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A Rare Case of β-hCG Production by a Solitary Fibrous Tumor of the Pleura

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 49
Final Diagnosis: Asystole with cardiac arrest
Symptoms: —
Medication: —
Clinical Procedure: Peripheral inserted central catheter • lung biopsy
Specialty: Pulmonology

Objective: Rare disease

Background: Solitary fibrous tumors are rare tumors of mesenchymal origins, most commonly seen arising from the pleural lining of the lungs. These are generally benign tumors, which in rare cases have been identified to be associated with multiple para-neoplastic syndromes.

Case Report: This is a case of a solitary fibrous tumor of the pleura in a 49 year old female which was found to be associated with elevated levels of serum beta human chorionic gonadotropin (β-hCG). Due to the lack of plausible causes for elevated β-hCG in the patient, immune-histochemical staining of the tumor specimen for β-hCG was obtained. This confirmed the patient's solitary fibrous tumor as the source of the β-hCG. The patient was also found to have a possible paraneoplastic syndrome with irregular menstruation and hot flushes from the secreted β-hCG.

Conclusions: This is the first reported case of solitary fibrous tumors of the pleura producing β-hCG. Multiple types of lung tumors have been associated with production of β-subunit of human chorionic gonadotropin. Production of β-hCG by these tumors has been associated with a poor prognosis. In this case, we find an aggressive form of solitary fibrous tumor associated with production of β-hCG and associated paraneoplastic syndrome secondary to the β-hCG. Further study is required to identify the frequency of this phenomenon and the implications of β-hCG production in the prognosis of the solitary fibrous tumors.

MeSH Keywords: Chorionic Gonadotropin, beta Subunit, Human • Paraneoplastic Syndromes • Solitary Fibrous Tumor, Pleural

Abbreviation: **SFTs** – solitary fibrous tumors; **SFTP** – solitary fibrous tumor of the pleura; **hCG** – human chorionic gonadotropin; **β-hCG** – β subunit of human chorionic gonadotropin; **α-hCG** – α subunit of human chorionic gonadotropin; **CT** – computed axial tomography; **N** – normal values; **FSH** – follicular stimulating hormone; **LH** – luteinizing hormone

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/891171

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Background

Solitary fibrous tumors (SFTs) are uncommon tumors, commonly seen arising from mesenchymal cells in the areolar tissue subjacent to the mesothelial line in the pleura [1,2]. These are generally benign tumors, but in about 13-37% of cases they are found to be malignant [1–3]. SFTs are known to produce paraneoplastic syndromes like hypertrophic pulmonary osteoarthropathy and refractory hypoglycemia secondary to the production of insulin-like growth factor 2 (IGF2) [1,2]. This paper presents a novel case of SFT associated with secretion of β-hCG(human chorionic gonadotropin beta subunit) with a possible paraneoplastic syndrome secondary to the secreted β-hCG.

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced by placental trophoblasts and is made up of two subunits α and β. The most common causes of elevated serum β-hCG are pregnancy and trophoblastic tumors [4]. However, some of the non-trophoblastic tumors have also been reported to be associated with either elevated serum β-hCG and/or positive for tissue β-hCG Immunochemistry staining and paraneoplastic syndrome secondary to β-hCG production [5].

Case Report

49-year-old female initially presented to the hospital with shortness of breath, cough and pleuritic chest pain worsening over 3–4 weeks. Her physical Exam was only remarkable for reduced air entry on the left side with unremarkable cardiovascular, neurologic, musculoskeletal exam and abdominal exam with no appreciable organomegaly. Patient's past medical history was significant for pyschosis treated with medication. On initial investigation, chest x-ray and chest CT scan showed left sided pleural effusion with a possible underlying mass which was considered to be arising from the lung or pleural cavity as seen in Figure 1. Chest x-ray obtained on a prior admission to psychiatry service 10 months ago was reported normal. The patient underwent thoracentesis and tube thoracostomy. The pleural fluid exam was consistent with exudative effusion and cell count showed predominantly atypical lymphocytes. After the draining of pleural effusion, repeat CT scan showed a well delineated mass in the lower left hemithorax, which was 12×8 cm in maximum diameter and heterogenous in density with multiple areas of tissue necrosis. Subsequent imaging of the mass did not show a major change increase in the size of the mass. Multiple tissue samples were obtained from different areas of the mass. All of which showed nonspecific fibrosis with islands of spindle-like cells and areas of necrosis. However, some cells revealed increased mitotic activity. Tissue samples underwent immunohistochemistry staining which came out to be positive for CD34, CD99, Vimentin,

