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RESEARCH ARTICLE

The role of the hepatocyte nuclear factor 4 alpha HNF4α and the homeobix protein CDX2 immunomarkers in diagnosis of metastatic colorectal carcinoma

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ABSTRACT

Background: Detection of the primary site of metastatic carcinoma of unknown origin is necessary to help in the choice of the treatment. CDX2 is routinely used in metastatic adenocarcinomas cases for identifying the gastrointestinal origin. HNF4α is a new immunohistochemical marker with a few studies showing that it is expressed in a majority of colorectal adenocarcinomas**. Aim:** To determine the expression of HNF4α and CDX2 in metastatic carcinoma cases for detection of gastrointestinal origin **. Material and methods:** We assessed HNF4α and CDX2 in 60 metastatic carcinoma cases in different organs, which were diagnosed retrospectively. HNF4-α and CDX-2 expressions were evaluated by light microscopic examination of all tissue sections by two different pathologists. The cut-off for positivity of HNF4α and CDX-2 was 1% of stained nucleus of metastatic tumor cells. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy of two markers and P value were calculated**. Results:** The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy of HNF4α were 90%, 82.5%, 72%, 94.3% and 85% respectively for diagnosis of colorectal carcinoma metastasis from other metastatic carcinomas. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CDX2 were 80%, 72.5%, 59.3%, 87.9% and 75% respectively. The P-value for comparing between their expression in metastatic adenocarcinoma from lower GIT and each other groups is less than 0.05. **Conclusions:** We concluded that HNF4α can be used as a supplementary marker with CDX2 to identify metastatic colorectal adenocarcinoma. HNF4α expression is a highly specific and sensitive marker of colorectal origin.

Keywords: CDX2, HNF4α, NPV, PPV

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INTRODUCTION

Metastatic carcinoma from an unknown primary site is a popular clinical problem, so the identification of primary tumor site needs clinical examination and further investigations (Varadhachary, 2007). The choice of treatment is depending on detection of the primary site of metastatic carcinoma of unknown primary, as this help in several steps in the identifying of the primary site. Clinical examination, including age, sex, past and family history with the site of metastases can give an initial indication. The histopathological results are beneficial, but cannot distinguish between several primary carcinomas. Immunohistochemistry is the most useful tool in the diagnosis of metastatic carcinoma of unknown primary origin (Park et al., 2007).

CDX2 is a homeobox gene that plays a role in the differentiation of intestinal epithelial cells. These genes have an important function in the monitoring of embryonal development of the alimentary tract. CDX2 is participated in the cell proliferation, differentiation, and apoptosis of the intestine. CDX2 is a transcription factor, which high expression of multiple gene products linked with maturation of epithelial cells of the intestine. (Li and Folpe, 2004).

Hepatocyte nuclear factor 4-alpha (HNF4 -α) is a nuclear transcription factor with essential roles in the development, differentiation, and metabolism of liver and gastrointestinal tract (Babeu and Boudreau, 2014). The organization of HNF4- α expression and activity is a complicated process. HNF4 -α regulation comes at multiple levels: Epigenetic, transcriptional and post-translational. Immunohistochemical detection of HNF4- α has a valuable diagnostic and prognostic role (Lu, 2016).HNF4 -α is expressed in the hepatic, gastrointestinal, pancreatic and renal tissues.No immunostaining is noted in the thyroid, lung,breast, ovarian, endometrial and prostatic tumors (Tanaka et al., 2006).

HNF4-α has a significant function in the development of the colon. It is involved in the differentiation, enteric metabolism, and epithelial intestinal adhesion (Garrison et al., 2006) In the gut, HNF4- α plays a crucial role in the regulation of intestinal genes. Inflammatory bowel disease (IBD) and carcinoma of the colon showed alternation of HNF4- α expression (Chellappa et al., 2016).

HNF4 belongs to the superfamily of nuclear receptors, one of the largest families of transcription factors. In mammals, two genes encode the different HNF4a (NR2A) and HNF4g (NR2A2) isoforms. HNF4a is expressed in the liver, stomach, pancreas, kidney and intestine, 14,15 whereas HNF4g is mostly intestinal.

