You can't judge a book by its cover or a tumor by its expression profile

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Abstract

Expression profiling has shown great promise in matching cancers of unknown primary to likely primary tumors of origin based on patterns of mRNA expression. However, it remains uncertain as to whether even well matched tumors will demonstrate the clinical features, such as rate of progression, of their matched counterparts. In this case report, we note that based on histology, immunohistochemistry and expression profile this patient's poorly differentiated neuroendocrine tumor would have been expected to grow very rapidly on no therapy. Instead, this cancer was very indolent, with only very little radiographic progression over several years. We believe this report represents a remarkable case of a tumor where features, including expression profile, would not at all have accurately predicted the clinical course seen. While some series have suggested that matching by expression profiling predicts outcome, this case shows a dramatically different result.

Introduction

Expression profiling of cancers of unknown primary has shown great promise in matching unknown primary malignancies with known primary cancers, based on patterns of mRNA expression seen in data banks of known primary malignancies. However, it remains somewhat unclear as to whether an unknown primary malignancy with an expression profile matching a particular known primary profile will likely have clinical characteristics, such as rate of cancer progression and response to therapy, as that of the known matched likely primary site.

Herein, we report a case of a poorly differentiated neuroendocrine tumor (PDNT) of unknown primary site where expression profiling was performed. The patient's clinical course was much more consistent with a well differentiated neuroendocrine tumor than that of a PDNT. We believe this case represents the first PDNT of unknown primary where expression profiling was performed and correlated with clinical outcome. The profiling was consistent with a *small cell* lung cancer (the term *small cell* was also used in the pathologic diagnosis). Such tumors which would be expected to rapidly progress without therapy, in spite of the fact that our patient's tumor demonstrated a very indolent nature, with only slight progression over years. Recent studies have shown that a matched expression profile to a particular tumor type predicts prognosis and clinical outcome. However, in this case the matched primary tumor would be expected to behave in a very different manner (i.e. much more rapid growth) than was seen for this PDNT.

Case Report

EH is a 40-year-old African American female patient who presented in 2005 with bilateral breast masses and a computed tomography (CT) scan demonstrating mediastinal and bilateral axillary lymphadenopathy as well as apparent adrenal, splenic, ovary and liver metastases. Biopsy of one of the breast masses was morphologically and immunohistochemically consistent with an *extremely high-grade* neuroendocrine tumor, such as a *small cell neuroendocrine* tumor. After two cycles of chemotherapy with carboplatin and etoposide, the follow-up CT scan showed substantial improvement in the metastatic disease and with additional carboplatin and etoposide there was further improvement. However, after six cycles of chemotherapy there was mild progression in the mediastinal lymphadenopathy. Nearly five years later (September 2010) the only evidence of progression of the malignancy was a slight increase in a 7 mm solitary pulmonary nodule, which the radiologist noted *dated back* to 2006. The mediastinal disease was again stable from September 2010 until February 2011, but the pulmonary nodule increased in size and was removed in February 2011 and pathology reported a PDNT of 1.5 cm with IHC Ki-67 staining of 90%. Molecular profiling (BioTheranostics, San Diego, CA, USA)[1] of this tumor suggested an 87% likelihood that the tumor represented small cell lung cancer and only a less than 8% likelihood of this tumor developing from a different tissue of origin. In neither the specimen from 2006 nor that from 2011 was there histologic evidence of a well or even moderately differentiated neuroendocrine tumor. A CT scan done 7 months after surgery revealed no evidence of progressive disease.

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Discussion

PDNT or small undifferentiated carcinomas of unknown origin are rare diagnoses and these tumors would be predicted to progress rapidly in patients not on treatment. Per Greco and Hainsworth[2] these tumors would be expected to be initially chemosensitive (as seen in our patient), with only an *occasional* patient showing long-term survival. Therefore, morphologically and immunohistochemically this patient's tumor would have been expected to progress quite rapidly. Yet, over roughly five years without therapy there was only minimal progression radiographically.

Expression profiling matches tumors of unknown origin with mRNA expression profiles of known primary, with the hope of identifying the likely primary site. The specific expression profiling assay test used in this case was performed by bioTheranostics. This technique has been validated and described per the product information from bioTheranostics. The expression profile of 92 genes is obtained by extracting RNA from tumor-enriched sections of formalin-fixed paraffin embedded tissue and performing real-time quantitative RT-PCR using TaqmanTM technology.[1] This test identifies the most likely tissue origin and histological type based on the degree of similarity of this 92-gene expression profile to those from tumors of known tissue origin and histological subtype.[3] The probability score is a measure of confidence for the classification. The method has been described by the National Comprehensive Cancer Network as an *emerging technology*.[4] The still largely unproven assumption is that such tumors would behave clinically and respond to standard therapy in a manner consistent with

the probable matched primary. For example, in a recently reported series of patients with cancers of unknown primary, where expression profiling was consistent with colorectal cancer, the natural history and response to treatment of the disease with standard colorectal cancer regimens was remarkably similar to that of colorectal cancer, rather than the historic results seen in series of cancers of unknown primary where expression profiling was not used, and patients had been treated with standard unknown primary chemotherapy regimens.[5] However, in our patient the expression profiling that was done was consistent with small cell lung cancer and therefore would have predicted rapid progression, while not on treatment, rather than the remarkably indolent disease course described above.

While it remains possible that this tumor had represented a well differentiated neuroendocrine tumor that only recently transformed into a PDNT, there was no histological evidence in either the 2006 or 2011 specimens to suggest a well differentiated neuroendocrine tumor component and, seven months after removing the lung focus, there still has been no evidence of progression in the mediastinal lymphadenopathy or elsewhere.

Taken together, these results show that in our patient's case, neither the morphology nor the extremely high Ki-67 staining nor the expression profiling were consistent with the clinical course experienced. Future studies of expression profiling and clinical outcome will determine whether this promising technology can be used to consistently predict clinical course when an unknown primary matches well with the expression profile of a known primary malignancy.

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