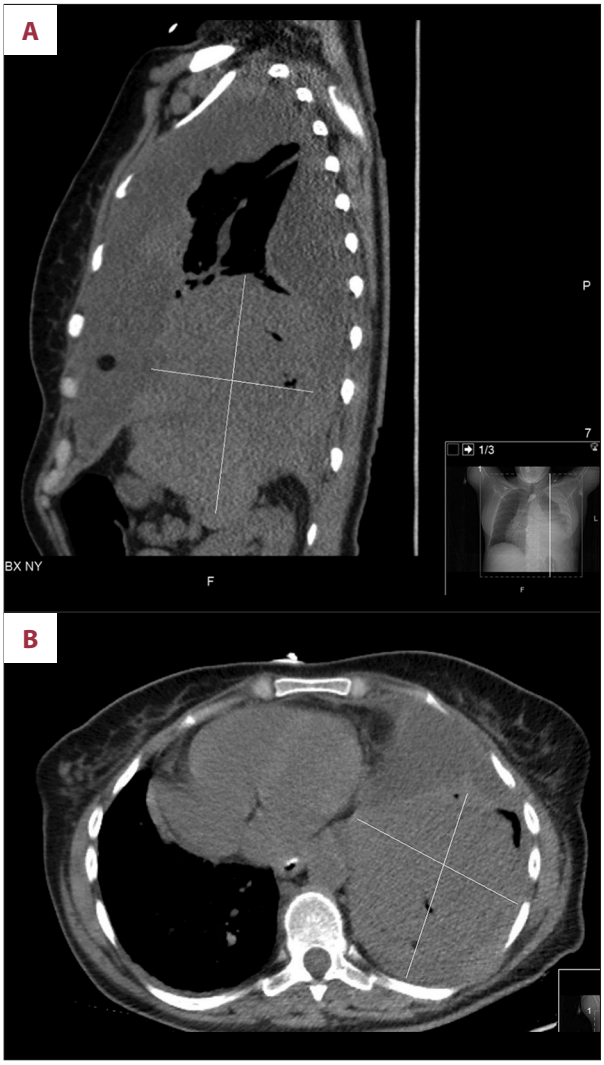

Figure 1. Sagittal and axial CT image of the left lung showing a mass arising from the left diaphragmatic pleura and growing towards the spleen, compressing the left lung and associated with pleural effusion. Also noticeable is the heterogeneity of the mass and air within the mass, which represents areas of necrosis and is a sign of a rapidly growing tumor.

bcl-2 and negative for p53, TTF1, CK5/6. The histopathologic and immunohistochemical findings were consistent with solitary fibrous tumor which was considered to be arising from the patient's left pleura.

Patient's initial work up showed urine positive for β-hCG, following which a serum quantitative β-hCG measurement was done, which was 1875 mIU/ml (normal: 5–50 mIU/ml). The patient reported that she had not been sexually active for many years and has been suffering from peri-menopausal symptoms of irregular vaginal bleeding and hot flushes for a couple of months. The patient denied any hormone replacement therapy

or oral contraceptive treatment. Subsequently, LH and FSH levels were obtained, which were undetectable. The patient had also been evaluated by CT scan of the abdomen and pelvis, which was negative for any lesions in the uterus, ovaries or adnexa. CT scan was also negative for any other intra-abdominal mass or lymphadenopathy. Over the course of hospitalization the serum β-hCG trended up from 1875 mIU/ml to 2174 mIU/ml. As there was no other explanation for the positive serum β-hCG the tissue samples were stained by β-hCG antibodies that showed the patient's tumor as the source of the β-hCG.