In vivo and in vitro studies have shown that HNF4a has pleiotropic roles in the liver. 17 In the gut, HNF4a has important functions and is a key regulator of enterocytic markers. 18,19 Conditional knockout of the Hnf4a gene in the mouse embryonic colon causes lethality because of the perturbation of organogenesis, cytodifferentiation and gene expression, 20 and its ablation in the adult intestine reveals its involvement in homeostasis, cell architecture and barrier function HNF4 belongs to the superfamily of nuclear receptors, one of the largest families of transcription factors. In mammals, two genes encode the different HNF4a (NR2A) and HNF4g (NR2A2) isoforms. HNF4a is expressed in the liver, stomach, pancreas, kidney and intestine, 14,15 whereas HNF4g is mostly intestinal. 16 In vivo and in vitro studies have shown that HNF4a has pleiotropic roles in the liver. 17 In the gut, HNF4a has important functions and is a key regulator of enterocytic markers. 18,19 Conditional knockout of the Hnf4a gene in the mouse embryonic colon causes lethality because of the perturbation of organogenesis, cytodifferentiation and gene expression, 20 and its ablation in the adult intestine reveals its involvement in homeostasis, cell architecture and barrier function HNF4 belongs to the superfamily of nuclear receptors, one of the largest families of transcription factors. In mammals, two genes encode the different HNF4a (NR2A) and HNF4g (NR2A2) isoforms. HNF4a is expressed in the liver, stomach, pancreas, kidney and intestine, 14,15 whereas HNF4g is mostly intestinal. 16 In vivo and in vitro studies have shown that HNF4a has pleiotropic roles in the liver. 17 In the gut, HNF4a has important functions and is a key regulator of enterocytic markers. 18,19 Conditional knockout of the Hnf4a gene in the mouse embryonic colon causes lethality because of the perturbation of organogenesis, cytodifferentiation and gene expression,20 and its ablation in the adult intestine reveals its involvement in homeostasis, cell architecture and barrier function

Detection of the primary site of metastatic carcinoma of unknown origin is important for proper assessment and management of the metastatic carcinoma patients. So this study aims to determine the expression of HNF4 -alpha and CDX2 in metastatic carcinoma from different primary sites, with the evaluation of sensitivity and specificity of these markers.

MATERIAL AND METHOD

Patients and specimens: Metastatic carcinoma tissues in different organs (breast, thyroid, breast and lymph node). All specimens used in the study were obtained from Pathology Department, Tanta University and private laboratories. None of the patients received preoperative treatment, either radiotherapy or chemotherapy. Metastatic carcinoma tissues were obtained from 60 patients.

IHC analysis: Formalin-fixed paraffin-embedded tissue sections (4-µm) were put on to APES-coated glass slides (Chenglin, Shanghai,

China). Slides were dewaxed in xylene twice for 10 min and rehydrated through graded ethanol. Antigen retrieval was performed in 0.01 mol/l citrate buffer (pH 6.0) by boiling for 10 min. Endogenous peroxidase activity was suppressed with 3% hydrogen peroxide for 10 min. After washing with phosphate-buffered saline (PBS), the slides were blocked with 5% BSA for 30 min at 37˚C. Sections were incubated with primary rabbit monoclonal antibody to human CDX-2 ((RM-2116-S0) (Labvision)) and primary rabbit monoclonal antibody to human HNF4-a ((p 41235) (cell signaling technology)) at 4˚C overnight, in a humidified chamber. After washing three times with PBS, sections were incubated for 30 min with the secondary antibody (peroxidase goat anti-mouse IgG; dilution, 1:300; catalogue no. 32230; Zymed, San Diego, CA, USA). After washing for three times in PBS, 3,3'-diaminobenzidine (as chromogen) was used. Slides were counter-stained with hematoxylin for 1 min. Sections were not incubated with the primary antibody, used as negative controls.

Immunohistochemical evaluation: HNF4- α and CDX-2 expressions were evaluated by light microscopic examination of all tissue sections by two different pathologists. The cut-off for positivity of HNF4-a and CDX-2 was 1% of stained nucleus of colorectal adenocarcinoma cells. So HNF4-α and CDX-2 Immunoreactivity was scored as negative (0, no immunostaining) or positive (Dabir et al., 2018; Saandi et al., 2013).

Statistical analysis: Statistical presentation and analysis of present study were conducted, using the mean, standard deviation, and chi-square test, person correlation by SPSS (version 15) software.

RESULTS

HNF4-α Expression (Figures 2,6,10 & Tables 1,2)

HNF4-α expression was identified in the nucleus of metastatic tumor cells of lower and upper gastrointestinal tract carcinoma and it was identified in the nucleus of metastatic non adenocarcinoma (from squamous cell carcinoma), and the positivity of tumor cells was only evaluated. It was expressed in metastatic tumor cells of 18 out of 20 cases metastatic adenocarcinoma from the colon (90%). Four cases of metastatic adenocarcinoma from upper gastrointestinal tract showed positive expression (20%). Two out of 10 cases of metastatic adenocarcinoma not come from gastrointestinal tract showed positive expression (20%). One case out of 10 cases of squamous cell carcinoma showed positive immunostaining for HNF4- α (10%).

