Zagazig University Medical Journal
www.zumj.journals.ekb.eg
Volume 29, Issue 1, January 2023, Page (368-375) Supplement Issue

Manuscript ID ZUMJ-1909-1479 (R2)

DOI **10.21608/zumj.2019.16509.1479**

ORIGINAL ARTICLE

The Diagnostic Utility of Immunohistochemical expression of CDX2, CK7 and CK20 in Colorectal Adenocarcinoma

Asmaa A. latif *[1], Ragaa M Abd Elwahab[1], Naira A Abd Elhamid[2], Amira A Salem[1]

[1] *Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt*

[2] *Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt*

***Corresponding author:**
Asmaa Abdullatif Mohammed
Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
Email: Asma_abdullateef@hotmail.com

Submit Date 2019-09-21
Revise Date 2019-12-01
Accept Date 2019-12-20

ABSTRCT

Background: Invoking of primary site of carcinoma of unknown origin using immunohistochemistry is essential for accurate diagnosis, particularly in the current era of targeted therapies, smaller sample sizes.

This study aimed to assess immunohistochemical expression of CK7, CK20, CDX2 in metastatic colorectal, gastric, pancreatic adenocarcinomas, to evaluate their possible diagnostic role when metastatic colorectal carcinoma suspected in carcinoma of unknown primary site.

Methods: A retrospective study was performed on 80 paraffin blocks including 40 cases of documented colorectal carcinoma, 20 cases of gastric carcinoma and 20 cases of pancreatic carcinoma were stained by immunohistochemical technique using CK7, CK20, CDX2. The resulted data were statistically analyzed.

Results: CK7-ve/CK20+ve immunoprofile had a specificity of 95% in predicting colorectal adenocarcinomas, which was superior to that of CDX2. CDX2 positivity had a higher sensitivity (95%) than the CK phenotype.

Conclusions: Both CDX2 expression, and CK7-ve/CK20+ve are the most sensitive, specific markers for colorectal carcinoma. CDX2 is a useful adjunct for diagnosis of intestinal adenocarcinomas, particularly when CK7, CK20 yield equivocal results. CK7-ve/CK20+ve expression is superior in its specificity, positive predictive value.

Key Words: Colorectal adenocarcinoma; Gastric; Immunohistochemistry; CDX2; CK7; CK20.

INTRODUCTION

Colorectal carcinoma (CRC) ranks as the third most common cancer, the second leading cause of cancer related death worldwide in 2018[1]. In Egypt, it is the sixth commonest cancer among both males, female according to 2014 National cancer registry program results [2]. CRC is representing 53% of gastrointestinal tract cancers [3and4]. Although diagnosis of colorectal cancer is usually not difficult in the primary site. Yet it may represent a diagnostic problem as a metastatic tumor of unknown origin [5].

Metastatic tumor of unknown primary site is a common clinical problem, that accounts for 3-5% of malignancy making it one of top 10 cancers in incidence and mortality in both men and women as 90% of which proved to be carcinoma [6]. The identification of the primary site is a key for further therapy. The correct diagnosis can be reached through a combination of clinical findings, diagnostic imaging modalities, routine evaluation of hematoxylin and eosin (H&E) and evaluation of immunohistochemical markers for more accurate diagnosis [7]. Cytokeratins represent intermediate filaments of cytoskeleton in all epithelial cells, comprise 20 different polypeptides [8]. The relative expression of CK7/CK20 is still the cornerstone in narrowing the differential diagnosis of metastatic carcinoma of unknown primary [9]. CK20 is specific for GI tract, especially colorectal, urothelial and Merckel cell carcinoma. On the other hand, CK7 is characteristic for glandular malignancies originating from breast, lung, biliary tract, thyroid and Mullerian epithelium [10]. Despite this apparent tissue-specific distribution, ectopic CK20 expression in sporadic cases of carcinomas, derived from normally CK20 negative tissues, has also been noted, but this aberrant expression is restricted to a relatively limited sub-population of tumor cells [11]. CDX2 is a nuclear transcription factor that has a key role in the processes of intestinal cell proliferation and differentiation that can be used as IHC marker for neoplasm of intestinal origin [12]. Although CDX2

is used for detecting adenocarcinoma of colon, small intestine, it is variably expressed in gastric, pancreatic ductal carcinoma, cholangiocarcinoma [13]. Also broad range of CDX2 expression was seen in primary ovarian mucinous carcinoma [14].

