Case Report

Sudden Suffocation with Cancer of Unknown Primary: A Case Report and Review of Diagnostic Approach

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Abstract

A case of a 31-year-old woman with sudden respiratory distress is presented. Preliminary evaluations and imaging studies did not reveal the underlying cause. Workup during hospital stay showed advanced metastatic cancer of unknown primary origin. This is an unusual presentation of cancer of an unknown primary involving the thyroid with sudden suffocation. It suggests that malignancies involving the thyroid gland should be considered in patients with abrupt onset of respiratory distress. Also, this case shows the application of fine needle aspiration in diffuse thyroid enlargements mimicking thyroiditis without nodules. Diagnostic approach to cancer of unknown primary origin (CUP) is reviewed in further detail.

Keywords: Anaplastic, cancer, metastatic, CUP, suffocation

Cite the article as: Tehrani OS, Ahmad O, Vypritskaya E, Chen E, Hasan S. Sudden Suffocation with Cancer of Unknown Primary: A Case Report and Review of Diagnostic Approach. *Arch Iran Med*. 2012; **15(10):** 652 – 654.

Introduction

Cancer of unknown primary origin (CUP) accounts for approximately 2% to 6% of all cancers.[1–3] Most patients present with an unusual mass, lymphadenopathy or effusions and have constitutional symptoms that include weakness, fatigue, and weight loss. CUP is mostly seen in older adults (6th and 7th decades of life).[1–3] Respiratory distress in cancer patients is usually seen in those with advanced disease that compromises the cardio-pulmonary system, airways, or central nervous system. Acute respiratory failure secondary to thyroid metastasis is very rare. A literature review showed only two such cases secondary to renal cell carcinoma, two secondary to colon cancer and one secondary to meningioma. Here, we discuss the case of a 31-year-old female who presented with sudden suffocation with CUP.

Case Report

A 31-year-old female was transferred to the emergency department by emergency medical services (EMS) due to sudden respiratory distress. The patient woke up at 4 AM with complaints of difficulty breathing. Soon, she became unresponsive and needed intubation. EMS reported a difficult and traumatic intubation. Past medical history was not significant, and no medical record was available. Physical exam did not reveal any abnormalities, except for the lack of significant breast tissues, in a thin, intubated, unresponsive female.

Initial laboratory studies did not show any significant abnormalities, except for significant lactemia without acidosis, mild normocytic anemia, leukocytosis without bandemia, hypokalemia and mild renal failure. Liver function tests, chest rontgenogram (CXR) and urinalysis did not show any abnormalities. The patient was admitted to the medical intensive care unit. Computed tomography (CT scan) of the head and electro-encephalogram (EEG) were compatible with anoxic brain injury. Urine drug screen, serum iron, ferritin, transferrin, folic acid and vitamin B-12 levels were all normal. CT scan of the neck showed reactive lymphadenopathy and thyroid swelling secondary to traumatic injury. Thyroid ultrasound showed diffuse heterogeneous thyroid enlargement compatible with thyroiditis. Thyroid function tests were normal. After stabilization, the patient was diagnosed as being in a vegetative state. Her family could not accept her dramatic prognosis and wanted to do "everything possible". Due to ventilator dependence, the patient received a tracheostomy and percutaneous gastrostomy for long-term care.

During prolonged hospital stay (more than 120 days), the patient developed several episodes of Clostridium difficile-negative diarrhea, nonspecific skin rash, pneumonia, and upper extremity deep vein thrombosis (DVT). The laboratory tests to study the cause of these reactions showed an elevated erythrocyte sedimentation rate and elevated C-reactive protein. Skin biopsy of the rash showed non-specific perivascular lymphocytic infiltrate, hypergranulosis and parakeratosis. Anti-nuclear antibody test was negative, and complement and immunoglobulin-E levels were normal. One of the follow up CXRs showed a lytic lesion in the right humerus head and a new hilar lesion. CT of the chest, abdomen and pelvis showed bone metastases, enlarged thyroid causing obstruction of the airway above the tracheostomy, a hilar mass, and pulmonary nodules (Figures 1a and b). Technetium (99mTc) medronic acidbone scan revealed involvement of the axial bones, skull and humerus (Figure 2). To find the primary origin, CA125 and LDH were tested. Both had increased levels. Pelvic CT and ultrasound however did not show any abnormalities in the uterus, adnexa or ovaries.

