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Case Report

Fine Needle Aspiration Diagnosis of a Metastatic Mixed Germ Cell Tumor from a "Burned Out" Testicular Primary with Florid Leydig Cell Hyperplasia

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Abstract

"Burned out" testicular germ cell tumors are rare, representing involuted primary tumors typically discovered during workup for metastatic disease with associated elevated serum tumor markers. Histologically, a hyalinized scar is seen, often with surrounding intratubular germ cell neoplasia. We report a 24 year-old man who presented with a two-month history of cough, dyspnea, and intermittent testicular pain. Ultrasound revealed an irregular, hyperechoic 6 x 5 x 5 mm lesion within the right testis. Chest imaging revealed innumerable pulmonary nodules and diffuse lymphadenopathy. Serum tumor markers were elevated (AFP: 432.9 ng/mL, LDH: 2606 U/L, and β-hCG: 97,575 mIU/mL) and the patient underwent a radical orchiectomy. Upon microscopic examination of the orchiectomy specimen there was a 5 mm circular focus of paucicellular fibrosis surrounded by intratubular germ cell neoplasia and diffuse Leydig cell hyperplasia extensively involving the interstitium. Fine needle aspiration of a left supraclavicular lymph node was performed, revealing a mixed germ cell tumor with components of embryonal carcinoma, seminoma, and choriocarcinoma. Diffuse Leydig cell hyperplasia in the setting of a germ cell tumor is rare, and is thought to be induced by markedly elevated serum β-hCG from a syncytiotrophoblastic component (which can be associated with seminoma, embryonal carcinoma, or choriocarcinoma). To the best of our knowledge, this case represents the first report of "burned out" testicular germ cell tumor with diffuse Leydig cell hyperplasia and subsequent germ cell tumor with mixed elements of seminoma, embryonal carcinoma, and choriocarcinoma diagnosed by fine needle aspiration.

ABBREVIATIONS

AFP: Alpha-Feto Protein; LDH: Lactate Dehydrogenase; β-hCG: Beta-Human Chorionic Gonadotropin; ITGCNU: Intratubular Germ Cell Neoplasia, Unclassified Type; PLAP: Placental Alkaline Phosphatase

INTRODUCTION

Mixed germ cell tumors account for approximately 90% of testicular tumors [1] and are the most frequent cause of non-hematopoietic malignancy-related mortality in young men [2]. In most cases, the primary tumor is readily identified on clinical exam and imaging. In rare instances, the primary tumor undergoes spontaneous regression, leaving a hyalinized scar and intratubular germ cell neoplasia with or without calcification in the residual seminiferous tubules. Concurrent distant metastases may be observed, and may confound the diagnostic picture, as primary germ cell tumors may arise within the retro peritoneum or mediastinum in 3-10% of cases [3,4]. Clinical examination, ultrasonography, and pathologic examination will often reveal the presence of the above described findings in order to guide the diagnosis [4]. A consensus has not been reached within

the literature regarding whether or not the testicular tumor represents the primary tumor or a metachronous germ cell tumor [5-6]. Fine needle aspiration of suspected metastases, combined with clinical information and imaging, can be critical in this determination.

Burned out primary testicular tumors have most commonly been associated with pure seminoma identified at sites of metastasis [7-11] syncytiotrophoblast and associated elevations in β-hCG in germ cell tumors has been associated with the development of diffuse Leydig cell hyperplasia, in which there is a proliferation of Leydig cells in the interstitium [12-13]. Until now, the combination of completely burned out testicular tumor with adjacent diffuse Leydig cell hyperplasia has exclusively been reported in association with cases of metastatic pure seminoma [14-15]. We present a case of metastatic mixed germ cell tumor diagnosed by fine needle aspiration in a 24 year-old man with a burned out primary testicular tumor and associated diffuse Leydig cell hyperplasia.

CASE PRESENTATION

A 24 year-old Hispanic man presented with a two-week history of non-productive cough, dyspnea and right-sided testicular pain. A chest X-ray revealed innumerable pulmonary nodules and hilar adenopathy. Although no clinically palpable testicular lesion was present, ultrasound showed a hyperechoic, heterogeneous mass (6 x 5 x 5 mm) within the inferior right testis. Laboratory tests drawn at that time showed elevated tumor markers (LDH = 2606 U/L; normal: 84-146 U/L, AFP = 432.9 ng/mL; normal: 0-8 ng/mL, β-hCG = 97,575 mIU/mL; normal: 0-1 mIU/mL). The patient underwent a right radical orchiectomy and fine needle aspiration of a palpable left supra clavicular lymph node.

