O diagnóstico é baseado em exames de imagem, imunohistoquímica e presença de marcadores tumorais. No YST, o hormônio gonadotrofina coriônica beta-humana é negativo. O tratamento é

quimioterapia e cirurgia adjuvantes à base de cisplatina.

O ponto crítico deste artigo é demonstrar como a evolução de um tumor mediastinal pode causar um quadro neurológico agudo, neste caso, a mielite transversal, que por vezes necessita de suporte em unidade de terapia intensiva.

Descrevemos um caso clínico raro de YST primário do mediastino anterior, apresentado clinicamente como pneumonia seguida de síndrome medular completa. Incluímos uma revisão completa deste tumor e discutimos o comprometimento medular para aumentar o conhecimento médico e a suspeita dos leitores. O tratamento imediato da síndrome medular e a caracterização do tumor são fundamentais para o tratamento definitivo e a estimativa do prognóstico.

1. Introduction

Mediastinal tumors are usually asymptomatic and are often accidentally detected on a chest X-ray. In symptomatic patients, clinical manifestations are secondary to compression of nearby structures resulting from tumor invasion. The main signs and symptoms are respiratory, such as coughing, dyspnea, hemoptysis, and shortness of breath. Fever and weight loss can also occur[Wright et al. (1990)].

In most cases, the location and etiology of the tumor are related to the patient's age. Thymic neoplasms, germ cell tumors, lymphomas, and neurological tumors are the primary mediastinal neoplasms. Germ cell tumors are neoplasms that most often affect the gonads but may primarily affect other body regions[Macchiarini and Ostertag (2004)].

Germ cell tumors (GCT) can be classified by location: gonadal or extragonadal or by type: seminomatous or nonseminomatous. YST, also called endodermal sinus tumor, is a nonseminomatous germ cell tumor mainly affecting young adults (15 to 35 years) [Globocan (2004)].

GCTs have a poorly known etiology. Current hypotheses include increased expression of the GATA-4 protein[Siltanen et al. (1999)] and, especially, the presence of the i12p isochromosome[Chaganti and Houldsworth (2000)].

Tumor markers and hormones are measurable and are valuable tools to indicate the presence of neoplasms. Markers such as beta-human chorionic gonadotropin (β- HCG) and alpha-fetoprotein (AFP) are essential in the diagnosis of germ cell neoplasms[Globocan (2004)]. Among all YST patients, pure or mixed, high alpha-fetoprotein levels are found in blood and tissue. Glypican3, cytokeratin, SALL4, and OCT3-4 are immunohistochemistry markers that may be important for YST diagnosis[Liu et al. (2010); Almeida Júnior (2004)].

These tumors are highly aggressive, and the prognosis seems related to the clinical stage and AFP levels[Globocan (2004); Silva et al. (2017)] In the present article, we report a rare, highly malignant case of the YST type with extramediastinal clinical manifestations, culminating in a thoracic vertebra fracture requiring rapid surgical intervention. Because it is a neurocritical patient with difficulty maintaining adequate breathing and ventilation and who needs strict monitoring, neurointensive care may be necessary. Paralysis and paresthesia resulting from compartment syndrome culminating in spinal compression fracture lead to a drastic loss of quality of life for the patient due to the loss of independence and autonomy.

Furthermore, mediastinal germ cell tumors can be confused with other differential diagnoses with symptoms common to lung diseases - fever, chest pain, dyspnea - such as pneumonia, pleural effusion, and atelectasis. Symptoms of paresthesia and paralysis can also be confused with differential neurological diagnoses such as Guillain-Barré syndrome, toxic neuropathy, epidural abscess, transverse myelitis, spondylosis, and spondylodiscitis. Therefore, it is crucial both intensive and non-intensive physicians know better about the possible complications of mediastinal germ cell tumors for a better approach and treatment.