During hospitalization the patient was frequently found to be hypoglycemic even when she was not on any insulin or oral hypoglycemic medications. This was treated with intravenous dextrose 50% push on multiple occasions and subsequently was kept on intravenous maintenance fluid containing dextrose 5%. Even with intravenous dextrose treatment, patient's blood glucose was always found to be borderline low. The patient over the course of hospitalization got severely deconditioned and was not considered a surgical candidate for excision of her tumor. Eventually, the patient died during her hospitalization from cardiac arrest secondary to massive pulmonary embolism.

Discussion

Solitary Fibrous tumors of the pleura are rare primary malignancies of the pleura. SFTs have been reported in all age groups with an increased occurrence in sixth and seventh decade and no significant gender predilection [2,6,7]. The SFTs are commonly benign but can also be malignant with recurrenc after excision [2,8]. Different case series in literature have reported different frequency of malignancy in SFTs which range from 13 to 37% [3]. The presenting symptoms of SFTs could be thoracic like cough, pleuritic chest pain and dyspnea or in less commonly extrathoracic like hypoglycemia also known as "Doege-Potter Syndrome" and hypertrophic pulmonary osteoarthropathy known as "Pierre-Marrie-Bamberger syndrome" [2,8]. These thoracic and extrathoracic symptoms (paraneoplastic syndrome) of SFTs are more commonly associated with large SFTs and typically resolve after excision of the tumor. Larger tumors are also considered to be more aggressive with the malignant SFTs being larger than the bening SFTs in general [9]. The criteria of differentiating malignant and aggressive tumors from benign is currently based on histopathologic evaluation of the tumor. The malignant tumors are identified by: (1) great cellularity; (2) infiltrative growth pattern; (3) nuclear variation; (4) prominent nucleoli; (5) more than 4 mitoses per 10 high-power fields; (6) necrosis [2,7]. However, this differentiation possible only after the resection of the tumor as the sensitivity of CT guided biopsy is very low [9,10]. It is also extremely difficult to distinguish the malignant from benign tumors and establish aggressiveness of the tumors on radiologic evaluation. However, Rosado-De-chirstino et al. proposed that the malignant tumors can be identified by their increased heterogeneity which is due to myxoid degeneration, necrosis and cystic changes along with associated pleural effusions [11]. Immunohistochemistry is very important in identifying and confirming SFTs and differentiating them from mesotheliomas and other connective tissue neoplasm of the thorax. Most importantly, STFs are positive for vimentin and negative for keratin proving their mesenchymal origin. They are also positive for CD34, CD99, bcl-2 [2,9,12]. In summary, due to their rarity and great variability of histopathologic features and the clinical behavior, SFTs remain a diagnostic and treatment enigma [3,11,12].

In the presented case, the patient most likely had an aggressive form of SFTs. This can be deduced firstly, from rapid growth of the tumor over couple of months as a chest X-ray done 10 months back was reported negative. Secondly the CT scan showing heterogeneous mass with areas of necrosis identified as areas of air in the mass and associated pleural effusion as seen in Figure 1. Thirdly, histopathology showing areas of high cellularity of spindle cells and increased mitoticaly active cells. Finally, the tumor was associated with paraneoplastic syndrome of hypoglycemia since there was no other explanation for the frequent drop in patients' blood sugar levels requiring intravenous dextrose replacement. The most unique feature of this case was the production of β-hCG by the tumor and the possibility of associated paraneoplastic syndrome induced by the secreted β-hCG producing irregular menstruation and hot flushes seen in peri-menopausal stage. This is a first reported case to the knowledge of the authors in which an SFT was found to be associated with secretion of β-hCG which produced systemic effects. Though the patient's irregular menstruation and peri-menopausal symptoms can be explained by natural progression to menopause, the low FSH and LH levels and the temporal association of the onset of the peri-menopausal symptom to the growth of the tumor support the paraneoplastic effect of the β-hCG produced by the tumor itself.

