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Case Report
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Mediastinal Nonseminomatous Germ Cell Tumor Metastatic to the Neck

*Coral Tieu[1], Stacie Gregory[1], Onsi Kamel[2] and Arun Sharma[1]**

[1]Division of Otolaryngology-Head and Neck Surgery, Southern Illinois University School of Medicine, USA

[2]Department of Pathology, HSHS St. John's Hospital, USA

Abstract

Objectives: When imaging and initial cytology contradict one another, a specific diagnosis may be impossible. This places the treating physician and patient in a less than ideal situation, as they must proceed with generic or presumptive treatment for a tumor of unknown prognosis. We present a case which highlights utilizing a molecular genetics test to help clarify tumor origin through the use of specific cell markers.

Methods: Chart review was used to obtain all pertinent information regarding this 55-year-old female who presented to head and neck oncology clinic with a firm, mildly tender left level V neck mass.

Results: Excisional biopsy of the left neck mass evidenced poorly differentiated, metastatic non-small cell, p16+ carcinoma on staining. PET/CT demonstrated a 1.4-cm spiculated nodule in the left upper lobe of the lung. CT-guided biopsy was negative for malignancy. The level V lymph node specimen was then sent for real-time reverse transcription polymerase chain reaction. Molecular diagnostics returned a 90% probability of a nonseminomatous germ cell tumor in this level V neck mass.

Conclusion: Proper diagnosis of the primary source of malignancy is critical not only for timely initiation of treatment and selection of appropriate therapy modalities, but also for appropriate discussions about prognosis and later monitoring of treatment response. We present a case of a mediastinal nonseminomatous germ cell tumor metastatic to the neck diagnosed by molecular diagnostics.

Keywords: Neck mass; Extragonadal nonseminomatous germ cell tumor; Neck metastasis; Molecular diagnostics; Tumor gene expression pattern

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Correspondence:
Arun Sharma, Division of Otolaryngology-Head and Neck Surgery, Southern Illinois University School of Medicine, 315 West Carpenter Street, Box 19677, Springfield, Illinois 62702, USA, Tel: 2175457068;
E-mail: asharma74@siumed.edu

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Introduction

Malignant mediastinal germ cell tumors are rare; representing 1-4% of all mediastinal tumors [1]. However, the true incidence of these tumors may in reality be higher because of failure to diagnose them properly. Other origins of mediastinal tumors include thymic neoplasms, lymphoma, neurogenic tumors and germ cell tumors, as listed in Table 1 [2,3]. Approximately 10% of germ cell tumors are extragonadal. The mediastinum is the most commonly affected extragonadal area, followed by the retroperitoneum, the sacrococcygeal area, and the central nervous system [4]. We present a case of a mediastinal nonseminomatous germ cell tumor metastatic to the neck diagnosed by molecular diagnostics. Metastasis to the neck is rare, with no reported cases in the literature. There was one case report of cervical extension of a primary mediastinal seminoma, but no reported cases of metastasis to the neck [5].

Case Presentation

A 55-year-old female with a 30 pack-year smoking history presented to clinic with a two-month history of a one centimeter, firm, mildly tender left level V neck mass. There had been no improvement after 2 weeks of antibiotics. A neck ultrasound demonstrated a 1 x 0.7 x 0.8 cm hypoechoic left level V mass. Ultrasound-guided fine needle aspiration revealed an epithelioid neoplasm with no further classification possible. The patient was at that point referred to the otolaryngology-head and neck surgery clinic, where flexible fiberoptic laryngoscopy was normal. CT of the chest and neck demonstrated a superior mediastinal mass with scattered pulmonary nodules (consistent with a primary lung tumor) and a 1-cm nodule in level V of the left neck.

Table 1: Mediastinal tumors.

Mediastinal Tumors	
Thymic neoplasms	31-42%
Lymphoma	22%
Neurogenic tumors	16%
Germ cell tumors	9% (1-4% malignant)
Miscellaneous	13%

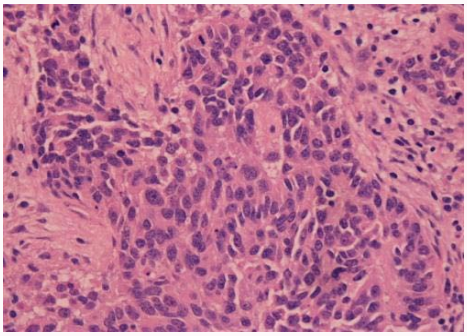

Figure 1: Left neck mass excision showing poorly differentiated, non-small cell carcinoma.