METHODS

Tissue specimens: A retrospective study was performed on 80 paraffin blocks. Cases were collected from the Pathology Department, Zagazig University, in the period from October 2016 to January 2019. The selected specimens were obtained by surgical excision. Metastatic colorectal carcinoma (n=40) [group A], gastric carcinoma (n=20) [group B], and pancreatic carcinoma (n=20) [group C].

All included carcinomas were classified into well, moderately, or poorly differentiated, corresponding to WHO criteria [15].

Immunohistochemical staining

The primary antibodies used were rabbit anti-CDX2 monoclonal antibody (ACI 3144 A, B, Biocare Medical, USA, 1:100 dilution) , mouse anti-Cytokeratin 7 monoclonal antibody (C.M.061A,B,C, Biocare Medical, USA, 1:100 dilution) and anti-Cytokeratin 20 monoclonal antibody(C.M.062A,C, Biocare Medical, USA, 1:100 dilution).

Colonic mucosa was considered as positive controls for CDX2, CK20. Normal pancreatic tissue was used as a CK7 positive control. Negative controls were done by replacement of the primary antibodies with usual saline

Technique : Positively charged slides at thickness 5 microns were embedded in xylene for 5 minutes. Series of xylene, alcohol were done, then slides were microwaved in 0.01 M sodium citrate (pH 6.0) for antigen retrieval for 25 minutes. Incubation for 10 minutes with 3% hydrogen peroxide was done, then in 1.5% bovine serum albumin at room temperature for 1 h. Primary antibodies (anti-CDX2 or anti-CK7 or anti-CK20) were incubated at room temperature for 30 minutes, then a secondary antibody from a streptavidin biotin complex peroxidase kit was used with the substrate 3,3′-diaminobenzidine tetrahydrochloride (D.A.B; Dako) for 10 minutes in D.A.B. then, slides were rinsed with distilled water and immersed in Mayer's hematoxylin.

Interpretation of immunostaining

Evaluation of CDX2 expression:

Nuclear reactivity was considered as positive staining for CDX2. Cases were divided into the following groups: (negative): no staining and only few scattered positive cells <5% was considered to be negative; (1+): 5-25% of cells stained; (2+): 25-50% of cells stained; (3+): 51-100% of cells stained [5].

Evaluation of CK7, CK20 expression:

CK7 and CK20 were expressed in a membranous and/or cytoplasmic pattern and the tumor was considered positive for these antibodies if more than 5% of the tumor cells showed membranous and/or cytoplasmic staining. The extent of positive cells were recorded in a semiquantitative method according to a scale from 1 to 3; 6 -25% (1), 26 - 50% (2), and 51-100% (3). The pattern of staining was recorded as focal (<50%) or diffuse (>50%)[16].

The combination of immunohistochemical findings of CK7/CK20 was divided into four classes as follows: CK7+ve/CK20-ve, CK7-ve/CK2+ve, CK7+ve/CK20+ve, CK7-ve/CK20-ve [17]. Two pathologists evaluated all slides in a blinded manner

Ethical Consideration

A written consent was obtained from all cases. This work has been carried out following the Code of Ethics of the World Medical Association (Helsinki Declaration of 1975, as revised in 2000) for humans' studies.Institutional Review Board (IRB) of the faculty of Medicine Zagazig University affirmed the study protocol

STATISTICAL ANALYSIS

The collected data were tabulated and statistically analyzed using SPSS program version 18.0. Chi square test was used to calculate difference between qualitative variables. P value of <0.05, <0.01 indicates significant and highly significant results, respectively.

RESULTS

Cases were distributed in the age group of 40-80 years, overall male: female ratio was 2: 1 approximately. About 46.3% of the cases (37/80) were grade 2.

Immunohistochemical expression of CK7 and CK20 among the studied groups (N=80): (figure1-5).

CK20 was expressed in 92.5% (37/40) of colorectal, 65% (13/20) of gastric, and 25% (5/20) of pancreatic adenocarcinomas. Positive CK7 immunostaining was found in 7.5% (3/40) of colorectal, 90% (18/20) of gastric, 95% (19/20) of pancreatic adenocarcinomas. In CRC, CK20 positive cases was statistically significantly higher than CK7 positive cases (P<0.001).