A 7 x 5 x 5 mm well-circumscribed white nodule was seen within the inferior pole of the right orchiectomy specimen, directly abutting the tunica albuginea. Microscopic examination showed a hyalinized scar with surrounding intratubular germ cell neoplasia, unclassified type (ITGCNU) (Figure 1,2). Leydig cell hyperplasia of the diffuse type was seen in all examined sections (Figure 2).

Modified Giemsa and Papanicolaou-stained smears of the left supraclavicular fine needle aspiration specimen showed cohesive sheets of cells with a high nuclear-to-cytoplasmic ratio, nuclear pleomorphism with vesicular chromatin and prominent macronucleoli, in a background of necrosis (Figure 3). A cell block showed three distinct tumor patterns: pattern #1 (most predominant) was composed of sheets of cells with markedly pleomorphic nuclei and prominent macronucleoli. Pattern #2 consisted of sheets of cells with cleared-out cytoplasm and moderately pleomorphic nuclei with prominent nucleoli. Pattern #3 showed multinucleated cells with large, bizarre, hyperchromatic nuclei and abundant eosinophilic cytoplasm. Immunohistochemical stains were performed. Pattern #1 was positive for CD30, pancytokeratin (AE1/AE3), and placental alkaline phosphatase (PLAP), and negative for CD117, D2-40 and β-hCG, consistent with embryonal carcinoma (Figure 4). Pattern #2 was positive for CD117, D2-40, PLAP and negative for CD30, cytokeratin AE1/AE3, and β-hCG, consistent with seminoma (Figure 5). Pattern #3 was positive for inhibin, cytokeratin AE1/AE3, and β-hCG and negative for CD30, CD117, PLAP, and D2-40, consistent with choriocarcinoma (Figure 6). Based on the morphologic and immunohistochemical findings, the diagnosis of mixed germ cell tumor with elements of seminoma, embryonal carcinoma, and choriocarcinoma was rendered, correlating with the patient's serum tumor marker levels.

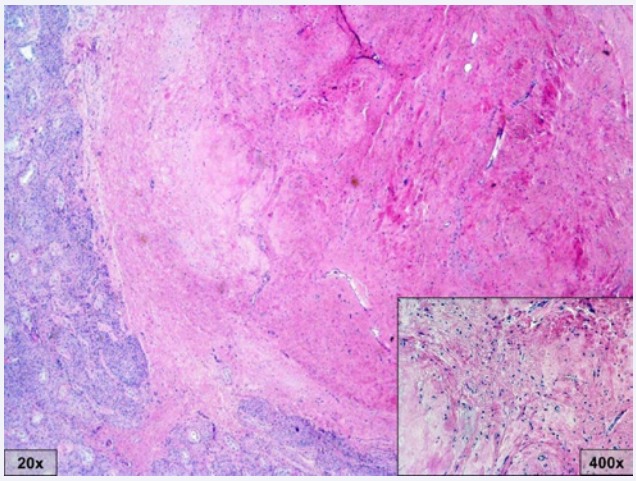

Figure 1 Hyalinized scar from right orchiectomy with ITGCNU and diffuse Leydig cell hyperplasia (inset shows higher magnification of scar).

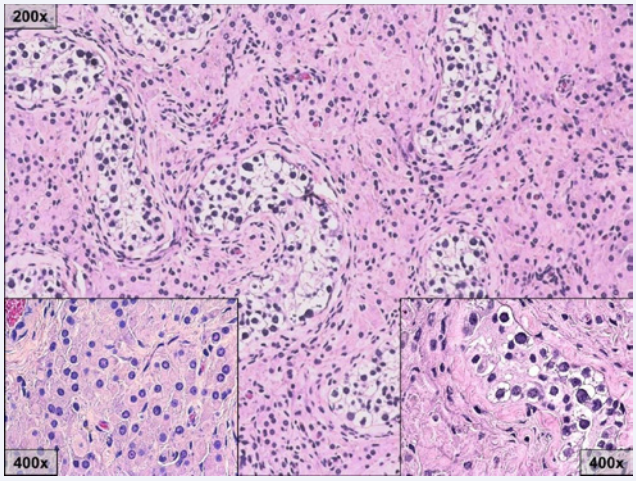

Figure 2 Seminiferous tubules with ITGCNU and intervening Leydig cell hyperplasia. Left inset: Leydig cell hyperplasia. Right inset: Seminiferous tubule with ITGCNU.

Given the patient's clinical presentation, a hyalinized testicular nodule with surrounding ITGCNU, and the presence of a metastatic mixed germ cell tumor diagnosed by cytology, the diagnosis of stage IIIC mixed germ cell tumor of testicular origin was made. The patient received six cycles of chemotherapy, although multiple brain metastases were identified over the ensuing months, accompanied by severe headaches and seizures. Approximately seven months after diagnosis, the patient was admitted in a comatose state with worsening cerebral edema due to progressive metastatic disease, and later expired.