The patient then underwent excisional biopsy of the left neck mass, evidencing poorly differentiated, metastatic non-small cell, p16+ carcinoma on staining (Figure 1). The specimen was positive for cytokeratin AE1/AE3, cytokeratin CAM5.2, cytokeratin 7, p16, synaptophysin, chromogranin, CD56, Ki-67 and CDX2. There was no reactivity with cytokeratin 20, TTF-1, CD5 and Napsin A. However, a more specific pathologic diagnosis could not be made from the excisional biopsy specimen. PET/CT demonstrated increased uptake in the left hilar region and mediastinum as well as a 1.4 cm spiculated nodule in the left upper lobe of the lung. CT-guided biopsy of the latter was negative for malignancy. Given the difficulty in arriving at a pathologic diagnosis, the level V lymph node specimen was sent for real-time reverse transcription polymerase chain reaction (RT-PCR) to determine its gene expression profile (BioTheranostics, San Diego, CA). This test revealed a 90% probability that the specimen was a nonseminomatous germ cell tumor (Figure 2). Beta-Human Chorionic Gonadotropin (HCG) was 2mIU/mL (<5 is negative, 5-25 = borderline, >25 = positive), alpha fetoprotein (AFP) was 4.3ng/mL (upper limit of normal = 6.1) and lactate dehydrogenase (LDH) was 184 units/L (reference range 125-220). Based on the likely diagnosis of a nonseminomatous germ cell tumor, the multi-disciplinary tumor board recommendation was for treatment with chemotherapy using Bleomycin, Etoposide and Cisplatin followed by radiation therapy and/or surgical resection of any residual lung tumor. IRB exemption was obtained for this case report.

Discussion

Given this patient's underlying risk factors and presentation, the anticipated diagnosis was squamous cell carcinoma (SCCa) of unknown primary. However, the patient posed a diagnostic conundrum when imaging and initial cytology contradicted one another with respect to tumor origin. Proper diagnosis is critical not only for timely initiation of treatment and selection of appropriate therapy modalities, but also for appropriate discussions about prognosis and later monitoring of treatment response. This case highlights utilizing a molecular genetics test to help clarify tumor

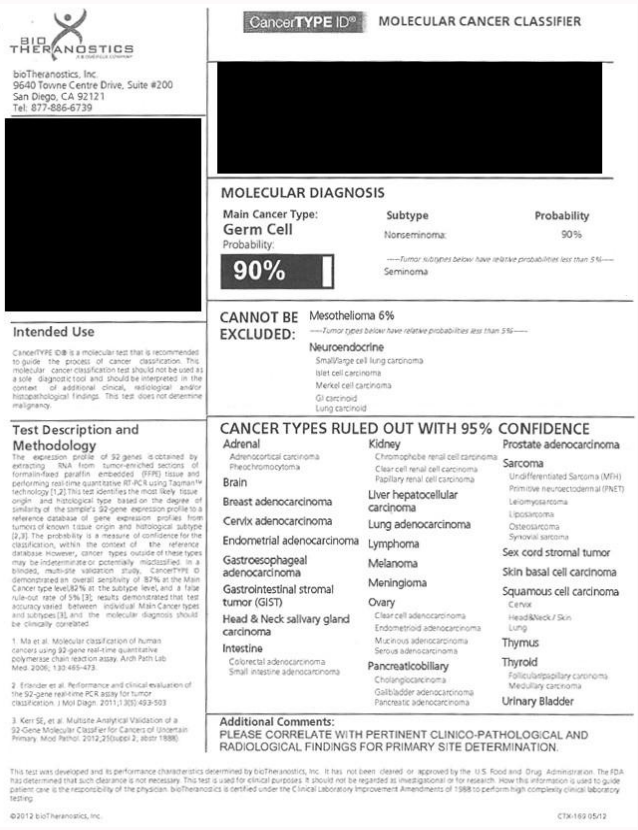

Figure 2: BioTheranostics molecular diagnostic report calculating a 90% probability of a non seminomatous germ cell tumor.

origin through the use of specific cell markers. The test uses real-time RT-PCR to measure the expression of 92-genes in the patient's tumor and classifies the tumor by matching the gene expression pattern of the patient's tumor to a database of known tumor types and subtypes, encompassing 50 tumor types. A minimum sample size of 300 cells is required and the overall accuracy of the test is 87% with results received in 5-7 days [6]. In this case, such testing afforded a greater than 90% probability of a germ cell primary tumor. Nonseminomatous germ cell tumors with mediastinal primaries are rare and carry a poor prognosis with a 5-year survival rate of 48% [7]. This patient received appropriate therapy for a nonseminomatous germ cell tumor, which differs markedly from management and treatment of SCCa of unknown primary site. One retrospective review of 89 patients with cancer of unknown primary treated with curative intent at a single institution, showed the overall 5-year survival rates to be 55% [8]. If our patient was treated for either a small cell lung primary or SCCa of unknown origin, she would have received a less ideal chemotherapy regimen and possibly worse outcome given the inability to appropriately target her therapy. Molecular diagnostic testing is a valuable tool in the oncologic surgeon's arsenal that can provide answers to diagnostic conundrums and ultimately help guide treatment for better patient outcomes.

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