Among the CK20 positive cases, CK20 expression showed a diffuse pattern in 86.5% (32/37) cases of colorectal carcinomas, and focal pattern in 76.9% (10/13), 100% (5/5) cases of gastric, pancreatic carcinomas respectively (p<0.001). On the other hand, CK7 expression had diffuse pattern in 66.7% (12/18), 84.2% (16/19) cases of gastric, pancreatic carcinomas respectively, and focal pattern in 66.7% (2/3) of colorectal carcinomas (p<0.001); as shown in **Table 1.**

Combination of CK20/CK7 immunoprofile showed that CK7-ve/CK20+ve was expressed by 35 of 40 (87.5%) colorectal, 2 of 20 (10%) gastric carcinomas, was not detected in any pancreatic carcinomas cases (p<0.001). CK7+ve/CK20+ve phenotype was detected in 2/40 (5%) of colorectal, 11/20(55%) of gastric, 5/20(25%) of pancreatic carcinomas. CK7+ve/CK20-ve was detected in 2% (1/40) of colon carcinomas, 35% (7/20) of gastric, 70% (14/20) of pancreatic adenocarcinomas (p<0.001). Only one case of pancreatic, 2 cases of colorectal and no gastric adenocarcinomas showed a CK7-ve/CK20-ve immunophenotype; as shown in **Table 2.**

Immunohistochemical expression of CDX2 among the studied groups (N=80): (figure 6,7).

The current study showed that CDX2 expression was detected in 38/40 (95%) colorectal, 12/20 (60%) gastric, 3 / 20 (15%) pancreatic adenocarcinoma cases (p<0.001).(**Table 2**)

Twenty four out of 38 (63%) of positive cases of CRC demonstrated strong, diffuse staining. On the other hand, 58.3% (7/12) positive cases of gastric carcinomas showed focal reactivity, All positive cases of pancreatic carcinoma showed focal CDX2 staining (p<0.001) as shown in **Table 1.**

Comparison between CK7/CK20 immuno-profile and CDX2 expression in our studied groups:

Thirty four out of 40 (85%) of colorectal carcinomas showed CK7-ve/CK20+ve/CDX2+ve immunoprofile. Conversely, CK7+ve/CK20+ve/CDX2+ve (8/20, 40%), CK7+ve/CK20-ve/CDX2-ve (12/20, 60%) were the commonest immunoprofile in gastric, pancreatic carcinomas respectively **as shown in Table 2.**

We also evaluated the diagnostic performance of CDX2, CK7-ve/ CK20+ve in distinguishing CRC from pancreatic and gastric adenocarcinoma. CK7-ve/CK20+ve immunoprofile had a specificity of 95% in predicting colorectal adenocarcinomas, which was superior to that of CDX2. CDX2 positivity had a higher sensitivity (95%) than the CK phenotype; as shown in Table 3.

Table (1): Distribution of CK7, CK20 and CDX2 staining with percentages of positive cells in primary colorectal, gastric and pancreatic adenocarcinomas

Cases		**negative**	**Positive**			**Total positive**
		0	1+	2+	3+	
Colorectal carcinoma (n=40)	CK7	37(92.5%)	2(5%)	1(2.5%)	0(0%)	3(7.5%)
	CK20	3(7.5%)	1(2.5%)	13(32.5%)	23(57.5%)	37(92.5%)
	CDX2	2(5%)	2(5%)	12(30%)	24(60%)	38(95%)
Gastric carcinoma (n=20)	CK7	2(10%)	1(5%)	8(40%)	9(45%)	18(90%)
	CK20	7(35%)	5(25%)	8(40%)	0(0%)	13(65%)
	CDX2	8(40%)	1(5%)	6(30%)	5(25%)	12(60%)
Pancreatic carcinoma (n=20)	CK7	1(5%)	1(5%)	2(10%)	16(80%)	19(95%)
	CK20	15(75%)	0(0%)	5(25%)	0(0%)	5(25%)
	CDX2	17(85%)	0(0%)	3(15%)	0(0%)	3(15%)

