

Mediastinal germ cell tumors. Surgical experience with twenty nine patients

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Abstract

Background: To review and inform about the experience acquired with management of germ cell tumors of the mediastinum at the Calderón Guardia Hospital.

Methods: Twenty-nine patients with mediastinal germ cell tumors were operated between 1986 and 2012 in the Thoracic Surgery Department. General information was obtained from the department's database and these patients' clinical files were reviewed with authorization from the Hospital's Ethics Committee.

Results: Subjects were predominantly young males with a gender ratio of 13.5:1 and a mean age of 26. Masses were located in the anterior mediastinum in 28 cases and in the middle mediastinum in 1 case. Twenty-seven cases were suspected due to mediastinal widening on chest x-ray examination, 1 to pleural effusion and 1 to pleural effusion and mediastinal widening. The most frequently found symptoms were dyspnea, retrosternal chest pain, fever, cough, weight loss, superior vena cava syndrome, hemoptysis and gynecomastia in one male with coriocarcinoma. Tissue for diagnosis was obtained in 14 cases by mediastinotomy, in 8 by thoracotomy, in 4 by video assisted thoracoscopy, in 1 by sternotomy, in 1 by mediastinoscopy and in 1 by bronchoscopy.

Conclusion: Germ cell tumors of the mediastinum are infrequent, with higher prevalence in young males. Complete surgical excision remains the treatment of choice for resectable tumors, which are usually of more benign histology. Cure is not guaranteed by apparent total resection of malignant germ cell tumors, therefore primary or adjuvant chemotherapy should always be considered given that it was curative for some partially resected tumors and others with apparent total resection recidivated.

Keywords: Germ cell tumors, extragonadal germ cell tumors, tumors of the mediastinum.

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Germ cells are those of the gonads, so their presence in other locations is the subject of several theories. One says that these tumors originate from totipotent cells in the morula or blastocyst stage during embryogenesis. Another explains such presence under the embryological origin of the reproductive organs, which originate during the fourth week at cranial level, between the endodermic cells of the yolk sac and then these subsequently migrate to the region along with the mesonephros rising from the cauda, which takes primate germ cells (blastomeres) and descends to deposit them at the pelvis or scrotum,¹ so the theory is that some of these cells may be left in the mediastinum and they give rise to germ cell tumors. Another theory says that they are metastatic tumor cells that originated in the gonads, however, it is rare to find the association of mediastinal germ cell tumors with gonadal tumors.²

Germ cell tumors are more common in young men, they are very rare in women, they are often malignant and symptomatic, and like other mediastinal tumors they are usually detected by chest x-ray which where there is a widening of the mediastinum. Compression symptoms are usually present, the most common are: retrosternal pain, cough, dyspnea, dysphonia, diaphragmatic paralysis, hemoptysis and superior vena cava syndrome. It is also expected the presence of symptoms, such as fever, weight loss and malaise. Some patients have gynecomastia, due to the production of beta-gonadotropin humana.³

The radiographic finding of a tumor is usually a large tumor, sometimes very large, which can range from an injury with well-defined edges that rejects mediastinal structures or the lungs; to lesions that frankly invade and surround the thoracic organs, that can be associated with pleural effusion. CT scan is useful to assess these characteristics; the mass is often heterogeneous, which implies the existence of necrotic areas, or the presence of various tissues of different consistency. To observe calcifications or bone structure formation is typical of teratomas.⁴

Like tumors originated in gonads, they are classified into seminoma and nonseminoma tumors. Nonseminomas most common are: teratoma, teratocarcinoma, embryonal carcinoma, choriocarcinoma and yolk sac tumor. In many cases they have a mixed pattern, and they may show a part malignant and part benign pattern. This feature is of great importance in relation with the management, where the malignant part responds well to chemotherapy, and it is not unusual to remove later the benign portion that remains after treatment.⁵

Mixed tumors are the most common, followed by teratoma, seminoma and embryonal carcinoma, but choriocarcinomas are rare. Like gonadal origin tumors, some mediastinal germ cell tumors produce substances that can be used as tumoral serological markers and may be used as a diagnostic element. Yolk sac tumors, teratocarcinomas and embryonal carcinoma tend to raise serum alpha-fetoprotein. Choriocarcinomas often, and very few seminomas, increase beta human chorionic gonadotropin. Pure seminomas rarely elevate biomarkers, but in some cases there is elevated lactate dehydrogenase. The presence of these biomarkers is of great help in the diagnosis and monitoring of patients, as they tend to become negative after appropriate treatment. It is important; when you have these markers, to rule out tumors in the gonads. The pelvic or testicular ultrasound is mandatory before treatment.⁵

The anterior mediastinostomy and videothoracoscopy are useful procedures to take a biopsy, but one must consider the possibility of mixed tumors that are not represented in the obtained tissue.⁶

The histological finding often correlates to the treatment. Teratomas, in most cases, are usually surgically removed in

a first approach; while the rest of tumors tend to present as an invasive pattern, but have a good prognosis using chemotherapy.⁷ In some cases, surgical resection of the residual tumor is necessary, being of a good prognosis the finding of necrotizing tissue.^{8,9}

The aim of this study was to review the experience in the management of mediastinal germ cell tumors, in the Hospital "Dr. R. A. Calderón Guardia"; to describe the clinical presentation, the procedure to establish the diagnosis, treatment and outcome of patients with these tumors, during the period of 26 years: between 1986 and 2012.