CDX-2 Expression (Figures 3,5 and Tables 1,2)

CDX-2 expression was identified in the nucleus of metastatic tumor cells of lower and upper gastrointestinal tract carcinoma and it was identified in the nucleus of metastatic non adenocarcinoma (from squamous cell carcinoma), and the positivity of tumor cells was only evaluated. It was expressed in metastatic tumor cells of 16 cases out of 20 cases metastatic adenocarcinoma from the colon (80%). Five cases of metastatic adenocarcinoma from upper gastrointestinal tract showed positive expression (25%). Four cases out of 10 of metastatic adenocarcinoma not come from gastrointestinal tract showed positive expression (40%). Two cases out of 10 cases of squamous cell carcinoma showed positive immunostaining for CDX-2 (20%).

The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), accuracy of two markers and p value for comparing between their expression in metastatic adenocarcinoma from lower GIT and each other group are shown in Table 2. The positive expression of HNF4- α showed 90% sensitivity however, specificity was 82-5%. The positive expression of CDX-2 showed 80% sensitivity and 72.5% specificity. So HNF4-α and CDX-2 positive expression can be used to diagnose metastatic colorectal carcinoma in different tissue.

DISCUSSION

Recently immunomarkers have been examined for their diagnostic role. Results remain inconclusive and controversial, and up till now, no molecular markers can be used in the routine assessment of metastatic carcinoma of unknown origin. The difficulty of the diagnosis of metastatic carcinoma of the unknown is the detection of primary site. This is a challenge to oncologists and pathologists, the detection of

Table 1. CDX-2 and HNF4-a expression in relation to different types of metastatic adenocarcinoma and metastatic nonadenocarcinoma.

Type	Number	Age	Sex		CDX-4		HNF4-a	
			Male	Female	+	-	+	-
Metastatic adenocarcinoma from lower GIT	20	30	15	5	16	4	18	2
Metastatic adenocarcinoma from upper GIT	20	50	15	5	5	15	4	16
Metastatic adenocarcinoma from non GIT source	10	55	7	3	4	6	2	8
Metastatic non adenocarcinoma	10	78	7	3	2	8	1	9

Table 2. Sensitivity, specificity, PPV, NPV, accuracy, and p-value of HNF4-α and CDX-2 to diagnose metastatic colorectal carcinoma in different tissue

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
HNF4-α(+ve)	90%	82.5%	72%	94.3%	85%
CDX-2 (+ve)	80%	72.5%	59.3%	87.9%	75%

	Metastatic adenocarcinoma rom lower GIT (n= 20)		Metastatic adenocarcinoma from upper GIT (n= 20)		Metastatic adenocarcinoma from non GIT source (n= 10)		Metastatic non adenocarcinoma (n= 10)	
	No.	%	No.	%	No.	%	No.	%
				TYPE				
CDX-4								
+	16	80.0	5	25.0	4	40.0	2	20.0
–	4	20.0	15	75.0	6	60.0	8	80.0
p			<0.001*		0.045*		0.004*	
HNF4-α								
+	18	90.0	4	20.0	2	20.0	1	10.0
–	2	100	16	80.0	8	80.0	9	90.0
p			<0.001*		<0.001*		<0.001*	

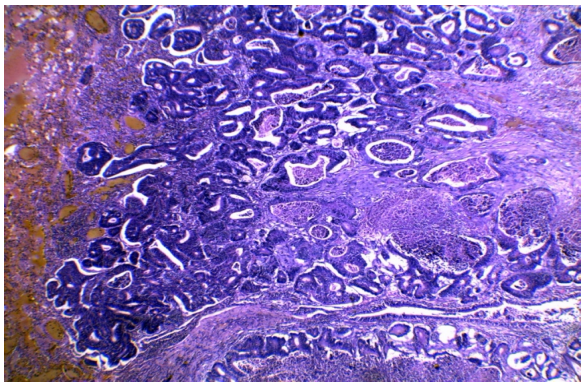

Figure 1. Metastatic grade (II) carcinoma from upper gastrointestinal tract carcinoma case in thyroid tissue (x40).