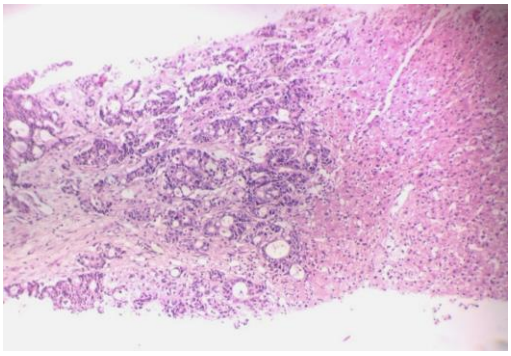
Table (2): Comparison of CK7/20 staining pattern and CDX2 expression in our studied groups

	Colorectal carcinoma (n =40)		**Gastric carcinoma (n =20)**		**Pancreatic carcinoma (n =20)**	
	CDX2+ve	**CDX2-ve**	**CDX2+ve**	**CDX2-ve**	**CDX2+ve**	**CDX2-ve**
CK7-ve/CK20+ve	34(85%)	1(2.5%)	2(10%)	0(0%)	0(0%)	0(0%)
CK7+ve/CK20+ve	1(2.5%)	1(2.5%)	8(40%)	3(15%)	1(5%)	4(20%)
CK7+ve/CK20-ve	1(2.5%)	0(0%)	2(10%)	5(25%)	2(10%)	12(60%)
CK7-ve/CK20-ve	2(5%)	0(0%)	0(0%)	0(0%)	0(0%)	1(5%)

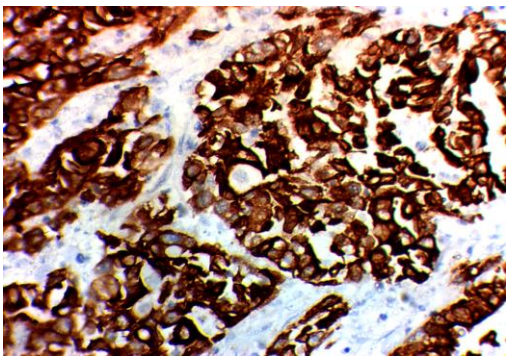
Table (3): Diagnostic performance of CDX2 expression and CK7-/CK20+ immunophenotype in differentiating colorectal adenocarcinomas from pancreatic and gastric adenocarcinomas

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
CDX2	95	62.5	71.7	92.5	78.8
CK7-ve/CK20+ve	87.5	95	94.6	88.4	91.2
CDX2 and CK7-ve/CK20+ve	85	95	94.4	86.4	90

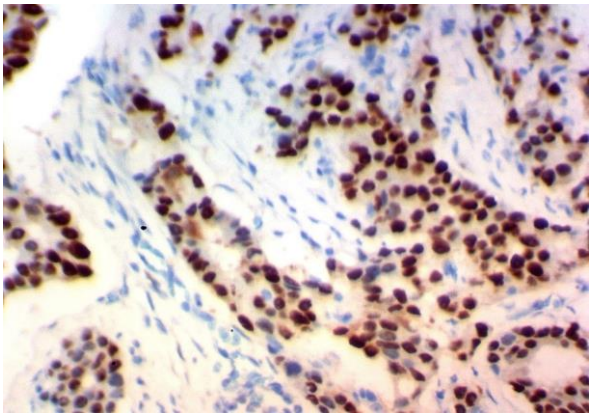
PPV: Positive Predictive Value **NPV**: Negative Predictive Value



(A)



(B)



(C)

Figure 1. A metastatic moderately differentiated colonic adenocarcinoma
(A: hematoxylin and eosin, X200) displayed diffuse, strong cytoplasmic and membranous staining for CK20 (B) and diffuse strong CDX2 nuclear expression(C). (B and C immunoperoxidase, X400).