Methods

Prior approval of the protocol by the Ethics and Research Committee of the Hospital, we conducted a retrospective analysis of all cases diagnosed with germ cell tumor, and operated in the Thoracic Surgery Department at the HCG between January 1986 and December 2012. The study did not include patients with germ cell tumors diagnosed by hormonal laboratory studies, which did not require biopsy or surgical resection and that were treated by the Medical Oncology Department.

The information was obtained from the database of the Department. We selected all patients with histologically confirmation of mediastinal germ cell tumor, during the study period. General information was extracted regarding age, gender, clinical presentation and radiological diagnostic or surgical procedure, complications, surgical mortality and histological diagnosis. Clinical records were reviewed to take information on the signs and symptoms, medical treatment, special studies performed and evolution. Since serological markers were not shown properly in the medical records, they were excluded from the study.

From the data obtained we report the frequency with which each was presented, and despite being a small number of cases, we report the trend, according to the histological subtype and response to treatment.

Results

We studied 29 cases, 2 females and 27 males, with a ratio of 1:13.5, that had ages between 15 and 40 years-old, with an average of 26 years-old. The location corresponded in 28 cases, to the anterior superior mediastinum, and one in the middle mediastinum.

The presentation, in 27 cases, was with widened of the mediastinum at the chest X-rat, one with a pleural effusion and one with pleural effusion and widened of the mediastinum. Only in 24 cases adequate clinical information

Table 1. Histological findings of 29 patients with mediastinal germ cell tumors	
Histological finding	Number
Seminoma	6
Teratoma	5
Teratocarcinoma	3
Choriocarcinoma	2
Yolk sac tumor	2
Mixed tumor	10
Embryonal carcinoma + teratocarcinoma	4
Embryonal carcinoma + seminoma + choriocarcinoma	3
Embryonal carcinoma + seminoma + yolk sac tumor	3

was found about symptoms in the clinical record; 4 patients were asymptomatic, 20 were symptomatic and the most common symptoms were: 16 cases with dyspnea, 12 cases with retrosternal pain or discomfort, 11 cases had fever, 9 cases had cough, 8 cases had weight loss, 8 cases had superior vena cava syndrome, 1 case had hemoptysis and 1 case had male gynecomastia in a patient with choriocarcinoma.

The sample for histological diagnosis was obtained in 14 cases, using an anterior mediastinostomy, 8 cases with thoracotomy, 4 cases with video-thoracoscopy, 1 case with sternotomy, 1 mediastinoscopy and 1 bronchoscopy.

The histological finding is shown in Table 1, where the highest frequency was mixed tumors, then followed by teratomas and seminomas, and it is less frequent to find choriocarcinomas and yolk sac tumors.

Twenty patients were operated with the intent to remove the tumor: 12 by thoracotomy 6 by sternotomy and 2 by videothoracoscopy. 12 patients underwent an apparent complete resection and 8 had a partial resection or biopsy only, considering it an unresectable lesion. Out of the 20 operated patients, 14 received pre- or postoperative chemotherapy. At the time of the study, it was found that out of 12 patients with apparently complete resection, 8 were found alive without disease (VSAT), 1 patient was alive but with tumor activity (VCAT) and 3 patients died with tumor activity (MCAT). Out of the 8 patients with incomplete resection, 4 were MCAT, 2 VSAT and 2 VCAT. In 9 cases that were considered unresectable at the moment of surgery, a biopsy was performed and they were treated with chemotherapy. Of these, 6 were MCAT and 3 VSAT.

Overall survival of all patients at the time of the study was 65%, with the longest survival of 26 years. Of the 19 patients who had more than five years after been treated, 11 were alive and 8 died, which represents a survival of 58% at five years. It was found that the 10 patients with mixed tumors, regardless of whether complete resection, incomplete or biopsy alone were performed, only two were alive. The three patients with teratocarcinomas were MCAT, the patients with choriocarcinoma: one was VSAT and one MCAT; and the patient with embryonal carcinoma was VCAT. By contrast, the 5 patients with teratomas and the two patients with yolk sac tumors were VSAT and the 6 patients with seminomas: 5 were VSAT and 1 was VSAT.

