Journal of the American Society of Cytopathology (2015) 4, 137–140

Available online at www.sciencedirect.com

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journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

Arginase-1 and HepPar-1 expression in fine-needle aspiration specimens of primary lung adenocarcinoma

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Received 22 October 2014; received in revised form 19 November 2014; accepted 28 November 2014

KEYWORDS
Arginase-1;
HepPar-1;
Hepatocellular differentiation;
Fine-needle aspiration;
Primary lung adenocarcinoma

Introduction Arginase-1 is a novel immunohistochemical (IHC) marker for hepatocellular differentiation. The purpose of this study was to evaluate the expression of Arginase-1 and HepPar-1 in lung adenocarcinoma to assess the potential value of these markers for diagnosing metastatic lung tumors, especially to the liver in fine-needle aspiration specimens.

Materials and methods Forty-four cytology specimens of lung adenocarcinoma, obtained by endobronchial ultrasound-guided fine-needle aspiration were retrospectively reviewed. IHC stains for Arginase-1 and HepPar-1 were performed on formalin-fixed paraffin-embedded cell blocks. Tissue from confirmed hepatocellular carcinoma was used as the positive control. TTF-1 IHC stain was performed in all cases.

Results All 44 lung adenocarcinoma cases (100%) were negative for Arginase-1, whereas HepPar-1 expression was detected in 3 (7%) of lung adenocarcinomas and negative in 41 (93%). The 3 HepPar-1–positive lung adenocarcinoma cases demonstrated positive TTF-1 IHC stain performed on the same cell block. Although both Arginase-1 and HepPar-1 are useful diagnostic IHC markers to differentiate metastatic lung adenocarcinoma from hepatocellular carcinoma, Arginase-1 IHC stain shows better specificity than HepPar-1 does (Arginase-1 specificity 100% and HepPar-1 specificity 93%).

Conclusions Arginase-1 IHC can be used in combination with other markers in the workup of metastatic lung adenocarcinoma, especially to the liver.

Presented as an abstract at the 103rd Annual Meeting of the United States and Canadian Association of Pathologists (USCAP); March 1 to 7, 2014; San Diego, California.

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2213-2945/$36
http://dx.doi.org/10.1016/j.jasc.2014.11.005

Introduction

Metastatic lung adenocarcinoma to the liver is common and occasionally may be difficult to distinguish from hepatocellular carcinoma (HCC), especially if the tumor has the morphology of poorly differentiated neoplasm. A panel of immunohistochemical (IHC) stains can be used to determine the site of origin. HepPar-1 and TTF-1 are the most common IHC markers used so far to differentiate the 2 neoplasms. Although HepPar-1 is a highly specific marker for HCC, several studies showed that lung adenocarcinoma can express HepPar-1 positivity ranging from 5.8% to up to 25% of the cases.[1,2] TTF-1 cytoplasmic staining is identified in HCC and nuclear staining in lung adenocarcinoma.

Arginase-1 is a key urea cycle metalloenzyme that demonstrates expression in normal human liver. In sections of normal liver and HCC, Arginase-1 produces either cytoplasmic or cytoplasmic plus nuclear reactivity. Recent studies have examined Arginase-1 as an IHC marker for hepatocellular differentiation and have shown high specificity and sensitivity in benign and malignant hepatocytes.[3-7]

The aim of the study was to evaluate the expression of Arginase-1 and HepPar-1 in lung adenocarcinoma and to assess the potential value of these markers to enhance the accuracy of diagnosing metastatic lung tumors, especially to the liver in fine-needle aspiration (FNA) cytology specimens.

Materials and methods

This study was approved under a protocol by the Institutional Review Board at Thomas Jefferson University Hospital. Forty-four cytology specimens, obtained by endobronchial ultrasound-guided FNA and diagnosed as lung adenocarcinoma at our institution, were retrospectively reviewed. The diagnosis was confirmed by 3 cytopathologists and a cytology fellow. Specimens with adequate cell block material were selected for the study.

IHC stains for Arginase-1 and HepPar-1 were performed on unstained slides from formalin-fixed paraffin-embedded cell blocks using Ventana Roche detection kits and automated slide stainer. We used Cell Marque Arginase-1 (SP156) and Cell Marque Hepatocyte Specific Antigen (OCH1E5) antibodies according to the manufacturer's specifications. Liver tissue with confirmed HCC was used as a positive control for both stains. Rabbit immunoglobulin G was used as the negative control. TTF-1 IHC stain (Confirm anti-Thyroid Transcription Factor-1, 8G7G3/1 antibody; Ventana) with adequate positive and negative controls was performed in all cases. Any cytoplasmic staining for Arginase-1 and HepPar-1 and any nuclear TTF-1 staining were considered positive. All 44 cases had adequate numbers of tumor cells on cell block sections to perform the 3 IHC stains. None of the cell blocks was exhausted. The immunohistochemically stained slides were independently evaluated by the same group of cytopathologists.

Results

All 44 (100%) lung adenocarcinoma cell blocks were negative for IHC stain for Arginase-1. HepPar-1 expression was detected in 3 lung adenocarcinoma cases (7%) (Fig. 1A, 1B, 1C, 1D) and negative in 41 (93%). Immunoreactivity for TTF-1 (Fig. 2) was seen in 41 (93%) of the cases and negative in 3 (7%). All 3 HepPar-1−positive lung adenocarcinoma cases demonstrated positive nuclear TTF-1 IHC stain performed on the same cell block.

The Arginase-1 and HepPar-1 IHC results are summarized in Table 1.

Although both Arginase-1 and HepPar-1 are very specific for hepatocellular differentiation, Arginase-1 IHC stain has higher specificity than HepPar-1 does (Arginase-1 specificity 100% and HepPar-1 specificity 93%).

Discussion

The liver is a common site for different tumors to metastasize. Morphologic differentiation of primary and metastatic liver malignancies can be a diagnostic challenge and is sometimes impossible without performing IHC studies. In cytology, choosing the right IHC panel is always very critical, due to the limited amount of material in the cell block. Very often there are only few adequate cell block sections available for special studies. Using highly specific and sensitive antibodies helps cytopathologists to arrive at the correct diagnosis, when working with such limited specimens.

HepPar-1 is among the most commonly used IHC markers for hepatocellular differentiation. Multiple studies performed on both resection specimens and FNA cell blocks of liver tumors have shown HepPar-1 to be a sensitive (75% to 90%) marker for hepatocellular neoplasms.[2,8,9] Although a useful marker, HepPar-1 is not entirely specific, showing frequent staining in gastric adenocarcinoma, yolk sac tumor, cholangiocarcinoma, adrenal cortical carcinoma, lung adenocarcinoma, colorectal adenocarcinoma, ovarian adenocarcinomas, and other tumors.[1,2,8,10]

FNA biopsy of liver lesions suspicious for metastases in patients with lung adenocarcinoma is a usual diagnostic method. Morphologic similarity of poorly differentiated adenocarcinoma of the liver and lung in cytology specimens very often precludes definitive diagnosis with conventional stains alone. IHC stains performed on cell blocks are essential in this setting. HepPar-1 antigen expression in lung adenocarcinomas has been reported from 5.8% to 25% of the cases.[1,2] In our study 3 of 44 lung adenocarcinomas (7%) expressed the HepPar-1 marker. All 3 cases showed positive nuclear TTF-1 staining.