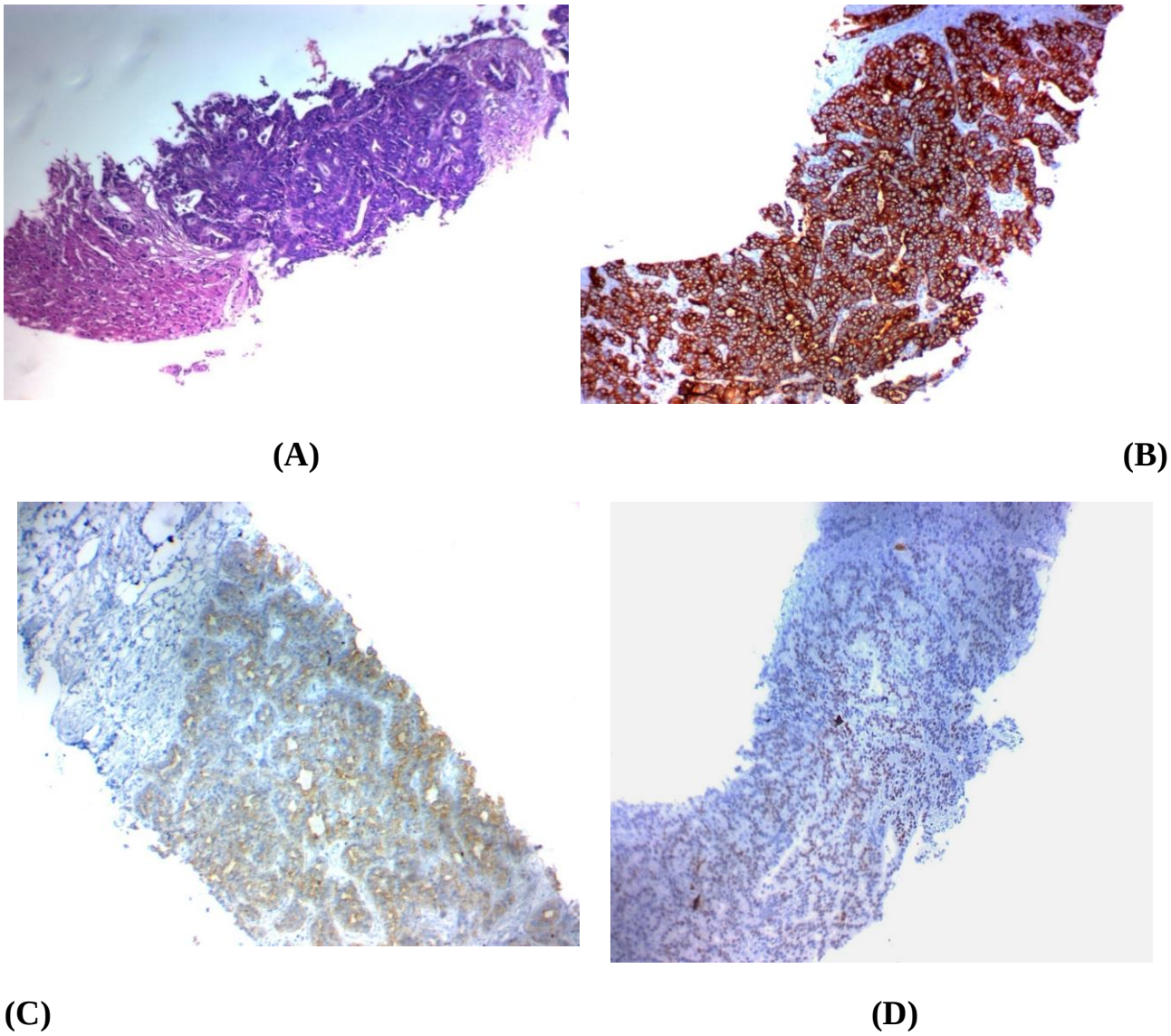


Figure 2. A metastatic moderately differentiated gastric adenocarcinoma (A: hematoxylin and eosin, X200) displayed diffuse, strong cytoplasmic and membranous staining for CK7 (B), weak cytoplasmic staining for CK20 (C), and diffuse moderate CDX2 nuclear expression(D). (B, C and D immunoperoxidase, X200).