Discussion

Germ cell tumors of the mediastinum are relatively infrequent.¹⁰ The Thoracic Surgery Department of HCG, is a reference center, and in a period of 26 years only 29 patients were operated with a rate of 1.1 case per year. Some tumors were diagnosed and treated using exclusively serological markers, so the frequency is higher than the one reported.¹¹ In a study by Navarro *et al*, in metropolitan hospitals in Costa Rica in 1996, germ cell tumor was the most frequent mediastinal tumor.¹²

The frequency was much higher in young men, aged between 15 and 40 years old. Most of the patients had symptoms when they were diagnosed, and these symptoms are the same as other tumors of the mediastinum described in literature.¹³ Diagnosis is performed when looking at an abnormal widening of the mediastinum and CT scan provides valuable information regarding the particular characteristics of the tumor, especially to plan the route to take a biopsy or to perform a surgical approach.¹⁴

The anterior mediastinostomy is the most practical and effective method to take a representative sample in order to make the histological diagnosis, in this study had no mortality and with the exception of one case that required a video-assisted thoracoscopy, in the remaining 13 cases it was sufficient for the diagnosis.^{15, 16}

It should be noted that because of the high frequency of mixed tumors, although a clear histological diagnosis established by biopsy of a specific mediastinal germ cell tumor, one must consider the possibility that in another site of the tumor, there is a different histological finding. This should encourage pathologists to study with multiple cuts, both biopsies and excised mediastinal masses, and oncologists, to keep it in mind.⁶

It was found that the main prognostic factor was the histological characteristics, where mixed tumors and the

teratocarcinomas had the worst prognosis. It was also found that benign teratomas and seminomas, had a very good response to chemotherapy. Out of the 19 patients who had more than five years after been treated, 11 were alive and 7 died: a survival of 58% at five years.⁹

Surgical excision is still the treatment of choice for resectable tumors, which are usually histologically more benign, however, the apparent complete resection is not a guarantee, therefore in all cases adjuvant chemotherapy should be considered; and it showed be more useful, since a number of partially resected tumors were cured with chemotherapy, and some with apparent complete resection relapsed.¹⁷

References

1. Ronson RS, Duarte I, Miller JI. Embryology and surgical anatomy of the mediastinum with clinical implications. *Surg Clin NA* 2000; 80:157-169.
2. Díaz VM, Muñoz P, Shahi, Hernández B, Encinas S, Arranz JA, Pérez G. Tumores germinales mediastínicos. *Ann Med Interna* 2008; 25:241-243.
3. Craig N. Testicular Cancer. *Curr Prob Cancer* 1998; 22:187-274.
4. Dowe BV, Sterman DH, Musani AJ. Tumors of the Mediastinum. *Chest* 2005; 128:2893-2909.
5. Moran CA, Suster S. Primary Germ Cell Tumors of the Mediastinum. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. *Cancer* 1997; 80:681-690.
6. Hiroshi D. Diagnostic Strategies for Mediastinal Tumors and Cysts. *Thorac Surg Clin* 2009; 19:29-35.
7. Bokemeyer C, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Kanz L, et al. Extragonadal seminoma an international multicenter analysis of prognostic factors and long term treatment outcome. *Cancer* 2001; 91:1394-1401.
8. Kesler K, Einhorn L. Multimodality Treatment of Germ Cells Tumors of the Mediastinum. *Thorac Surg Clin* 2009; 19:63-69.
9. Ganjoo K, Rieger K, Kesler K, Sharma M, Heilman D, Einhorn L. Results of modern therapy for patients with mediastinal nonseminomatous germ cell tumors. *Cancer* 2000; 88:1051-6.
10. Johnson DE, Laneri JP, Mountain CF, Luna M. Extragonadal germ cell tumors. *Surgery* 1973; 73:85-90.
11. Hori K, Uematsu K, Yasoshima H, Yamada A, Sakurai K, Ohya M. Testicular seminoma with human chorionic gonadotropin production. *Pathol Int* 1907; 47:592-599.
12. Navarro M, Luis G, Salazar C. Análisis y seguimiento de pacientes con tumores mediastinales egresados de los hospitales metropolitanos de Costa Rica durante 1996. *Acta Méd Costarricense* 2003; 45:68-74.
13. Silverman NA, Sabiston DC. Mediastinal masses. *Surg Clin North Am* 1980; 60:757-777.
14. Muller NL. Computed tomography and magnetic resonance imaging: past, present and future: *Eur Resp J Suppl* 2002; 35:2-12.
15. Olak J. Paraesternal mediastinotomy: *Chest Clin N Am* 1996; 6:31-40.
16. Yim AP, Lee TW, Izzat MB, Wan S. Place of video thoracoscopy in thoracic surgical patients. *World J Surg* 2001; 25:157-161.
17. Schomoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberg C, Fossa SD, et al. European consensus on diagnosis and treatment of germ cell cancer; a report of the European Germ Cell Cancer Consensus Group. *Ann Oncol* 2004; 15:1377-1399.