Metastatic Germ Cell Tumor to the Heart Presenting with Syncope

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Summary: Malignant nonseminomatous germ cell tumors (NSGCT) rarely metastasize to the heart. The first such case presenting with syncope is described. Eight previously described cases of NSGCT with intracaval metastasis to the heart are reviewed and the literature to date is discussed. Transesophageal echocardiography is the diagnostic study of choice and treatment consists primarily of platinum-based chemotherapy followed by surgical resection of residual deposits.

Key words: syncope, cardiac tumor, testicular tumor

Introduction

Testicular cancer accounts for 1% of all male neoplasms, but is the most common carcinoma in the 15 to 35 years age group. Tumors of germ cell origin constitute over 90% of all testicular neoplasms, the rest being comprised of sex cord-stromal tumors, sarcomas, and lymphomas. Pure seminomas account for about 40% of testicular germ cell tumors and tend to occur in older patients. The nonseminomatous germ cell tumors (NSGCT) include embryonal carcinoma, teratoma, teratocarcinoma, choriocarcinoma, endodermal sinus (yolk sac) tumors, and mixed tumors. The NSGCT are treated primarily by platinum-based chemotherapy, which has a 90% overall cure rate. In 90% of cases, the levels of one or both of the tumor markers, β -hCG and α -fetoprotein (AFP), are increased. Surgery is reserved for those patients who continue to harbor residual tumor masses after chemotherapy. The NSGCT is a model for curable solid neoplasm and demonstrates that cure can be achieved by partial remission with

chemotherapy followed by surgical resection of residual disease.¹ We describe the first case of metastatic malignant NSGCT presenting with syncope and its subsequent resolution with chemotherapy and surgery.

Syncope has many etiologies and associations and can be benign or the presentation of a more serious illness. Most commonly it is associated with compromised cerebral blood flow resulting in loss of consciousness, which may be brief, following the adoption of the supine position with a resultant restoration of cerebral blood flow. Structural and obstructive abnormalities of the heart are well known to cause syncope. The NSGCT is well known to metastasize to the lung, brain, and liver, but metastases to the heart are rare and, as far as we are aware, resultant syncope has not been described.

Case Report

A 21-year-old Caucasian male with a past medical history of mild mental retardation presented to the emergency room with three syncopal episodes over the previous 5 days, a history of shortness of breath on exertion, chest and back pain, and a 30 pound weight loss over 5 months. His heart rate was 120 beats/min, respiratory rate 22/min, and blood pressure 110/60. Physical exam was unremarkable except for a 2/6 systolic ejection murmur at the left lower sternal border. Baseline electrocardiogram (ECG) showed sinus tachycardia at 125 beats/min, α QRS 90°, rare premature ventricular contractions (PVCs), and nonspecific ST-T wave changes. Laboratory investigations were notable for a hemoglobin of 11.6 g/dl, platelets of 21,000/ μ l, and lactose dehydrogenase (LDH) of 1530 U/l. Transthoracic echocardiogram showed a right atrial mass extending to the right ventricle, but the study was suboptimal. Therefore, transesophageal echocardiogram was performed which showed a large pedunculated right atrial mass, 5 $\times$ 5 cm, originating from the lateral aspect of the tricuspid annulus. This mass was visualized in the inferior vena cava extending through the right atrium and right ventricle into the pulmonary outflow tract (Fig. 1). Computerized tomography (CT) of the chest was then performed, which revealed a right atrial mass and mediastinal adenopathy. Because of the high suspicion of malignancy, CT of the abdomen and pelvis was performed to locate the primary tumor. The CT of the abdomen showed extensive retroperitoneal

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FIG. 1 Transesophageal echocardiogram showing 5×5 cm right atrial mass originating from the lateral aspect of the tricuspid annulus. The mass is visualized extending from the right atrium into the right ventricle and pulmonary outflow tract.

adenopathy and that of the pelvis showed an infiltrative process in the right testis that was confirmed by ultrasound. Because of the findings of testicular infiltrate and mediastinal adenopathy in a young man, a germ cell tumor was suspected; however, the thrombocytopenia would be unusual. Bone marrow aspiration and biopsy showed focal increase of megakaryocytes. There was no laboratory evidence of disseminated intravascular coagulation.