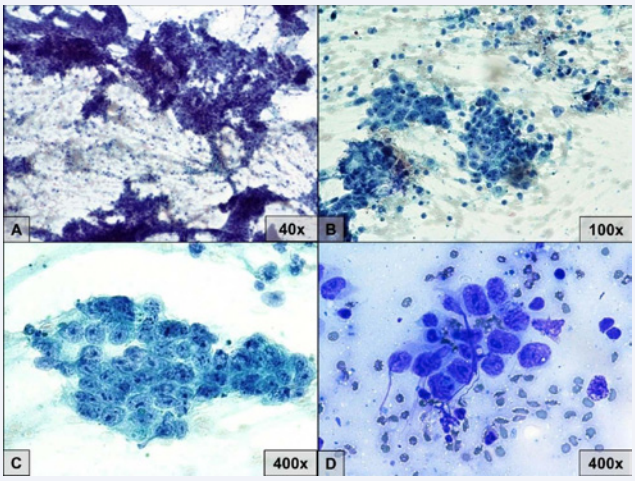

Figure 3 Left supraclavicular lymph node FNA. A: Cohesive sheets of tumor cells, Pap stain. B: Tumor cells with large, prominent nucleoli in a necrotic background, Pap stain. C. Tumor cells with granular chromatin and prominent nucleoli, Pap stain. D. Cluster of tumor cells with high nuclear-to-cytoplasmic ratio and delicate, easily crushed nuclei, modified Giemsa stain.

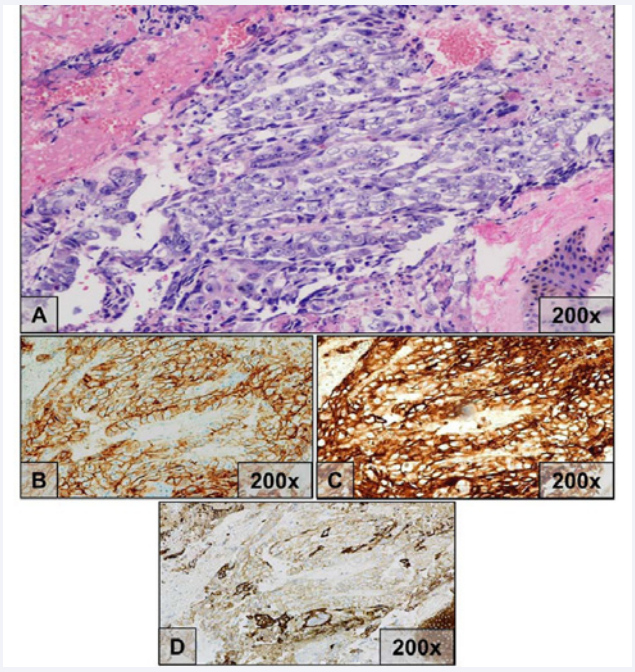

Figure 4 H&E-stained cell block of patient's FNA. A: Neoplastic cells with prominent nucleoli, vesicular chromatin and a scant amount of amphophilic cytoplasm. B: CD30 immunostain. C: PLAP immunostain. D: Cytokeratin AE1/AE3 immunostain.

DISCUSSION

Burned out testicular tumors are thought to arise from spontaneous regression of germ cell tumors that have metastasized to extra-gonadal sites in the body. Despite the overall lack of certainty as to whether or not these represent primary or metachronous tumors, [5-6] imaging findings, histopathologic characteristics of the scar associated with the burned out tumor (i.e. intratubular germ cell neoplasia, incomplete regression, etc.), and correlation with fine needle aspiration of suspected metastatic lesions generally indicate that these likely represent the primary tumor.

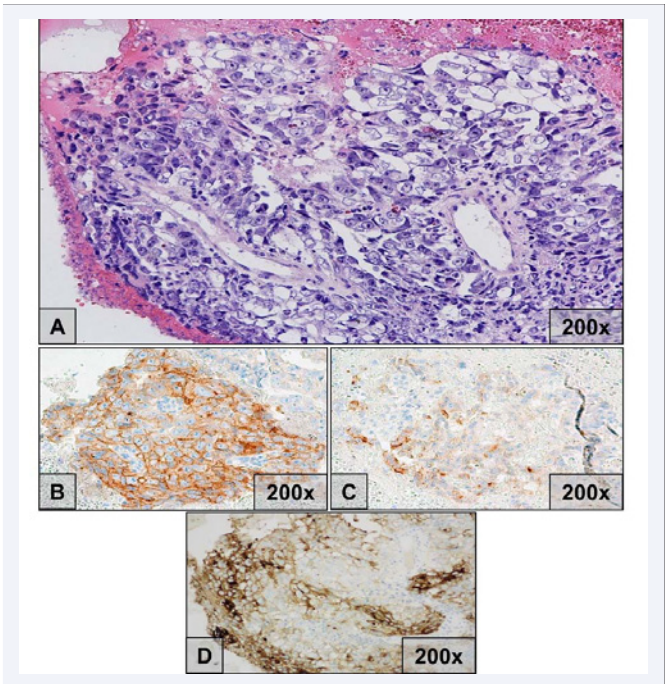

Figure 5 H&E-stained cell block of patient's FNA. A: Neoplastic cells with prominent nucleoli and cleared-out cytoplasm. B: CD117/c-kit immunostain. C: D2-40 immunostain. D: PLAP immunostain.

