Case Report

Patient with synchronous low grade leiomyosarcoma of the thigh, primary pancreatic neuroendocrine tumor, and lung metastases: Why biopsy of metastases should be the standard

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Introduction

A group of well-defined adult neuroendocrine tumors (NETs) have variable but most often indolent biologic behavior and characteristic well-differentiated histologic features (1). The majority arise in the gastrointestinal (GI) tract (although carcinoid tumors may also arise in the lung and ovary), and collectively, they are referred to as gastroenteropancreatic NETs. They include carcinoid tumors, pancreatic islet cell tumors (gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma), paragangliomas, pheochromocytomas, and medullary thyroid carcinomas.

Neuroendocrine tumors comprise only 0.5% of all malignancies. The incidence is approximately 2/100,000. The main primary sites are the gastrointestinal tract (62-67%) and the lung (22-27%), and 12-22% present with metastatic disease. The 5-year survival is mainly associated with stage: 93% in local disease, 74% in regional disease and 19% in metastatic disease (2).

Treatment of localized disease is surgical resection if possible. In metastatic or advanced disease, locoregional treatments, as well as radionuclide therapies, may be considered. Additionally, in selected cases resection of the primary and metastatic tumors may impact outcome favorably. Although it has no significant effect on tumor growth, biotherapy with somatostatin analogs and/or interferon-α is recommended for either well-differentiated or functioning tumors for symptomatic relief. On the other hand, chemotherapy may be effective in the treatment of those tumors characterized by a poor differentiation grade and a high proliferation rate (3). Soft tissue sarcomas include a large variety of malignant neoplasms that arise in the extraskeletal mesenchymal tissues of the body. Approximately 10,390 cases are diagnosed annually in the United States, representing only 0.72 percent of all new cancers (4). Roughly 80 percent of sarcomas originate from in soft tissue, the remainder from bone (4). The histopathologic spectrum of sarcomas is broad, presumably because the embryonic mesenchymal cells from which they arise have the capacity to mature into striated skeletal and smooth muscle, adipose and fibrous tissue, bone, and cartilage. Low grade sarcomas are capable of aggressive local growth but tend not to disseminate. Overall survival of patients with sarcoma has been shown to correlate with grade in multiple studies (5,6). The sensitivity of PET scanning for primary sarcomas ranges from 74 to 100 percent (7,8) and is greater for high and intermediate grade sarcomas (7) than it is for low grade sarcomas (7,9). In one report, 50 percent of low-grade sarcomas did not take up more FDG than adjacent muscle (10).

Case report

A 47 yo woman presented to our clinic with a diagnosis of resected left thigh low grade leiomyosarcoma and

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"metastatic pancreatic neuroendocrine tumor to the lungs" . She had noticed slowly increasing size of the anterior region of her left thigh for several years; however, secondary to insurance issues had not sought medical care nor had undergone a biopsy of the mass. Two years prior to her visit to our clinic she underwent a biopsy of the thigh mass, which revealed smooth muscle neoplasm consistent with low grade leiomyosarcoma. The immunostains for smooth muscle actin, desmin, calponin were positive; immunostains for S100, CD34, CD117 were negative. The MID-I revealed 5% of the cells were proliferating. There were 2 mitotic figures per 50 high power fields. The tumor was 4.5 cm in dimention and the margins were positive. The patient subsequently underwent a PET scan for staging and was discovered to have numerous lung lesions which were not FDG avid, the largest being 2.1 cm, as well as a 4.8 x 3.3cm mass in the tail of the pancreas which was PET avid. Next, the patient underwent CT guided fine needle aspiration of the FDG avid pancreatic lesions. The biopsy was consistent with neuroendocrine carcinoma of the pancreas. An assumption was made by the previous oncology team that the numerous lung lesions were metastatic neuroendocrine tumors of the pancreas. She was then initiated on long acting octreotide injections for symptomatic relief of ongoing diarrhea and facial flushing, and did not receive any local therapy to the pancreatic tumor. Following the octreotide injections, her symptoms of facial flushing and diarrhea improved. At this point, approximately 24 months after initial diagnosis of pancreatic neuroendocine adenocarcinoma, she presented to the University of Miami Sylvester Comprehensive Cancer Center GI oncology clinic with symptoms of facial flushing and diarrhea, as she had not received any octreotide injections due to a lapse of insurance. Imaging done at our institution revealed a 4.8 x 3.3cm mass in the tail of the pancreas. CT of the chest revealed multiple bilateral noncalcified pulmonary nodules greater than 20 in left lung, largest measuring 1.3cm, and greater than 30 pulmonary nodules throughout the right lung, largest measuring 2.5cm. Based on outside reports the size of lung lesions had been stable over the preceeding 24 months. Subsequently, an Indium-111 Pentetreotide scintigraphy scan with SPECT imaging revealed an abnormal radiotracer accumulation in the region just antero-medially to the spleen at the level of the pancreatic tail but no abnormal activity noted in the lung lesions.

Relevant labs performed were Glucagon <50 pg/mL (normal 60 or less pg/ml), Chromogranin A 5.9 ng/ml (normal 36 or less ng/mL), 24 hour urine 5-HIAA 2.3 mg (normal less than 6 mg), WBC 12 10x3/uL (normal 4-11 10x3/uL), hemoglobin 14 Gm/DL (normal 12-16 Gm/DL), platelets 447 10x3/uL (normal 140-440 10x3/uL), and Vasoactive intestinal polypeptide 21.7 pg/ml (normal less than 6 pg/ml).

As the pulmonary nodules did not exhibit abnormal uptake on the Indium-111 Pentetreotide scintigraphy scan octreotide scan, nor were they PET avid on an outside scan, we decided to biopsy one of the lesions. A CT guided fine needle biopsy of one of the lung lesions revealed low grade leiomyosarcoma consistent with her previous thigh biopsy.