Multiple prolonged sessions with the family revealed that patient had visited another facility for neck and back pain. Documents from the other medical facility showed visits for pain in

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Accepted for publication: 14 February 2012

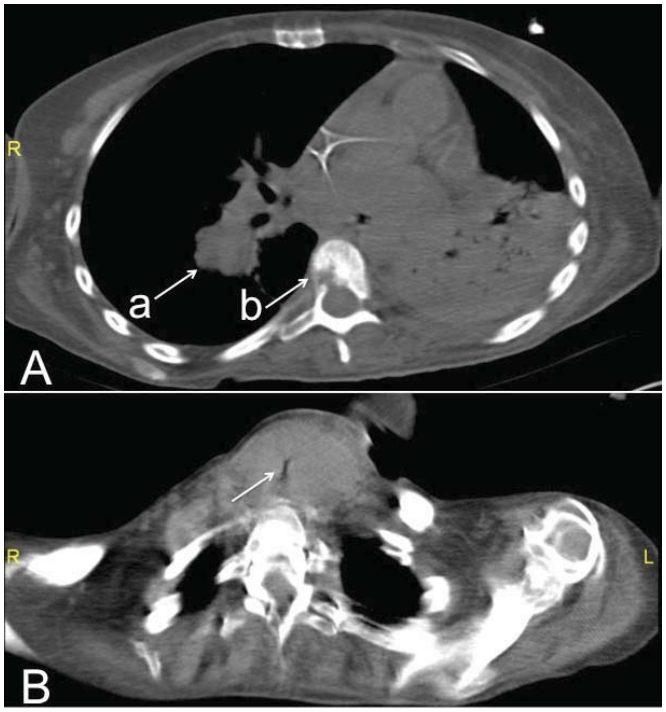

Figure 1. A) CT of the chest, showing a hilar mass **(a)** and metastatic bony lesion **(b).** Patient also has remnants of pneumonia on the left side. **B)** Enlarged thyroid closes the trachea above tracheostomy (arrow).

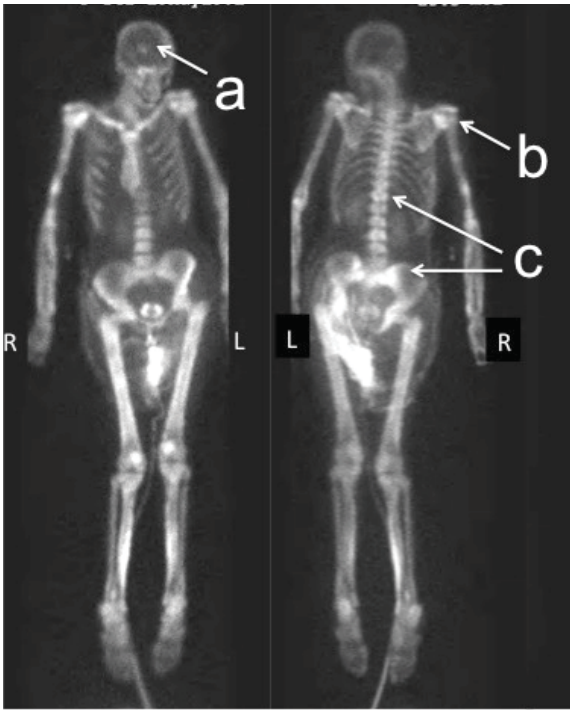

Figure 2. Bone-scan showing increased uptake in the skull **(a)**, right humerus **(b),** and axial bones **(c)**.

the back and neck, and treatment for thyroiditis. Also, thyroid ultrasound had shown a lesion suspicious for thyroiditis. With such history, despite a lack of nodules in the thyroid, fine needle aspiration (FNA) was performed. Immunohistochemistry showed poorly differentiated malignant cells positive for pancytokeratin, cytokeratin 7 (CK7), TTF-1, and weakly positive for EMA. Cells were negative for thyroglobulin, CK20, CD45, CD20, CD138, kappa and lambda light chains, CA125, and WT-1. Pathologic diagnosis was compatible with poorly differentiated carcinoma, and recommended clinical correlation for the definitive diagnosis. Additional immunoassay was done for chromogranin and synaptophysin to rule out poorly differentiated medullary thyroid cancer, which did not support that diagnosis.