Human chorionic gonadotropin (hCG) is a glycoprotein hormone generally produced by placental trophoblasts. hCG belongs to glycoprotein hormone family, which also includes luteinizing hormone(LH), follicle-stimulating hormone(FSH), and thyroid-stimulating hormone(TSH). All of these hormones are composed of α and β subunits. The α subunit is common to all of glycoprotein hormones, but β subunit is specific for each one and is responsible for their biologic activity [4,5]. The most common cause of elevated β-hCG in the serum is pregnancy making it the most sensitive test for pregnancy diagnosis and follow up the disorders related to pregnancy. The second most common cause for elevated hCG is trophoblastic tumors of placental

Table 1. Non-trophoblastic tumors with serum β-hCG positivity and/or tissue positivity.

Type of tumor	Serum β-hCG positivity	Tissue β-hCG positivity*
Lung carcinoma	+	+
Osteosarcoma	+	
Pancreatic	+	+
Cervix carcinoma	+	
Leiomyosarcoma	+	
Squamous cell carcinoma of maxilla	+	
Colorectal cancers	+	+
Hepatocellular carcinoma	+	
Eccrine adenocarcinoma of vulva	+	
Meningioma	+	
Bladder Cancer	+	+
Renal Cell Cancer		+
Gastric Carcinoma	+	+
Breast Cancer		+
Melanoma		+

* Tissue β-hCG positivity identified on immunohistochemical staining of the tissue specimen with.

and germ cell origin [5,13]. Some of the non-trophoblastic tumors like gastrointestinal cancers, lung cancers, urinary tract cancers etc are also known to produce hCG, which in most cases is only the β subunit of hCG [13]. In some cases with non-trophoblastic tumors only the tissue showed positivity for β-hCG on immunohistochemical stain with no detectable serum or urine β-hCG. This has been summarized in Table 1 [5,13]. The presence of serum β-hCG in non-trophoblastic tumors especially gastrointestinal cancers, urinary tract cancer and to some extent in lung cancers has a prognostic value and higher levels of β-hCG are associate with worse prognosis [5,13,14]. This could be attributed to the anti-apoptotic effect of the β-hCG on the cancer cells [5]. β-hCG production in some of these non-trophoblastic malignancies was associated with paraneoplastic syndromes like gynecomastia in men, precocious puberty in children and amenorrhea and dysfunctional uterine bleeding in women [15–19]. Unfortunately, as the frequency of elevated serum β-hCG in non-trophoblastic tumors is only about 10–30% it cannot be used as a tumor marker [20,21].

From all this it can be understood that due to the versatility and variability of the SFTs it is very difficult to identify the aggressive forms of tumors from the indolent ones without complete resection and histopathologic examination of the tissue specimen. However, the association of β-hCG production by SFTs could provide an alternative prognostic marker preoperatively to identify aggressive SFTs along with other radiologic and histopathologic features. But more research is required to test this hypothesis.

Conclusions

This article reports a novel case of solitary fibrous tumor of the pleura secreting β-hCG and producing paraneoplastic syndrome secondary to the β-hCG. More testing and research is needed to determine the frequency of this phenomenon and also if any other hormones can be produced by the highly versatile SFTs. This would help in addressing the prognostic implications of association of β-hCG productions by the SFTs.

Conflict of interest

All the authors of the article state that there have been no conflicts of interest among the authors.

