Lung adenocarcinoma mimicking metastatic pancreatic cancer, a diagnostic dilemma

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ABSTRACT

Aim: Solid tumors rarely metastasize to the pancreas, but multifocal pancreatic cancer is practically unheard-of. Modern genetic and molecular tumor profiling can more accurately determine a tissue of origin than standard immunohistochemistry techniques. When dealing with widely metastatic disease with multiple pancreatic masses, it is imperative to have an accurate diagnosis of primary pancreatic cancer versus metastasis from another site to the pancreas, as that would significantly alter treatment options and overall outcomes. Case Report: Here, I present a case of molecularly confirmed lung adenocarcinoma with widespread metastasis including the pancreas, liver, and lymph nodes leading to an initial clinical misdiagnosis and improper treatment recommendations. Fortunately, the correct diagnosis was made in a timely manner and molecular profiling of the tumor determined the appropriate treatment strategy leading to near-complete remission. Conclusion: Modern molecular assays are now a critical part of our diagnostic armamentarium and besides identifying targetable mutations, can help to determine the site of origin in cases of poorly differentiated metastatic disease.

Keywords: Immunotherapy, Lung cancer, Metastasis to pancreas, Molecular profiling

INTRODUCTION

Cancer metastasizing to the pancreas is rare, with reports of this phenomenon occurring from renal, colorectal, breast, melanoma, and lung primaries [1]. Since the prognosis and treatment options for metastatic primary pancreatic cancer differ greatly from most other sites of primary disease, accurate diagnosis is critical. Traditionally, simple immunohistochemistry has been used to determine the tissue/organ of origin in a metastatic tumor sample but can often be misleading in poorly differentiated tumors due to their highly varied phenotype based on the protein-expression level [2]. Modern molecular assays can help to clarify the site of tumor origin by examining the transcriptome using mRNA and miRNA, and validation studies for the commercially available assays have shown a clinically meaningful success rate ranging 75.6–89% [3–6]. Biotheranostic’s CancerTYPE ID® is a molecular test that can be used to help identify the tissue/organ of origin in a metastatic sample [7]. The assay uses real-time RT-PCR that measures the relative expression of 92 genes (87 tumor-specific genes plus five reference/control genes) and matches that gene expression pattern to an established database of known primary tumor types.

CASE REPORT

E.C. is a 73-year-old woman, never smoker, who presented to the hospital in August 2018 with a...
complaint of abdominal pain and bloating with early satiety. On clinical exam, she appeared slightly cachectic and jaundiced, with a distended abdomen and obvious ascites. She had an Eastern Cooperative Oncology Group (ECOG) performance status of 3 (capable of only limited self-care, confined to bed or chair more than 50% of waking hours) and a Karnofsky Performance Score (KPS) of 50 (requires considerable assistance and frequent medical care), and was unable to walk more than a few steps.

Abdominal imaging with magnetic resonance imaging (MRI) demonstrated marked intrahepatic and extrahepatic biliary ductal dilatation with the common duct measuring 1.9 cm. A mass was present in the head of the pancreas, measuring 4.4 cm (Figure 1). A second noncontiguous mass was present within the body of the pancreas, measuring 4.8 cm. A third discrete mass measuring 3.9 cm was also located in the pancreas body. Multiple hepatic masses were identified but appeared to be confined to the right lobe. Chest imaging was not immediately performed. Laboratory analysis included sodium 125 mmol/L, alkaline phosphatase 1349 U/L, aspartate aminotransferase (AST) 139 U/L, alanine aminotransferase (ALT) 115 U/L, total bilirubin 12.3 mg/dL, lipase 322 U/L, Ca19-9 105 U/mL, and carcinoembryonic antigen (CEA) 9.7 ng/mL. Based on initial impressions, she was told she had metastatic pancreas cancer with a very poor prognosis, even before a biopsy or medical oncology consultation. Two days later, a biliary drainage catheter was placed (without biopsy) and a medical oncology consultation was requested. On review of the initial MRI, it was apparent that there were three discrete (noncontiguous) masses in the pancreas, which would be very unlikely for primary pancreatic cancer. Multifocal primary pancreatic adenocarcinoma or intrapancreatic metastasis has been reported, but only in the context of a preexisting intraductal papillary mucinous neoplasm (IPMN) [8, 9]. I recommended further work-up with tissue sampling, and a computed tomography (CT)-guided biopsy of one of the liver metastases demonstrated a poorly differentiated carcinoma with the following immunohistochemical staining profile: Positive (AE 1/3, Oscar, CK7, and TTF-1); Negative (CK20, HepPar, CDX2, and Gata3). This suggested the possibility of metastatic lung cancer. A subsequent positron–emission tomography (PET) scan showed the three discrete pancreas masses and innumerable liver metastases as well as enlarged hypermetabolic lymph nodes in the mesentry, medial right supraclavicular, and right infraclavicular region, but there were no apparent lung nodules nor mediastinal, hilar, or axillary lymphadenopathy (Figure 2A). The liver mass biopsy sample was sent for molecular assessment with Cancer TYPE ID® (Biotheranostics, San Diego, CA). Based on this tumor’s unique mRNA expression profile, it was determined to be a primary lung adenocarcinoma with 90% probability while a pancreaticobiliary origin was ruled out with 95% confidence. Further molecular profiling and next-generation sequencing with Caris Molecular Intelligence® (Caris Life Sciences, Phoenix, AZ) demonstrated wild-type estimated glomerular filtration rate (EGFR) and Braf with no rearrangements in Alk, or Ros1. However, PDL-1 expression was 100% with a high tumor mutational burden (10/megabase). Further, there was loss of thymidylate synthase (TS) expression and the
presence of Kras (G12D) and TP53 (V203L) mutations with full expression of mismatch repair enzymes and no evidence of microsatellite instability.