2. Case report

A 25-year-old male arrived in the emergency room with dyspnea, fever, and chest pain. A chest X-ray showed a pneumonic process and a large mass in the mediastinal region **Figure 1**. The patient was admitted and started administration of Ceftriaxone and Azithromycin. During hospitalization, the patient develops compartment syndrome with pedicle fracture and spinal cord compression at the T7 level **Figure 2**, leading to paraplegia and paresthesia. It was necessary to perform some chest drainage procedures to alleviate the compartment syndrome partially. The complication of the disease by spinal cord compression is difficult to diagnose early since most bone metastases are accidental imaging findings (58%). In this case, it was only diagnosed due to the large extension of the tumor mass.

Vertebral fixation was performed by arthrodesis surgery from T5 to T9. Tomographic studies identified a large mass in the anterior mediastinum, measuring 20.0 x 11.0 cm, posteriorly displacing the structures and extending to both hemithoraces **Figure 3**. Chemotherapy was scheduled as soon as the patient stabilized, and an immunohistochemical was requested. The biopsy result showed positive parameters for 40, 48, 50, and 50.6 kDa cytokeratins, alpha-fetoprotein, germ cell transcription factor (OCT-3/4), SALL4 (zinc finger TC, Drosophila spalt (salt) gene), negative for CD30 – Ki-1 antigen, inconclusive for beta-HCG and focally positive for glypican. These findings made it possible to confirm the diagnosis of an endodermal sinus tumor with stage IIIB and metastases to bones and lungs. After stabilization, dexamethasone, etoposide, cisplatin, and bleomycin were treated. There was a significant reduction in pain but little change in dyspnea. The patient responded poorly to the chemotherapy and had a new respiratory infection, evolving into sepsis and septic shock. After a year of treatment, the patient died.

3. Discussion

Germ cell tumors (GCT) are rare neoplasms that most frequently attack the gonads, but they can also affect other sites, such as the mediastinum, pineal gland, retroperitoneum, and

sacral area. YST is a highly malignant subtype of GCT [Papaioannou et al. (2013)], considered non-seminomatous. It is more frequent in young adults aged between 15 to 35 years old [Macchiarini and Ostertag (2004)].

Mediastinal GCTs (GCTM) can also be classified according to their stage of development. Well-delineated tumors without microscopic evidence of invasion into neighboring structures, with or without focal invasion of the pleura or pericardium, are considered stage I. In stage II, the tumor has evidence of macroscopic and microscopic infiltration in nearby structures, despite being restricted to the mediastinum. In stage III, the tumor has metastasized and is subdivided into A (for intrathoracic organs) and B (for extrathoracic organs) [Moran and Suster (1997)].

Regarding the epidemiology and clinical presentation, malignant GCT in the mediastinum account for 1% to 6% of all mediastinal tumors [Dulmet et al. (1993)] and, within this group, non-seminomatous mediastinal GCT represents 1.0% to 3.5% of all anterior mediastinal tumors and have an incidence of 1% to 2% in male patients [Collins (1964)]. GCM can grow slowly and have few symptoms, so many of these tumors are diagnosed at an advanced stage. In a case series of 341 patients with mediastinal GCT published by Bokemeyer et al., the most common symptoms were: dyspnea (25%), chest pain (23%), cough (17%), fever (13%), weight loss (11%), superior vena cava syndrome (6%), fatigue (6%) and pain in sites other than the chest (5%). Less frequent symptoms and signs were: mass in the chest or neck wall (2%), hemoptysis, hoarseness, nausea, or dysphagia (1% each) [Bokemeyer et al. (2002)].

In addition, some clinical conditions are associated with YST, according to the literature, such as Klinefelter's syndrome (about 20% of cases) [Nichols et al. (1987)], early sexual development [Floret et al. (1979)], hematologic neoplasms, such as leukemia and myelodysplastic syndrome [Nakhla et al. (2016); Hartmann et al. (2000); Orazi et al. (1993)].

In the present case, in addition to dyspnea and chest pain, the patient had a fracture of the thoracic vertebra with medullary structures. This syndrome causes symptoms of complete spinal cord injury with paraplegia, loss of sensation at the pain level (T7), and retention of feces and urine. Thus, in this specific case, the fracture has a multifactorial consequence, secondary to the size of the neoplasm, increased intrathoracic pressure associated with force overload on the thoracic spine, and the clinical conditions of a patient with malignant neoplasm.