With no clear etiology of the thrombocytopenia, the patient received dexamethasone followed by high-dose gammaglobulin, with no significant improvement of the platelet count. The low platelets were considered to be secondary to intravascular consumption by the intracaval tumor and thrombus. Because of the thrombocytopenia, tissue diagnosis was not possible, so tumor marker levels were measured to characterize the nature of the tumor further. All tumor markers were negative, except β -hCG which was measured at 48,000 IU/l and AFP at 8,454 μ g/l. Even though tissue histology was not available, a diagnosis of NSGCT was made on the basis of clinical presentation, age, radiological findings, and tumor markers. Because of the cardiac compromise as well as severe pain suffered by the patient, chemotherapy was started without delay. The patient was classified as having stage 3 disease because of supradiaphragmatic spread and was treated with bleomycin, etoposide, and cisplatin. He had an excellent response symptomatically, reduction of tumor mass in the mediastinum and retroperitoneum, and reduction of β -hCG to 5.9 IU/l and AFP to < 5.0 μ g/l. Four months later he was admitted for removal of the residual intracaval mass and right testis; however, his thrombocytopenia that had initially improved after chemotherapy recurred, precluding surgery. There was no response to high-dose methylprednisolone or gammaglobulin, and therefore his surgery was rescheduled.

Two months later the patient presented with a solitary brain metastasis that was surgically resected and followed with radiation therapy. Pathology showed an extensively hemorrhagic and necrotic papillary adenocarcinoma that was positive for keratin, hCG, AFP, and placental alkaline phosphatase by immunohistochemistry. These results supported a diagnosis of a metastatic germ cell tumor.

Because of persistent abnormalities in the vena cava and intracardiac areas and the risk of emboli (with normal tumor markers), he underwent cardiac surgery; the platelet count was normal at that time. A standard median sternotomy incision was made and the pericardium was opened in the midline. The heart was normal in appearance; however, the tumor mass could be palpated, occupying a normal sized right atrium and extending into the superior vena cava and innominate vein. The vena cava exhibited some inflammatory thickening of its wall. Intraoperative transesophageal echocardiogram confirmed the above findings. Cardiopulmonary bypass was instituted and, through a right atriotomy incision, a pedunculated myxoid-like tumor with finger-like projections into the right ventricle was delivered into the wound. The stalk was attached to the superior vena cava and was incised separately with a portion of the cava. A separate incision was made in the innominate vein and some residual fibrous tissue was excised. A frozen section of the tissue removed from the innominate vein was consistent with chronic inflammation.

After the right ventricle was carefully inspected and found to be free of disease, the patient was rewarmed and taken off bypass after closure of the atriotomy and repair of the superior vena cava and innominate vein with pericardial patches. Bypass time was 42 min and arrest time was 12 min. The pathologic specimen consisted of a fibromyxoid thrombus with mature cartilage and calcifications (Fig. 2). Immunohistochemical stains of the heart lesion were negative for the previously mentioned tumor markers, and a few atypical cells seen within the thrombus appeared to be reactive fibroblasts.

FIG. 2 Intracardiac mass showing mature cartilage and calcifications (left) (H&E, $\times 23$).

One year after surgery, follow-up echocardiogram showed a small mass on the leaflet of the tricuspid valve not present before. Ultrasound of the testicles revealed a new lesion adjacent to the old mass in the right testicle. At this time, the patient's β -hCG was < 2 IU/l and his AFP was $14.5 \mu\text{g/l}$. He was therefore admitted for salvage chemotherapy with ifosfamide, cisplatin, vinblastin, and bleomycin. He also underwent orchiectomy of the right testis for possible tumor sanctuary site, but pathologic examination revealed scar tissue only with no evidence of tumor. Since his initial chemotherapy, his tumor marker levels remained within normal limits ($\text{hCG} < 2.1$ IU/l, $\text{AFP} < 32 \mu\text{g/l}$) until 3 years after surgery, when his AFP level rose to $486 \mu\text{g/l}$ and the β -hCG level remained < 2.1 IU/l. Exploratory laparotomy and retroperitoneal dissection of persistent adenopathy was undertaken and a retroperitoneal metastatic germ cell tumor was resected. Pathologic examination revealed a mature teratoma with a malignant carcinomatous component. The mass was composed of a proliferation of glandular structures admixed with mature cartilage and sheets of anaplastic round tumor cells (Fig. 3). Immunohistochemical staining showed strong positivity for CAM 5.2 (low molecular weight cytokeratin) and CD 99 antibodies. Electron microscopy showed well-formed desmosome-type intercellular junctional and basal lamina deposition in the anaplastic round tumor cells. Both electron microscopy findings and immunohistochemical staining supported the diagnosis of a primitive, poorly differentiated carcinoma within a mature teratoma. Following this procedure, AFP levels have returned to normal and the patient remains asymptomatic.