Discussion

CUP is composed of different types of cancers. The median age of patients is between 59 and 66 years, with equal distribution between men and women.[1–3] They are diagnosed either as an incidental finding on imaging (incidentaloma), or during work up for a mass, effusion or an unknown lesion. Many of these patients go through extensive work up to find the original tumor, which may help with therapeutic options. However, the cost effectiveness of an extensive work up has been questioned. Most commonly used diagnostic tests are fecal occult blood, blood cell count, urinalysis, liver and renal function tests and prostate specific antigen (PSA) in men.[3–5] CXR is the most widely used imaging technique. CT of the abdomen/pelvis and mammography in women are also used.[3–7] When a primary site is favored, tumor markers have been used. The most widely used are alpha-fetoprotein (AFP) and beta-hCG for germ cells, CA125 for ovarian, CA27.29 for breast, CA19.9 for the pancreas, and carcino-embryonic antigen (CEA) for colon cancer.[5,8] Depending on the clinical situation, upper gastro-duodenoscopy, colonoscopy, and in case of suspected head and neck cancers, pan-endoscopy of the upper aerodigestive pathways or diagnostic tonsillectomy may be considered.[9] Clinical judgment and the risks and benefits should be considered before extensive investigation. Light microscopy and immunohistochemistry are extensively used to define the type of cancer and locate its origin. The immunohistochemistry approach is usually started with CK7 and 20.[10] CK7 and 20 are positive in cells that are from an epithelial origin, leukocyte common antigen (LCA) is positive in lymphoma, S-100 in melanoma, thyroid transcription factor 1 (TTF-1) in lung and thyroid, prostate specific antigen (PSA) in the prostate, hCG in germ cells, AFP in germ-cell and hepatomas, estrogen receptor (ER), progesterone receptor (PR) and Her-2 in breast cancer.[8] Adenocarcinoma is responsible for 60%–70% of CUPs and carries a poor prognosis.[4] It is noteworthy that even with full work up, the origin is identified in less than 30% of cases.

In the present case, CT scan showed extensive bony lesions, a mass in the hilar region and enlarged thyroid blocking the trachea above the tracheostomy. Immunohistochemistry CK7 was positive and CK20 was negative, which was compatible with a lung, breast, thyroid, endometrium, cervix, or cholangio-pancreatic origin; however, there were no lesions detectable in the breast, pelvis, hepatic, or pancreatic regions.[10] This made the thyroid and lung as the primary suspected organs of origin, both of which were involved in the CT scan. TTF-1 is positive in both and EMA is mainly from epithelial secretory tumors.[11] Interestingly, this patient had elevated CA125 in the serum, but the tumor did not stain positive, and CT scan and pelvic ultrasound did not show any tubo-adnexal lesions, which showed the lack of specificity and inefficiency of this marker in CUP.

Although clinically rare, there are reports of metastasis to the thyroid gland. FNA is well established in approaching a single thyroid nodule or mass. However, in this case, FNA from the

thyroid itself revealed the pathology, and should be considered in similar cases in the future. The prevalence of metastasis to the thyroid gland varies in autopsies from 1.25% in unselected patients to 24% in those with widespread malignancies.[12] Most frequent metastases are from breast, lung, and to a less extent renal cancer and melanoma. Among lung cancers, adenocarcinoma is the most common type.[12] Within primary thyroid cancers, anaplastic thyroid cancer comprises only 2%–3% of tumors, and is the most aggressive type. Highly resistant to chemotherapy and radiation, the best chance for treatment is when it is resectable.[13] Most patients with advanced disease die of invasion of the upper airways despite tracheostomy. The median age is 60 to 70 years old. Differential diagnosis of this cancer includes poorly differentiated medullary carcinoma and lymphomas. Proper diagnosis usually needs special immunohistochemistry staining. Histologically, the present case was not distinguishable from poorly differentiated lung cancer, and differential diagnoses included poorly differentiated medullary thyroid cancer and lymphoma. Lymphoma was excluded by the initial immunohistochemistry. Medullary thyroid cancer, however, needed special staining. A quarter of medullary thyroid cancers are due to RET proto-oncogene mutation and are hereditary. Unlike other types of thyroid cancer, which occur later in life, these cancers occur in the second and third decades of life. Relatives of patients should be checked for the RET mutation.[14] In the present case, the patient was a 31-year-old with two kids; exclusion of medullary thyroid cancer was necessary. Had the results been positive, the patient's first-degree relatives would have needed genetic counseling and RET mutation analysis.

Thyroid malignancies should be considered in the differential diagnosis of young patients who present with abrupt onset of respiratory distress due to upper airway obstruction. Also, this case shows the importance of FNA as the method of choice for diagnosing thyroid malignancies, even in diffuse thyroid enlargements that mimic thyroiditis.

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