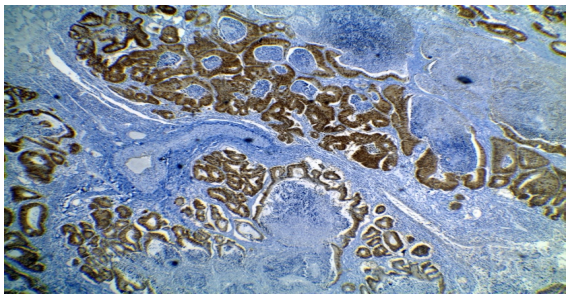

Figure 2. Metastatic grade (II) carcinoma from upper gastrointestinal tract carcinoma case in thyroid tissue showing positive HNF4- α nuclear immunostaining (x40).

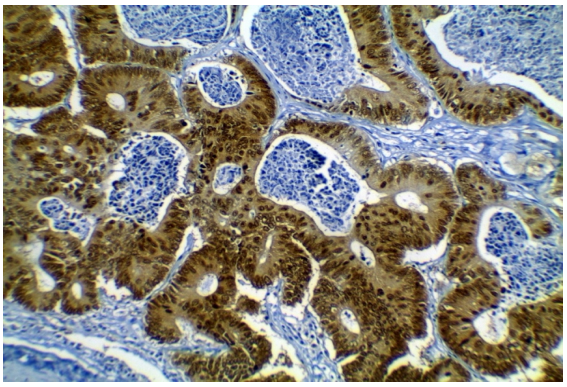

Figure 3. Metastatic grade (II) carcinoma from upper gastrointestinal tract carcinoma case in thyroid tissue showing positive CDX-2 nuclear immunostaining (x200).

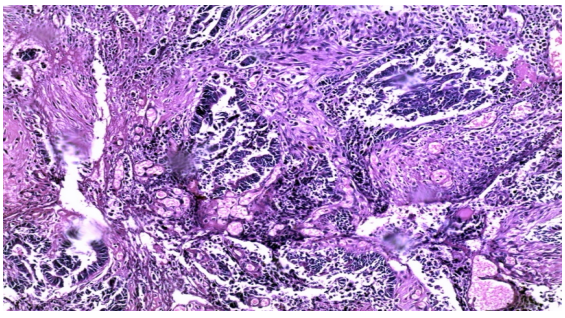

Figure 4. Metastatic grade (II) carcinoma from colon carcinoma case in breast tissue (x100).

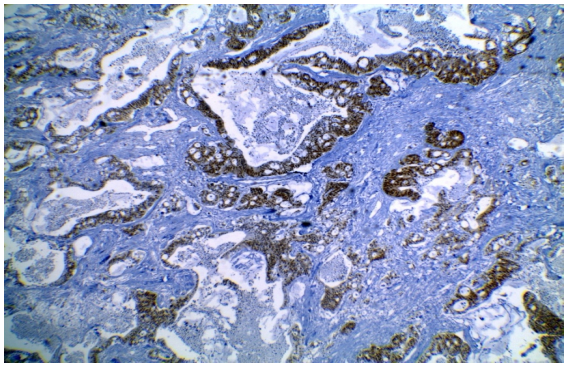

Figure 5. Metastatic grade (II) carcinoma from colon carcinoma case in breast tissue showing positive CDX-2 nuclear immunostaining (x40).

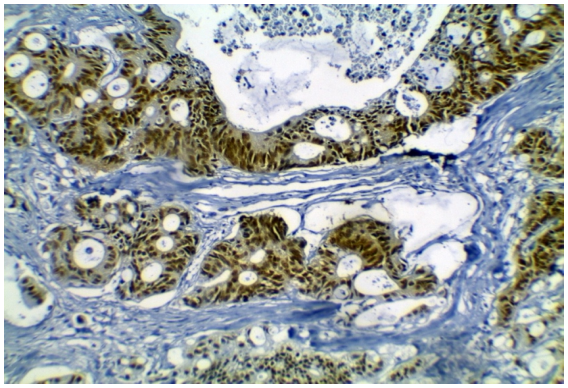

Figure 6. Metastatic grade (II) carcinoma from colon carcinoma case in breast tissue showing positive HNF4- α nuclear immunostaining (x200).