Based on the diagnosis of highly symptomatic metastatic lung adenocarcinoma with a high tumor burden leading to organ compromise, systemic cytoreductive treatment was clearly indicated. Loss of thymidylate synthase expression predicted a good response to pemetrexed or other anti-folate agents, while the high tumor mutational burden and high PDL-1 expression predicted an excellent response to anti-PDL-1 antibodies [10–13]. Indeed, the prognosis of Stage IV non-small cell lung cancer in the modern age of immunotherapy is improved with a quadrupling of the historical 4% five year overall survival rate to 16% with immunotherapy [14]. The patient was treated with a combination of carboplatin (AUC 5), pemetrexed (500 mg/m²), and pembrolizumab (200 mg) given every three weeks based on the KEYNOTE-189 study [15]. After the 4th cycle (12 weeks), she was clinically much improved and functioning at near-baseline (ECOG 1, KPS 90) while a PET scan demonstrated complete resolution of all pathologic lymphadenopathy, near-resolution of all sites of liver metastasis, and significant improvement in all three pancreatic masses (each ~1.5 cm, compared to 3.9–4.8 cm at diagnosis; $\text{SUV}_{\text{max}}$ 3.6, previously $\text{SUV}_{\text{max}}$ 14.3) (Figure 2B). Now, more than one year after her initial diagnosis, she continues with maintenance pembrolizumab (200 mg every three weeks); the disease is stable and she is functioning normally with an ECOG performance score of 0 and KPS 100 and is completely asymptomatic.

DISCUSSION

Cancer metastasizing to the pancreas is rare, with reports of this phenomenon occurring from renal, colorectal, breast, melanoma, and lung primaries [16]. Non-small cell lung cancer commonly metastasizes to bone, liver, and adrenal glands, but spread to the pancreas is a rare phenomenon [17]. Cases of metastatic malignancy involving the pancreas typically involve widespread involvement of other tissues, but cases isolated pancreatic metastases have been reported [18–20].

Radiologically, it may be difficult or impossible to determine the site of origin in widely metastatic malignancy, especially since the clinical presentation and the radiological characteristics for both primary and secondary pancreatic tumors can be very similar [21]. Pancreatic metastases can mimic the characteristics of primary pancreatic ductal adenocarcinoma, thus confounding the diagnosis.

Triantopoulou et al. have described three distinct patterns of pancreatic involvement by extrapancreatic malignancy [22]. They reported that about 5–10% of cases are characterized by numerous small nodules scattered throughout the pancreas, whereas diffuse infiltration is seen in 15–44% of cases [23]. However, the majority (50–75%) of cases demonstrate a solitary mass [24].

The presence of multiple distinct tumors within the pancreas should prompt suspicion for metastasis from another primary source, and not be assumed to be primary pancreatic cancer. Proper pathology assessment of the tumor sample can help confirm a metastatic deposit rather than primary pancreatic cancer.

Modern molecular assays are now a critical part of our diagnostic armamentarium. Besides identifying targetable mutations for treatment, these assays can help to determine the site of origin in cases of poorly differentiated metastatic disease. This distinction is particularly important since the prognosis and treatment options are determined by the underlying primary tissue of origin and assessment of appropriate molecular markers. Indeed, some advanced malignancies, even when widely metastatic to visceral organs, can be considered essentially curable in the age of personalized medicine and immunotherapy.

CONCLUSION

Accurate diagnosis is critical in providing prognosis and treatment recommendations for advanced malignancy. Metastasis to the pancreas is rare (<5% of all pancreas lesions), but should be strongly suspected in cases of multifocal pancreatic tumors. In cases of lung cancer that respond to immunotherapy, there can be a 100% radiologic response with improvement in quality of life and indefinite survival. In this case, if the patient had gone directly to Hospice care based on the inaccurate presumed diagnosis of metastatic pancreatic cancer in a patient with a poor performance status, she would have been denied the opportunity to benefit from immunotherapy and potentially live out her normal lifespan.

REFERENCES


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Author declares no conflict of interest.

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