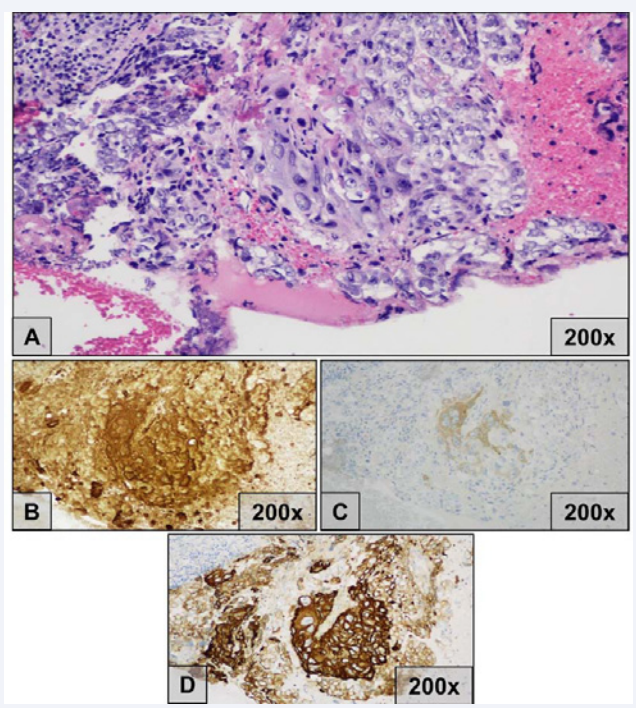

Figure 6 H&E-stained cell block of patient's FNA. A: Syncytiotrophoblast and cells with bizarre, hyperchromatic nuclei. B: β-hCG immunostain. C: Inhibin immunostain. D: Cytokeratin AE1/AE3 immunostain.

Prior reports have shown that most cases of burned out testicular tumors with concurrent metastases are due to pure seminoma, with choriocarcinoma, other mixed germ cell tumors, and pure embryonal carcinoma as relatively minor contributors [2,7-11]. Leydig cell hyperplasia has also been documented in non-regressed/incompletely regressed primary testicular germ cell tumors, estimated to occur in approximately 23%, according to one series [12]. Of these cases, the predominant tumor type is pure seminoma, although cases of Leydig cell hyperplasia arising in association with embryonal carcinoma and choriocarcinoma have been reported [16,17]. One series found that there was no difference in the incidence of Leydig cell hyperplasia in seminoma versus other pure or mixed germ cell tumors [18].

Less common yet is the presence of completely regressed burned-out germ cell tumor with adjacent Leydig cell hyperplasia. Although one case series reports that 43% of a series of 42 burned-out germ cell tumors are associated with Leydig cell hyperplasia, the authors do not make a clear quantitative distinction between Leydig cell hyperplasia occurring in completely regressed versus partially regressed tumors. They do, however, state that Leydig cell hyperplasia is more common in incompletely regressed tumors [18]. Two other case reports document burned-out testicular germ cell tumors with complete regression, adjacent Leydig cell hyperplasia, and concurrent metastatic pure seminoma [14,15]. Interestingly, in these two cases, a normal serum β-hCG was reported; the reasoning for this is unclear, although one potential explanation may be paracrine hormone effect.

The specific combination of completely burned out testicular germ cell tumor with diffuse Leydig cell hyperplasia and concurrent metastatic mixed germ cell tumor has not been previously described in the literature. Although various authors have explored various components of this constellation of findings, none have documented a fully regressed burned-out testicular tumor with associated Leydig cell hyperplasia and metastatic mixed germ cell tumor. Previous case reports documenting Leydig cell hyperplasia typically describe this phenomenon in tumors that are not burned out, or incompletely regressed. Additionally, previous reports have described burned out tumors in association with Leydig cell hyperplasia and metastatic germ cell tumor, but in these cases, all of the documented metastases were pure seminomas. The pathogenesis of this rare constellation of findings is not clearly understood, and can certainly confound the clinical picture. Thus, the critical role of cytologic diagnosis in the accurate characterization of tumors like this cannot be overemphasized.

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