GCTs have little known etiology. The most accepted hypothesis for the genetic origin of tumors is related to the increased expression of genes located on the short arm of chromosome 12. The only chromosomal structural aberration consistent in GCT is the gain of 12p sequences, either in the form of isochromosome or tandem duplications, which are present in 80% to 100% of GCTs in adults [Sandberg et al. (1996); van Echten et al. (1995); Chaganti and Houldsworth (2000)].

In addition to the hypotheses above, overexpression of the GATA-4 protein also appears as a possible etiological factor. The GATA-4 protein belongs to a superfamily capable of regulating gene expression, thus being a transcription factor. In this sense, the GATA-4 protein controls the function and differentiation of the yolk sac endoderm, specifically for this tissue type. Therefore, besides being a possible element in the etiology of GCTs, this protein is a marker of malignancy in this tumor. However, other tumors with endodermal aspects may also express this marker, so joint analysis of other markers and histological aspects is necessary for better differentiation and diagnosis [Siltanen et al. (1999)].

3.1. ***Diagnosis***

Tumor markers are an essential tool for diagnosis and prognosis [Globocan (2004)].

3.1.1. ***Alpha-fetoprotein (AFP) and Beta-human chorionic gonadotropin (beta-HCG)***

The elevation of AFP and beta-HCG correlates with the type of GCT the patient has. The first is seen only in patients with teratomas or YST, while the second can be seen in any patient with a tumor involving syncytiotrophoblast cells [Globocan (2004)]. Therefore, the increase in AFP indicates a non-seminomatous element of the tumor [Couto et al. (2006)]. The diagnosis of YST is based on high levels of AFP and characteristic histopathological findings [Nakhla et al. (2016)], with AFP being essential for diagnosis and monitoring response to treatment [Couto et al. (2006)]. On the other hand, beta-HCG is a glycoprotein that plays a vital role in developing non-gestational neoplasms as a promoter of malignant transformation and a sign of poor prognosis [Sisinni and Landriscina (2015)]. Endodermal sinus tumors rarely produce beta-HCG [Murray et al. (2016); Stenman and Alfthan (2002); Bosl and Motzer (1997)]. This type of tumor is not formed by trophoblasts, cells that produce beta-HCG [Globocan (2004)].

3.1.2. ***Other important bookmarks***

Cytokeratins (CQ) are components of the cytoskeleton of epithelial cells and have a specific pattern for each type of epithelium and appendages. Therefore, they can be good markers of epithelial differentiation. Hyperproliferative CQ (6, 16, and 17) can be found in pathological conditions such as psoriasis and tumors. Low specificity antibodies, markers of several CQ, can be used to diagnose undifferentiated neoplasms such as germ cell tumors [Almeida Júnior (2004)].

We can also mention Glypicans (GPCs). These extracellular proteins belong to the heparin sulfate proteoglycan family [Zynger et al. (2006); Guo et al. (2020)]. It is speculated that they regulate growth factors. [Guo et al. (2020)] Tumors express GPC3 with a certain level of fetal differentiation. Still, it is absent in neoplasms of poorly or highly differentiated tissues, revealing a clear relationship between the developmental stage of the germ cell that constitutes the tumor and the expression of the protein [Zynger et al. (2006); Esheba et al. (2008)].

Furthermore, some markers such as SALL4 and OCT4 have diagnostic utility, with high specificity, as sometimes GCT of the primary mediastinum presents diagnostic difficulties. SALL4 is a sensitive marker for primary mediastinal YSTs, even more so than AFP and glypican 3 [Liu et al. (2010)].

3.1.3. ***Image exams***

Imaging exams are also helpful tools for diagnosing CTGM. In 95% of cases, these tumors are found in the anterior mediastinum, which can be seen on plain radiography. The exam of choice is computed tomography (CT), contrasted in the axial section. Compared to CT, magnetic resonance imaging (MRI) does not usually provide additional information [Couto et al. (2006)]. However, in the clinical case presented in this article, a chest MRI was necessary, as there was spinal cord involvement.

