Long-term Survival of Large Cell Neuroendocrine Lung Carcinoma with Bony Metastases: A Case of Immunoprotectivity?

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) is a rare, highly malignant neoplasm with a dismal prognosis. The majority of patients will present with metastatic disease with a median overall survival of 6 months for this group. We present a case of metastatic LCNEC to the pelvis with a 10 year survival after tumor resection, radiation, and chemotherapy. We hypothesize that his survival and cancer stability are the result of an immune response brought on by a sub-acute turned chronic wound infection. After adjuvant therapies, he remained disease-free for 4 years until a recurrence in his lung and new metastases to his spine, which were treated with radiation. He remained disease-free for an additional 6 years, during which time, he discovered to have a chronic infection of his right femur with Staphylococcus lugdunensis. To the best of our knowledge, this is the first long-term survivor of LCNEC with bony metastases.

Keywords: Lung carcinoma; Bone metastasis; Immunoprotection; Infection; Survival

Case Report

The patient, a fifty-five year old male, initially presented in 2003 with complaints of several months of worsening activity-related right hip pain that improved with rest. Initial plain radiographs of the hip and pelvis were read as negative and the patient was treated for presumed muscle strain. When symptoms persistently worsened, the patient presented to the emergency department in March of 2003 and was noted at that time to have an abnormality on plain film and CT scan. The patient’s social history was remarkable for 50-100 pack per year smoking history, 2 drinks of alcohol daily, and employment as a life-long laborer. The patient had no significant family history of cancer but a significant family history of coronary artery disease and diabetes.

Plain radiographs of the pelvis obtained in the emergency department revealed a destructive lytic lesion involving the right hemipelvis and acetabulum. Further work-up included serum laboratory tests, a bone scan, and chest, abdomen and pelvis CT. An elevated serum alkaline phosphatase at 149 U/L was the only significantly abnormal serum laboratory value. The bone scan revealed sites of abnormal uptake at the 5th rib, left scapula, right sacrum, left proximal femur and the right hemipelvis, which were read as concerning for metastatic disease. The CT scan revealed a 2.5 cm by 1.5 cm lung mass. His ECOG score was determined to 2 due to decreased mobility from right hip pain.

In April of 2003, the patient underwent a non-diagnostic needle biopsy of the lung mass. An image-guided needle biopsy of the pelvis was then performed. Findings revealed adenocarcinoma with immunostaining positive for cytokeratin-7, negative for cytokeratin-20 and positive for TTF-1 and were deemed consistent with metastatic non-small cell lung cancer. In May of 2003, the patient was taking to the operating room for surgical stabilization and treatment of the pelvic lesion, which included a modified Harrington pelvic and acetabular reconstruction (Figure 1). The patient received 10 liters of crystalloid and had an estimated blood loss of 4500 milliliters for the approximate 6 hour surgery. Specimen from this procedure stained positive for synaptophysin and chromogranin. Final pathologic diagnosis was metastatic large cell neuroendocrine carcinoma (Figure 2).

The patient’s post-operative course was complicated by persistent wound drainage with an 1 cm wound dehiscence at the inferior aspect of the incision. He also developed post-operative pneumonia requiring a readmission and IV antibiotics 3 weeks after his initial surgery. The wound drainage continued for approximately 3 months and then closed by secondary intent. The patient was cleared at that point for radiation and chemotherapy. He underwent an 5 day course of fractionated external beam radiation therapy with dosing of 40 Gy to the right femur and hemipelvis. He was also started on monthly intravenous zolandrocinic acid (4 mg) and on a carboplatinin and taxol based chemotherapy in September of 2003 for 4 full cycles. He received no further chemotherapy after these initial 4 cycles.

The patient had a remarkable course from this point forward as he returned to work full time and had minimal disease progression over

Figure 1: One year postoperative radiographs of surgical stabilization and reconstruction of pelvic metastatic Large Cell Neuroendocrine Carcinoma (LCNEC) including a cemented long-stem total hip arthroplasty.

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the next several years. He reported occasional right hip and leg pain, but his functional status was unaffected. He discontinued the zolendronic acid treatment in 2005. In August of 2007 (4 years after diagnosis) he received 55 Gy of radiation to the right upper lobe lung mass because there was evidence of growth on follow-up chest CTs. He also developed intermittent right leg pain that is manageable with anti-inflammatories daily). As of August 2015, the patient remains stable with reports of pulmonary symptoms and <20% present with cough or hemoptysis [2,5].

On a molecular level, LCNEC has a high cellular proliferative rate, highly positive staining for p21<sup>wti/cip1</sup>, increased microvessel density, and both regulation of apoptosis and angiogenesis are intimately involved in this disease process. Patients who had greater than 3.5% staining for p21<sup>wti/cip1</sup> and a microvessel density greater than 3.0% have been found to have a less favorable prognosis for survival [6]. LCNEC cytomorphologically reveals basaloïd palisading, organoid nesting rosettes with necrosis [7]. As compared with other large cell carcinomas, LCNEC has high expression rates of Bcl-2 and Ki-67. The expression of Ki-67, p53, and Rb distinguish LCNEC from SCC or other carcinoid tumors while the expression of K-ras-w and C-raf-1 are genetically similar to SCC. This molecular profile may be responsible for the high local disease recurrence rate of these tumors found to be 52.4% [8].
LCNEC has a poor prognosis with a reported five year survival rate of 15–57% [9]. In a study by Veronesi et al, the overall five year survival rate for stage I was 52%, stage II 59%, stage III 20%. The rate of distant metastases is 65% with documented greatest propensity to metastasize to brain, liver, bone, and adrenal gland in descending order respectively [10,11]. Patients with stage IV LCNEC have a life expectancy of approximately six months [12].