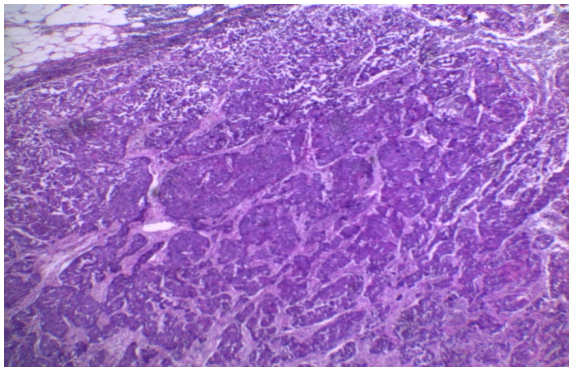

Figure 7. Metastatic grade (II) carcinoma from squamous cell carcinoma case in lymph node tissue (x40).

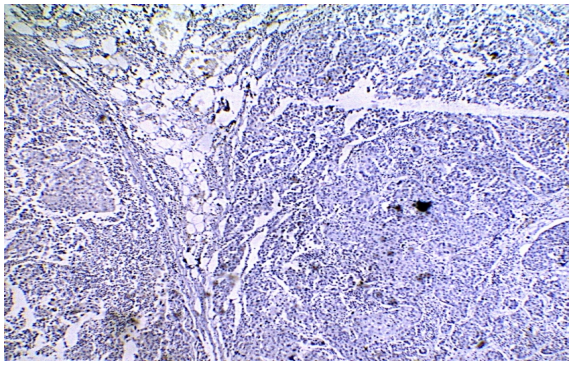

Figure 8. Metastatic grade (II) carcinoma from squamous cell carcinoma case in lymph node tissue (x40).

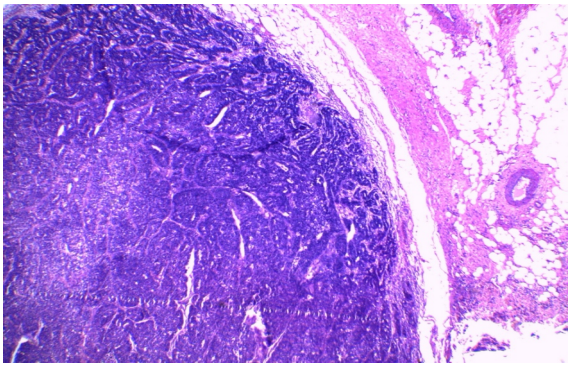

Figure 9. Metastatic grade (II) carcinoma from colon carcinoma case in lymph node tissue (x40).

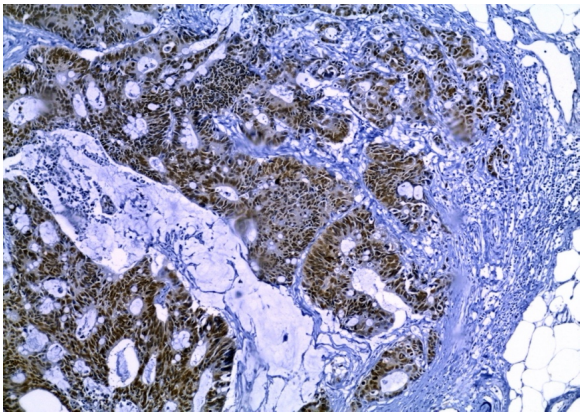

Figure 10. Metastatic grade (II) carcinoma from colon carcinoma case in lymph node tissue showing positive HNFa-4 nuclear immunostaining (x100).

the primary site has important diagnostic and therapeutic outcomes. The clinical, pathological correlation and a panel of immunostains are useful to determinate the origin for proper management of the patients (Park et al., 2007). Human CDX2 protein is one of homeobox genes that encodes an intestinal specific transcription factor. CDX2 protein can regulate the development of the intestine and is showed nuclear expression of epithelial intestinal cells through the intestinal tract in embryonal and post-natal life. The expression of CDX2 is highly restricted to intestinal epithelium (Silberg et al., 2000). Recently, the sensitivity and specificity of CDX2 protein as immunomarker of metastatic colonic carcinoma is evaluated in many types of research. CDX2 is a useful marker and can be included in the IHC panel, as it is a relatively sensitive and specific marker for colorectal adenocarcinomas (Borrisholt et al., 2013).

In the current study, CDX2 was expressed in 16 of 20 (80%) colorectal adenocarcinoma, 25% metastatic adenocarcinoma from the upper

gastrointestinal tract, and 40% metastatic adenocarcinoma of non-gastrointestinal origin and 20% metastatic carcinoma. Our results revealed that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CDX2 were 80%, 72.5%, 59.3%, 87.9% and 75% respectively for the diagnosis of colorectal carcinoma metastasis from other metastatic carcinomas. These findings were in agreement with Dabir et al. (2018) who reported that CDX2 is used for identifying colorectal metastatic carcinomas, but many cases of other metastatic carcinomas showed positivity with this immunomarker. The calculated sensitivity and specificity of CDX2 in their study for colorectal metastatic carcinoma diagnosis were 93% and 67% respectively.