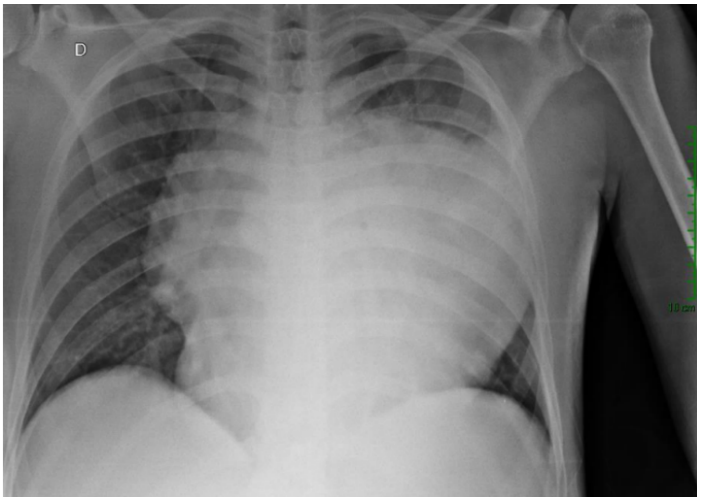

Figure 1: Chest X-ray showing pneumonic process and large mass in the mediastinal region.

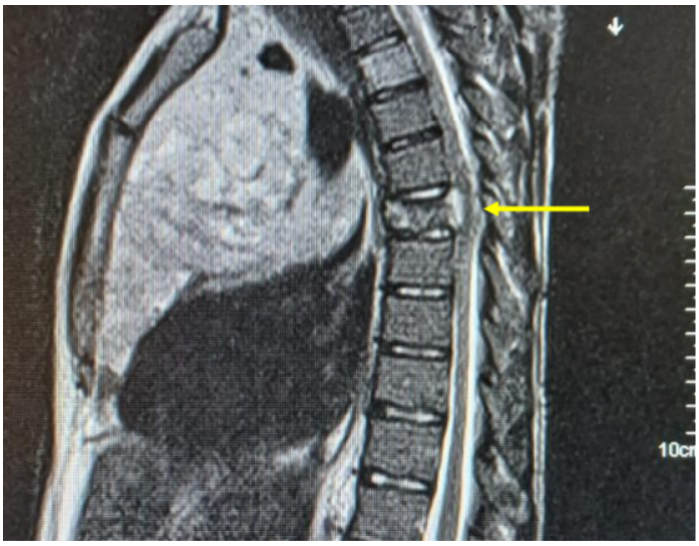

Figure 2: Nuclear magnetic resonance exam, showing compression of the vertebral bodies, especially at T7 level, leading to spinal cord compression (arrowhead).

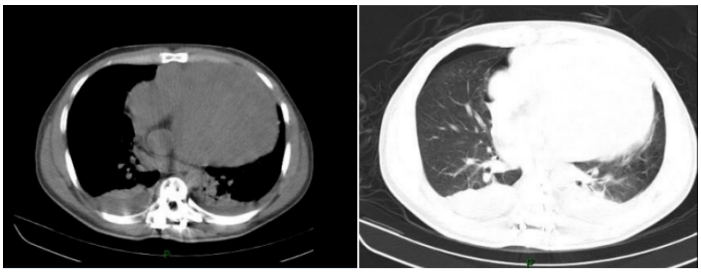

Figure 3: Computed tomography that allows the visualization of a voluminous mass in the region of the anterior mediastinum, compressing the adjacent posterior structures.

3.1.4. ***Spinal cord compression***

Bone metastases occur in approximately 30-70% of cases during the disease. Among these, spinal metastases occur in 50% of cases. Among spinal tumors, approximately 90% correspond to metastatic disease [Telera et al. (2021)].

Patients who develop vertebral metastasis may experience pain, fractures, and spinal cord compression [Grommes et al. (2011)]. Therefore, spinal cord compression is one of the leading causes of morbidity and disability in cancer patients [Telera et al. (2021)].

In the present case, metastatic vertebral lesions produced osteoclastic factors, weakening the vertebra. Additionally, the large extent of the primary tumor in the mediastinum increases intrathoracic pressure and culminates in a fracture by contiguity. This pathological fracture causes spinal cord compression, which, in turn, is an oncological emergency and can generate motor and sensory neurological deficits (paralysis and paresthesia) in addition to severe pain [Telera et al. (2021)].