This led to a significant change in the management, due to the stability of the pulmonary lesions, and she was referred for chemoradiation to the localized pancreatic neuroendocrine tumor with capecitabine. The patient was not a candidate for surgery due to her concurrent metastatic malignancy.

Discussion

Pancreatic and peripancreatic neuroendocrine tumors are uncommon neoplasms with an annual incidence of five cases per million persons. The first account of an islet cell tumor of the pancreas was published in 1902 by Nicholls. In 1927 Wilder at El reported the first malignant pancreatic endocrine tumor, an insulinoma that had infiltrated most of the pancreas and metastasized to the liver in 1929. Several other clinical syndromes have been described for tumors producing gastrin, glucagon, vasoactive intestinal polypeptide (VIP), and somatostatin. Although Priest and Alexander (11) first described the association of an islet cell tumor with severe watery diarrhea, Vernon et al (12) further defined the syndrome now known to be related to excess circulation in VIP. The somatostatinoma syndrome was first reported in 1977 by Ganda et al who described a woman with diabetes, cholelithiasis, and a pancreatic tumor demonstrating high levels of somatostatin. For neuroendocrine tumors of the pancreas and periampullary region, the main role for surgery in non metastatic disease and selected cases of metastatic disease is for an intent to cure. Since functional tumors are diagnosed earlier than nonfunctional tumors, they have less of a chance of having metastasized, and therefore, have a more favorable prognosis. Patients with functional tumors have a significantly better 5-year survival (77%) as compared to those with nonfunctional tumors (52%, P=0.025) (13,14). Somatostatin receptor scintigraphy (SRS) is a useful imaging modality for the detection of neuroendocrine tumors (15-17). Over 90 percent of gastroenteropancreatic NETs, including non-functioning pancreatic islet cell tumors and carcinoids, contain high concentrations of somatostatin receptors and can be imaged using a radiolabeled form of the somatostatin analog octreotide (indium-111 [111-In] pentetreotide, OctreoScan) (15,16,17).

Although not yet clinically available, two positron emission tomography (PET) tracers for functional imaging have emerged (18-F-dihydroxy-phenyl-alanine [18F-DOPA] and 11-C-5-hydroxytryptophan [11-C-5-HTP]), which, in combination with high resolution PET, holds promise for improved detection and staging of NETs in the future. In a study of patients with carcinoid (n=24) or pancreatic islet cell tumor (n=23) who had at least one lesion on conventional imaging, integrated PET/CT imaging with 18F-DOPA had a diagnostic sensitivity of 98 percent for carcinoid tumors, compared to 49, 73, and 63 percent for SRS, SRS/CT and CT alone, respectively (18). In our case, SRS was accurate in predicting that lung metastases were not of neuroendocrine origin. The most common site of metastases for pancreatic neuroendocrine tumors is the liver. Pulmonary metastases are rare.

Sarcomas constitute less than 1% of all cancers in the United States. Leiomyosarcomas (LMS) are malignant neoplasms of smooth muscle that arise most commonly in the smooth muscle of visceral organs, i.e., uterus, gastrointestinal tract, and retroperitoneum (19). Cytogenetically, they are usually characterized by hyperploids chromosome complements and complex chromosome changes (20). Mutations of the K-ras oncogene are seen frequently in leiomyosarcoma, and they may be associated with a worse prognosis. In a study of 51 patients with leiomyosarcoma, mutations of K-ras were present in 14 percent and associated with significantly worse median survival (25 *vs* 42 months for wild-type K-ras) (21). Low grade sarcomas are capable of aggressive local growth, but tend not to disseminate. Most likely, the reason why our patient presented with metastatic low grade leiomyosarcoma to the lungs was because the malignancy had gone unattended for over a decade even though it was palpable and growing in the left thigh region.

The management of metastatic leiomyosarcomas to the lungs can be quiet challenging. For appropriately selected patients with isolated, limited pulmonary metastases from soft tissue sarcoma, pulmonary metastasectomy rather than palliative systemic chemotherapy should be considered. There is no consensus as to the optimal selection of surgical candidates; however, the following criteria are generally agreed upon (22). First, there should be no extrathoracic disease, pleural effusion or mediastinal/hilar adenopathy. Second, the primary tumor should be controlled. Third, the patient is a medically appropriate candidate for thoracotomy and pulmonary resection. Fourth, Complete resection appears feasible

Nevertheless, there is also no consensus among thoracic surgical oncologists or sarcoma specialists as to what disease burden represents an unresectable case. There is general agreement that chemotherapy following metastasectomy is generally not recommended. Since our patient had too numerous lung metastasis in both lungs, she was neither a surgical candidate nor a candidate for RFA of pulmonary lesions.

New understanding of molecular pathology in this area has helped to theorize about treatment options. Akt Mtor pathway activation plays a crucial role in the development of leiomyosarcomas. Upstream regulators or intrinsic components of this pathways were found to be overexpressed in human leiomyosarcomas (23). In mutant mice with upregulation of this pathway, it was demonstrated the early development of leiomyosarcoma as well. Mice treated with Mtor inhibitior Everolimus had a deceleration in tumor progression. Combination of Mtor inhibitors with traditional chemotherapy such as gemcitabine had demonstrated stabilization of metastatic disease in humans (24). Phase II clinical trials are needed to further establish its role in the clinical setting.

Conclusion

Neuroendocrine tumors often present with metastatic disease at presentation. However this patient had a history of a second primary. This case illustrates the importance of obtaining tissue confirmation of metastases. Tissue confirmation of metastatic sarcoma to the lungs which had been essentially stable for 24 months, altered the management of the pancreatic neuroendocrine tumor in this patient.

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