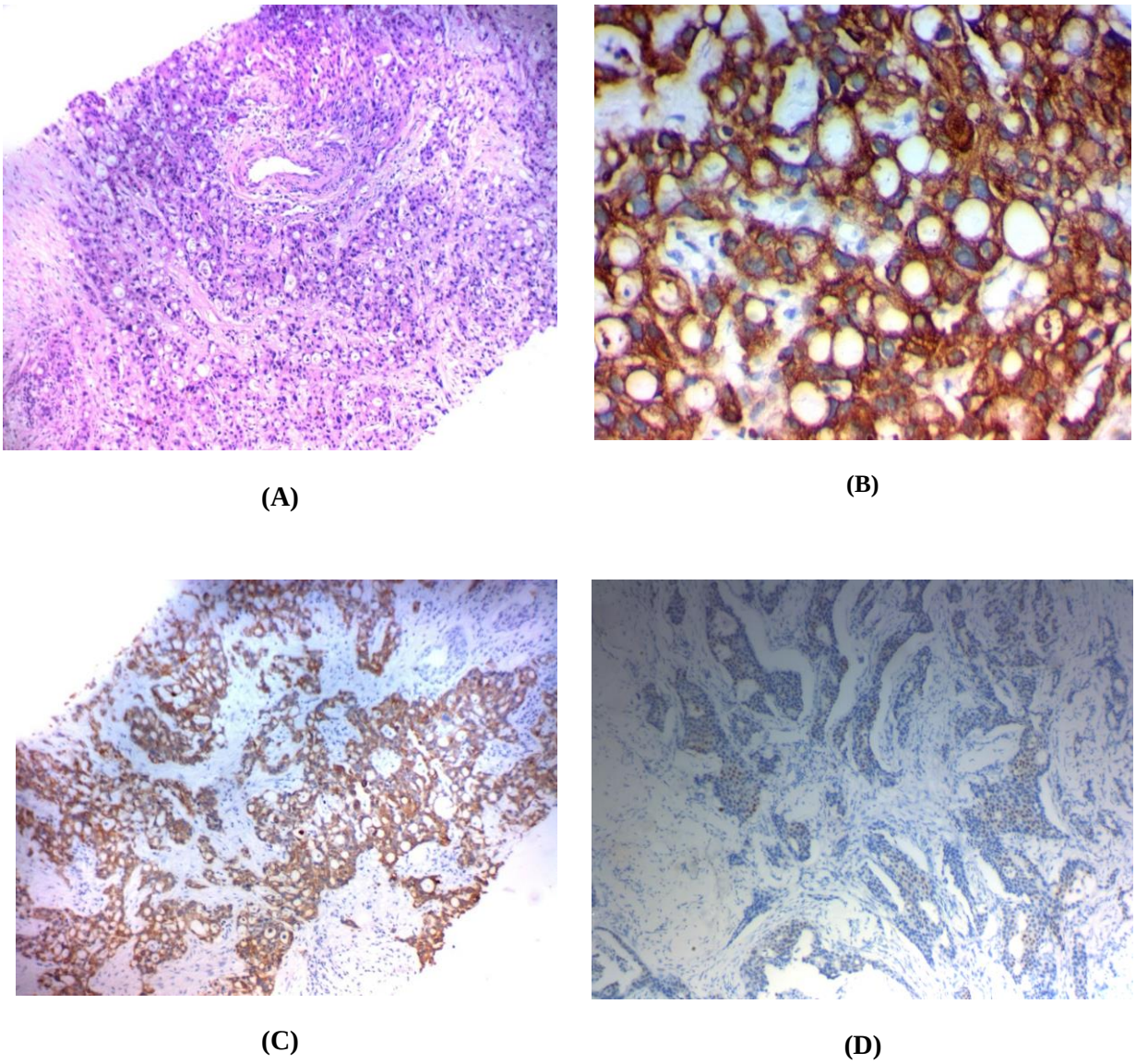


Figure 3. A metastatic poorly differentiated pancreatic adenocarcinoma (A: hematoxylin and eosin, X200) displayed diffuse, strong membranous and cytoplasmic staining for CK7 (B), diffuse, moderate cytoplasmic staining for CK20 (C), and focal, weak CDX2 nuclear expression(D). (B, C and D immunoperoxidase, (B),original magnification X400; (C)-(D), original magnification X 200

DISCUSSION

Carcinoma of unknown primary origin (CUP) is defined by histologically confirmed metastatic carcinoma in the absence of clinical, radiographic, or pathologic identification of a primary site [18].

Metastasis is a major cause of death of CRC patients who almost present with metastases before primary tumor is found. In such cases, immunostaining is one of the helpful methods to identify the primary site [19].