3.2. ***Treatment***

Among germ cell tumors (GCTs), primary non-seminomatous tumors in the mediastinum represent the worst prognosis [Albany and Einhorn (2013)]. The treatment strategy for primary mediastinal yolk sac tumors (YST) consists of adjuvant chemotherapy and surgical resection of the residual tumor. Such an approach may promote long-term survival [Albany and Einhorn (2013); Ma et al. (2019)]. In this context, cisplatin-based chemotherapy regimens have significantly improved the outcome of patients with non-seminomatous tumors, being the preferred choice [Takeda et al. (2003); Albany and Einhorn (2013)].

There are two main chemotherapy regimens: bleomycin, cisplatin, and etoposide (BEP) or etoposide, ifosfamide, and cisplatin (VIP), administered for at least four cycles. The ifosfamide regimen is more recommended than bleomycin, especially for patients undergoing extensive chest surgery after chemotherapy, as it helps prevent pulmonary complications [Nakhla et al. (2016); Albany and Einhorn (2013); Kesler et al. (2008)]. In the presented case, the BEP regimen was used due to challenges in accessing ifosfamide, according to the Brazilian Public Health System (SUS).

Surgery is recommended even if tumor markers remain elevated, as salvage chemotherapy regimens are lacking, and

long-term survival is low [Nakhla et al. (2016); Albany and Einhorn (2013); Couto et al. (2006)]. However, in the reported patient, resection surgery was not performed due to the extent of the lesion and the debilitating conditions of the patient. Therefore, chemotherapy was intended for palliative care, even though the patient showed a poor response to the treatment.

The reduction in serum AFP after chemotherapy or surgical treatment and the complete response to chemotherapy with cisplatin are associated with a higher survival rate [Nakhla et al. (2016); Couto et al. (2006)]. However, a total reduction in AFP is observed in no more than 5% of patients after treatment [Nakhla et al. (2016)]. Studies suggest that patients who received first-line chemotherapy or first or second platinum-based salvage regimens had a better life expectancy when treated with chemotherapy alone [Grommes et al. (2011)]. In a study by Jamal-Hanjani M *et al.* [Jamal-Hanjani et al. (2013)], only 21% had a complete response to the medication after first-line chemotherapy treatment in patients with bone metastases. Among patients with bone marrow compression, all were treated with palliative radiotherapy, and some underwent tumor resection surgery. However, all patients with bone metastases died within less than one year after diagnosis, indicating a poor prognosis for this type of tumor.

4. Conclusion

Primary yolk sac tumors (YST) of the anterior mediastinum are rare and typically remain asymptomatic for an extended period until diagnosis. Consequently, complications, as highlighted in this case report, such as compartment syndrome, may be challenging to prevent, leading to more severe consequences like thoracic vertebra fracture and compression of the spinal cord. However, for physicians recognizing a primary mediastinal yolk sac tumor and being aware of potential clinical complications that impact the patient's morbidity and mortality, early treatment may suffice to prevent such fractures and improve overall survival.

The diagnosis of YST is primarily established by identifying elevated levels of markers, especially alpha-fetoprotein (AFP), and specific immunohistochemistry patterns. The patient in this case received treatment following the guidelines of the public health system (Sistema Único de Saúde - SUS) in Brazil: chemotherapy cycles with cisplatin-based regimens were initiated after stabilizing the fracture, aligning with recommendations in the literature and considering the financial constraints of SUS. Despite the medical team's efforts, the patient ultimately succumbed to the disease.

The uniqueness of this neoplasm lies in the limited information available about its etiology, the generally poor prognosis due to the tumor's aggressiveness, and the scarcity of case reports in the medical literature. Consequently, this article aims to contribute to a deeper understanding of the topic, enabling other health professionals to comprehend the tumor's development and the diverse nature of its complications. It underscores the necessity for further studies and the development of new therapies to enhance the quality of life for patients dealing with this specific type of cancer.

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