Management of LCNEC is controversial [13]. Current treatment for LCNEC is a hybrid of the regimen for NSCLC and SCLC. All non-metastatic stages of LCNEC undergo surgical resection, like NSCLC, and receive adjuvant chemotherapy as per a SCLC regimen [14]. Additional adjuvant treatment options are currently under investigation. A study by Sun et al revealed a response rate of LCNEC to a platinum-based chemotherapy was 60% as compared to 11% when treated with a non-platinum based chemotherapy. A cisplatin-based chemotherapy to treat LCNEC has been reported to have comparable response rates to that of small-cell carcinomas. Unfortunately, LCNEC differs from other lung cancers as it has been shown to have higher rates of recurrent lung cancer/relapse rates (52.4%) as well as higher resistance to the available treatment options [15].

There have been a few cases reported in the literature of long-term disease free survivors with metastatic LCNEC. In one case report, a patient diagnosed with LCNEC and brain metastases relapse free for two years due to a novel therapeutic approach [16]. An abysmal prognosis was reported in a case study of a patient with LCNEC with a multitude of locations including the lumbar spine [17]. There are very few documented case reports of LCNEC with bony metastasis and we found no case reports in the literature of stage IV LCNEC and distant metastasis with survival greater than 2 years; this highlights the exceptional nature of our case.

We believe this patient’s long-term survival and cancer stability relates to his chronic infection. Both infections and cellular neoplasms elicit activation of the immune system. This activation varies to address the responsible pathogens through the activation of the general innate system and specific adaptive system. During an infection, the inflammatory response is usually immediate and characterized by the presence of phagocytic cells and other host derived protective factors to the site of infection [18]. By contrast, some neoplasms are able to evade the immune system early on during their development and delay recognition and attack by the host immune system by suppressing the inflammatory response [19]. It is not until the later stages when a stable tumor microenvironment has been established that these neoplasms cause an inflammatory response to be recognized by the host immune system to produce the robust immune response seen in the early stages of infections in the immunocompetent host [20]. After the tumor becomes established in the host organism with the expression of various growth and angiogenic critical factors, inflammation is recognized and the immune system initiates a cascade of events to try to respond to the tumor microenvironment.

This suggests that the ability of some neoplastic cells to delay an inflammatory response is protective and allows it to grow malignant and initially evade the host immune response compared to the initial immediate immune response seen during an acute infection [18]. Current research focuses on this possible relationship between the immune response and cancer through the use of immunotherapy agents as possible effective treatment options in the management of cancer. Immunotherapy centers on the T cell mediated response of the adaptive immune system that is often suppressed by protective factors produced by neoplastic cells during their establishment of the tumor microenvironment. This role of the immune system can be elucidated by further investigating the role of the immune response through chronic infections seen in the setting of cancer. While there are no current cases to better examine this relationship, we can look at the role of immunotherapy as a rapidly emerging alternative in cancer treatment.

Cancer immunotherapy focuses on magnifying the ability of the host’s immune system to respond to neoplastic cells through T cell recognition and activation. Antigen presenting cells present various foreign peptides to their respective major histocompatibility complex that will connect with a T cell for activation and stimulate a generation and expansion of a specific T cell repertoire. This process requires various checkpoints and cancer cells are able to evade these checkpoints by acting on cytotoxic T-lymphocyte antigen-4 (CTLA-4) in various cancers including lung cancer [22]. The successful use of immunotherapy in the treatment of cancer patients show that the immune system is capable of eliciting a response to neoplastic cells if it can identify the cells as foreign and generate specifically differentiated T-cells to target those cells. The ability to manipulate and activate the immune system to recognize these foreign cells merits further research. Studying cancer in the setting of a chronic infection provides this opportunity.

After an extensive review of literature, we found no cases where a chronic infection has provided an immunoprotective effect in the setting of cancer. This is possibly due to the reality that opportunistic infections are a significant part of the morbidity and mortality of cancer patients. There are several historical and recent reports suggesting a link between improved survival and local infection in patients treated with surgery for sarcomas [23]. However, there have also been several more recent reports of retrospective data refuting this claim and it appears that conclusive data is still lacking on this question [24]. The possibility that a local infection may incite an immune response that in turn suppresses tumor cell activity is an enticing prospect. Studying cancer in the setting of an infection poses a significant challenge; a potential area of focus are patients with chronic infections early on in their cancer diagnosis with particular attention for those who are able to recover from multiple relapses of infections. Our case is one such opportunity to explore the possible protective role of a chronic infection in the setting of cancer over a 12-year period and to continue the discussion of the immune system’s role in cancer.

References