Bayrak et al. (2012) demonstrated that the sensitivity, specificity, positive predictive value, and negative predictive value of CDX2 expression and CK7-/CK20+ immunophenotyping to distinguish colonic carcinoma from gastric and pancreatic carcinomas. CK7/CK20 immunohistochemistry was more specific than CDX2 expression in the differentiation of colorectal adenocarcinoma from pancreatic and gastric adenocarcinomas with specificity 96.7%. They stated that CDX2 expression had a higher sensitivity and higher negative predictive value than the cytokeratin immunophenotype. The high sensitivity of CDX2 makes it useful marker for determining primary of metastatic colorectal carcinoma, but its specificity may be of concern.

Saad et al. (2013) noticed that CDX2 is a helpful immunomarker for colorectal metastatic adenocarcinoma. However, expression of CDX2 may be present in other tumors, especially tumors with intestinal differentiation, regardless of their site. They recommended that CDX2 could not be used alone for the detection of the primary origin of metastatic colorectal adenocarcinomas, should be used as a part of the immunohistochemical panel.

HNF4α is one of the nuclear receptor family of transcription factors. Its location on chromosome 20 is regulated by two promoters (P1, P2). HNF4α expression has been detected in liver, kidney and intestine. It has a role in liver and intestinal development (Davison et al., 2017). Besides, its biological action in colorectal tissue, HNF4α showed expression in CRC. HNF4α is detected as the main transcription factor for colonic functions in both physiological and pathological conditions (Yao et al., 2016).

HNF4α is the new marker that showed high specificity in metastatic colorectal adenocarcinoma. In the current study, HNF4α was expressed in 18 of 20 (90%) colorectal adenocarcinoma, and 20% metastatic adenocarcinoma from upper gastrointestinal tract, 2 of 10 (20%) metastatic adenocarcinoma of non-gastrointestinal origin and 10% metastatic carcinoma. The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy of HNF4α were 90%, 82.5%, 72%, 94.3% and 85% respectively for diagnosis of colorectal carcinoma metastasis from other metastatic carcinomas. Our results suggested that HNF4α is a novel marker that showed higher sensitivity and specificity in colorectal carcinoma metastasis than CDX2.

Kriegsmann et al. (2018) stated that HNF4α may be useful in the differentiation of pulmonary adenocarcinoma and metastatic colorectal carcinoma. They found that HNF4α exhibit positive expression in 77 of 80 cases (96%) of colorectal adenocarcinoma. However, they noticed this marker was not shown an improvement over the routinely used CDX2 and CK20.

In contrast to the current results, Tanaka et al. (2006) and Koyama et al. (2011) noted that HNF4α is not specific to gastrointestinal adenocarcinomas, as positive immunoreactivity in some cases of renal cell carcinomas, HCC, and ovarian neoplasms may be present. Tanaka et al., 2006 claimed that HNF4α immunomarker showed difference in neoplastic immunoreactivity for two isoforms. For instance, all 10 examined cases of renal cell carcinomas were positive for P1 and negative for P2. While gastric and colonic carcinomas were positive for P2 and less positive for P1. The difference may be due to variation of samples, difference in evaluation techniques, different isoforms, and included tumors variables.

In our study, HNF4α was expressed in 4 of 20 (20%) metastatic adenocarcinoma from the

upper gastrointestinal tract. Moore et al. (2016) and Colleypriest et al. (2017) explained HNF4α expression in some upper gastrointestinal tract carcinoma cases, as HNF4α showed positivity in gastric carcinoma cases with intestinal metaplasia. HNF4α was also expressed in esophageal goblet cell metaplasia (Barrett esophagus). They found that Overexpression of HNF4α in esophageal epithelium is suggestive of columnar phenotype of esophageal carcinoma.

We concluded that using HNF4α as a supplementary marker with CDX2 to detect metastatic colorectal adenocarcinoma is helpful. HNF4α expression is a highly specific and sensitive marker of colorectal origin. HNF4α may be a useful immunomarker for detection of intestinal adenocarcinomas.

Conflict of interest

The authors claim no conflict of interest.

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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

EACR **Chairman,**
Prof. Mohamed Labib Salem, PhD
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