Discussion

We believe this to be the first described case of metastatic malignant NSGCT initially presenting with syncope. Syncope, brought about by hypotension with reduction of cerebral blood flow, was secondary in this case to pulmonary outflow obstruction by the intracardiac tumor. We know of no case where intracardiac tumor causing syncope has led to the diagnosis of NSGCT. Although the intracardiac tumor appeared to consist of an organizing thrombus, mature cartilage within the thrombus points toward metastasis of mature teratoma, the other elements of which may have been eradicated by chemotherapy. Intracaval metastasis to the heart from malignant NSGCT is rare. In addition to the case presented, eight other cases are summarized in Table I.

The first report of an intracardiac metastasis from testicular teratoma was in 1822 in an autopsy by Coates who described the tumor as filling the whole inferior vena cava and extending to the edge of the eustacian valve.² An autopsy series of 154 patients with testicular cancer (including 16 patients with seminomatous testicular tumor) reported by Bredael *et al.* identified three patients with metastasis to the heart and two to pericardium.³ Johnson *et al.* reviewed the pattern of metastases in an autopsy series of 59 cases of NSGCT and identified 2 cases with metastases to the heart and 1 to the pericardium.⁴ Both studies showed the main sites of metastases in the order

FIG. 3 Carcinomatous component with metastatic retroperitoneal teratoma showing sheets of poorly cohesive anaplastic round tumor cells having large vesicular nuclei with prominent nucleoli (H&E, $\times 130$).

of decreasing frequency to be lung, retroperitoneal lymph nodes, liver, mediastinal lymph nodes, brain, kidney, gastrointestinal tract, and bone.

Few cases with symptoms secondary to intracaval metastasis have been described. Case 8 presented with dyspnea on relapse 9 months after initial diagnosis, and Case 4 presented with acute right ventricular failure 3 years after initial diagnosis and treatment. Labib *et al.* reviewed 14 cases with obstruction of the right ventricular outflow tract caused by intracavity metastatic disease.⁵

They found that right heart failure, shortness of breath, chest pain, hypotension, systolic murmur, and right axis deviation or right bundle-branch conduction abnormality were universal features. Syncope, however, was not reported as a feature. Echocardiography proved valuable in the delineation of metastatic cardiac involvement and the detection of intracardiac gradients. Adverse hemodynamic consequences developed in 3 of 10 patients who underwent right heart catheterization during which 2 died. They recommend that this procedure only be performed when biopsy of the metastatic mass is absolutely necessary. In the case report described, the patient exhibited features consistent with this study: shortness of breath, chest pain, a systolic murmur, and probable hypotension associated with syncope. He did not, however, have right heart failure, right-axis deviation, or right bundle-branch block.

In five cases,^{1, 2, 6, 7, 9} attention to the intracaval metastases was initiated by the finding of new cardiac murmurs. In Case No. 3, attention was drawn to the heart after the patient presented with a cerebrovascular accident 13 years after initial diagnosis and treatment. Case No. 6 underwent echocardiography following studies that revealed extensive thrombus formation in the inferior vena cava and left renal vein. All of

TABLE I Summary of reported cases of nonseminomatous germ cell tumor with intracaval cardiac metastasis