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References:

1. Robinson L: Solitary Fibrous Tumor of the Pleura. Cancer Control, 2006; 13(4): 264–69
2. de Perrot M, Fischer S, Brundler M et al: Solitary fibrous tumors of the pleura. Ann Thorac Surg, 2002; 74(74): 285–93
3. Ardissone F: Thracic malignant solitary fibrous tumors: Prognostic factors and long-term survival. J Thorac Dis, 2011; 3: 84–85
4. Cole LA: Use of hCG tests for evaluating trophoblastic diseases: choosing an appropriate hCG assay, false detection of hCG, unexplained elevated hCG, and quiescent trophoblastic disease. 2 ed. London: Chapman and Hall, 2002
5. Stenman U, Alfthan H, Hotakainen K: Human chorionic gonadotropin in cancer. Clin Biochem, 2004; 37(7): 549–61
6. Briselli M, Mark EJ, Dickersin GR: Solitary fibrous tumors of the pleura: eight new cases and review of 360 cases in the literature. Cancer, 1981; 47(11): 2678–89
7. England DM, Hochholzer L, McCarthy MJ: Localized benign and malignant fibrous tumors of the pleura. A clinopathologic review of 223 cases. Am J Surg Pathol, 1989; 13(8): 640–58
8. Sung SH, Chang JW, Kim J et al: Solitary fibrous tumors of the pleura: surgical outcomes and clinical course. Ann Thorac Surg, 2005; 79(1): 303–7

9. Cardillo G, Carbone L, Carleo F et al: Solitary fibrous tumors of the pleura: An analysis of 110 patients treated in single institution. Ann Thorac Surg, 2009; 88: 1632–37
10. Li Z, Wang J, Zhu Q et al: Huge solitary fibrous tumor of the pleura with hypoglycemia and hypokalemia: a case report. Ann Thorac Cadiovasc Surg, 2014; 20(2): 165–68
11. Rosado-de-Christenson ML, Abbott GF, McAdams HP et al: From the Archives of the AFIP: Localized Fibrous Tumors of the Pleura. Radiographics, 2003; 23(3): 759–83
12. Magdeleinat P, Alifano M, Petino A et al: Solitary fibrous tumor of the pleura: clinical characteristics,surgical treatment and outcome. Eur J Cardiothorac Surg, 2002; 21(6): 1087–93
13. Demirtas E, Krishnamurthy S, Tuladi T: Elevated serum beta-human chorionic gonadotropin in nonpregnant conditions. Obstet Gynecol Surv, 2007; 62(10): 675–79, quiz 691
14. Dirnhofer S, Freund M, Rogatsch H et al: Selective expression of trophoblastic hormones by lung carcinoma: neurendocrine tumors exclusively produce human chorionic gonadotropin alpha-subunit (hCGalpha). Hum Pathol, 2000; 31(8): 966–72
15. Yaturu S, Harrara E, Nopajaroonsri C et al: Gynecomastia attributable to human chorionic gonadotropin-secreting giant cell carcinoma of lung. Endocr Pract, 2003; 9(3): 233–35
16. Rivarola, Belgorosky A, Mendilaharzu H et al: Precocious puberty in children with tumours of the suprasellar and pineal areas: organic central precocious puberty. Acta Paediatr, 2001; 90(7): 751–56
17. Yoshida J, Nagai K, Nishimura M et al: Secretion of hCG/βhCG by squamous cell carcinoma of the lung in a 31-year-old female smoker. Jpn J Clin Oncol, 2000; 30(3): 163–66
18. Sagaster P, Zojer N,Dekan G, Ludwig H: A paraneoplastic syndrome mimicking extrauterine pregnancy. Ann Oncol, 2002; 13(1): 170–72
19. Okutur K, Hasbal B, Aydin K et al: Pleopmorphic carcinoma of the lung with high serum beta-human chorionic gondaotropin level and gynecomastia. J Korean Med Sci, 2010; 25(12): 1805–8
20. Bagshawe KD: Choriocarcinoma; A model for tumour markers. Acta Oncol, 1992; 31(1): 99–106
21. Jacobs EL, Haskell CM: Clinical use of tumor markers in oncology. Curr Probl Cancer 1991; 15(6): 299–360