Case No.	Year Ref. No.	Age (years)	Clinical presentation of intracaval met	Cardiac imaging	Extent of disease	Rx of cardiac tumor	Pathology intracaval mass	Outcome
1 (present case)	'97	21	Syncope, SOB, chest + back pain weight loss, SM	TEE; mass in RA, RV + pulmonary outflow tract	Mets to brain + RP	Cx + Sx excision	Mature teratoma	RM 5 years post Dx
2	'93 (9)	26	SM on routine exam 6 years post Dx	TTE; RV mass	Mets to lungs	Sx excision	Mature teratoma	RM 3 years post Sx
3	'93 (10)	41	Cerebral infarct 13 years post Dx	TEE; LA mass	Mets to brain, lung, RP	Sx excision	Mature teratoma	RM 1 year post Sx
4	'92 (11)	26	Acute RV failure, 3 years post Dx	TTE; mass in RV + outflow tract	Mets to lungs	Cx	No autopsy	Died 1 month later of H. influenza pneumonia
5	'92 (11)	41	SM + DM on physical exam 1 year post Dx	Cardiac angiogram; mass in RA, RV, LA	Mets to post-M, para-aortic + left cervical lymph nodes	Sx excision	Differentiated teratoma	RL in retrocrural area resis. to Cx; died 2 years post Sx
6	'92 (6)	25	Persistent bulky RP mass 7 months post Cx + orchiectomy	TTE; RA mass	Mets to lungs + RP + invasion of pancreas + duodenum	Sx excision	Benign cysts with squam. + columnar epithelium	No change in tumor size 2 years post Sx
7	'91 (12)	31	SM, pleuritic pain, hard right. testicle	TTE; mass in LA, LV, + inf. pulm. vein	Mets to lung	Cx + Sx excision	Embryonal testicular carcinoma	RM 2 years post Sx
8	'91 (7)	42	SOB on exercise 9 months post Dx	TTE; RA mass	Mets to lung + M	Cx + Sx excision	Mature teratoma	RM 13 months post Sx
9	'86 (13)	42	SM, SOB, l. sub-clavian vein occlusion 2 years post Dx	Cardiac angio; mass in RA, RV	Mets to neck, abdomen, M	Cx + Sx excision	Mature teratoma	RL 1 year later. Died 18 months post Sx

Abbreviations: Cx = chemotherapy, Dx = diagnosis, DM = diastolic murmur, LA = left atrium, M = mediastinum, mets = metastases, RA = right atrium, RL = relapse, RM = remission, RP = retroperitoneum, RV = right ventricle, SM = systolic murmur, SOB = short of breath, Sx = surgical, TEE = transesophageal echocardiogram, TTE = transthoracic echocardiogram.

the cases described with intracaval metastasis to the heart had widespread disease and were classified as stage 3 due to supradiaphragmatic spread. Testicular cancer occasionally may remain localized for long periods, but early lymphatic and hematogenous spread is more typical. These neoplasms spread via the lymphatics to the retroperitoneal nodes while hematogenous spread is primarily to the lungs. Occasionally metastases to the liver, brain, or other areas occur. The malignant tumors that most frequently extend into the right atrium are renal cell cancer, adrenocortical cancer, and melanoma.

Most cases of advanced NSGCT are now effectively treated and controlled with platinum-based chemotherapeutic regimens. However, in a significant proportion, bulky residual disease persists. The evolution of mature teratoma from malignant NSGCT of the testis is common, particularly following treatment with chemotherapy. Approximately 40% of the pa-

tients with residual disease following induction chemotherapy for metastatic NSGCT of the testis will have teratoma in the surgically removed specimen. The finding of teratoma in 82% of patients with enlarging metastatic masses despite chemotherapy for NSGCT led Panicek *et al.* to conclude that if serum tumor marker levels are normal, most enlarging masses represent mature teratoma or necrotic tumor without malignancy.⁸ Operative resection of residual tumor allows identification of patients who may require further chemotherapy, permits resection of teratoma (which may be creating local morbidity), and allows cure of some patients with teratoma with malignant transformation refractory to chemotherapy. The long-term prognosis after excision of a metastasis is dependent upon the histologic type and completeness of excision; hence, we feel that the multiple surgeries in our patient were not only justified but contributed to his favorable response.

Conclusion

Malignant nonseminomatous germ cell tumors can metastasize to the cavities of the heart. The new development of a cardiac murmur or cardiac symptoms should alert the clinician to this possibility. Echocardiography, preferably transesophageal, is the diagnostic study of choice. This condition is curable in the majority of patients and surgery plays a major role. Patients with residual masses after chemotherapy require complete surgical excision and histologic examination of the resected specimen. There may be a combination of histologic types indicating the need for further chemotherapy. Surgery can reduce local morbidity, such as the resolution of pulmonary outflow obstruction in the case we have described. Patients with NSGCT require regular and prolonged follow-up to detect evidence of recurrence, which should be treated aggressively with both chemotherapy and surgery.

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