Previous studies reported that CK7-ve/CK20+ve pattern identifies in CRC between 65% to 95% [16, 21, and 22], compared with one third of gastric carcinomas, and less than 10% of pancreatic carcinomas[23,24,25, 26]. These results are consistent with the current results in which 87.5% of CRC, 10% of gastric carcinoma showed CK7-ve/CK20+ve immunophenotype. However, non of pancreatic carcinomas expresses this pattern.

Our results also are in line with results of studies convoyed by **Bayrak et al.,** [5], who found that CK7-ve/CK20+ve phenotype showed a specificity of 96.7% % in identifying CRC.

Heterogeneity of gastric and pancreatic carcinomas was noticed having a non-specific immunoprofile. Also there is overlapping between CK7 and CK20 expression in CRC and other adenocarcinomas [27]. In the present study, 5% of CRC, 55% of gastric, 25% of pancreatic carcinomas showed CK7+ve/CK20+ve profile. This profile is not useful to suggest a specific anatomic site of origin. However, CK20 expression was diffuse in the majority of CRC cases, mainly focal in gastric, pancreatic adenocarcinomas as in previous studies [6, 27, 28].The utility of CK7 and CK20 are not

helpful in predicting site of origin of adenocarcinoma in the absence of morphologic or immunohistochemical support [18]. CDX2 is a nuclear transcriptional regulator of intestinal cell differentiation and survival. It is considered specific for enterocytes [29, 30].

The expression of CDX2 was found in 95% of CRC, 60% of gastric carrcinomas, and 15% of pancreatic adenocarcinomas ($p<0.001$). These findings support the view of **Logani et al [**31].**Yang et al**[32].**and Moskaluk et al [**33] who concluded that CDX2 is typically used for diagnosis GIT adenocarcinomas, particularly duodenum, and colon. Results obtained by **Altree-Tacha et al**[34] and **Barbareschi et al**[35] stated that CDX2 expression is highly sensitive for metastatic colorectal carcinoma, but also stains gastric, pancreatiobillary, ovarian carcinoma.

Results of this study also are consistent with results of **Zhang et al**[36] who showed that CDX2 expression is significantly higher in gastric carcinoma compared to normal gastric mucosa, indicating that CDX2 is up-regulated in the gastric tumorigenesis with a reported positivity in 53.3% of 60 cases. **Kaimaktchiev et al [**37] also found CDX2 expression in 22.5% of gastric carcinomas cases particularly in intestinal-type.

With regard to CDX2 expression in pancreatic ductal adenocarcinoma. **Chu et al [**38] and **Xiao et al [**39], both reported heterogeneous CDX2 expression in 22%, 36.1% of studied cases, respectively, which has been challenged by others showing no CDX2 expression. [40]

Based on previous studies, we noted that CDX2 cannot differentiate CRC, from gastric carcinoma, pancreatic carcinomas, although CDX2 had a higher sensitivity for CRC than for gastric and pancreatic one. The pattern of CDX2 positivity can also be of diagnostic value; in most carcinomas of the stomach, pancreas, and biliary tract, CDX2 staining is usually observed at low levels in scattered tumor cells, in contrast to the uniform, robust CDX2 immunostaining characteristic of CRC. We also found that CK7-ve/CK20+ve expression displayed a higher specificity for CRC than CDX2 alone (95% vs 62.5%), but less sensitive (87.5% vs. 95%). A panel of CK7, CK20, and CDX2 has been used to assess GIT carcinoma of unknown primary.

CONCLUSION

This study point to the CK20+ve/CK7-ve immunophenotype which is more specific in predicting the colorectal origin of metastasis than CDX2 expression. Both the CK7-ve/CK20+ve phenotype, CDX2 expression are highly specific, sensitive markers of CRC.

Conflicts of interest: no conflicts of interest.

Financial Disclosures: non

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence, mortality worldwide for 36 cancers in 185 countries. Cancer j clin 2018; 68(6):394-424.
2. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol 2014; 2014:1-18.
3. Gohar SF, AlHassanin SA, El-Assal M, Hussein AM. Clinico-Epidemiology Study of Colorectal Cancer in Menofia University Oncology Department. Nat Sci 2015; 13(11):98-105.
4. Metwally IH, Shetiwy M, Elalfy AF, Abouzid A, Saleh SS, Hamdy M. Epidemiology, survival of colon cancer among Egyptians: a retrospective study. J Coloproctol (Rio J) 2018; 38(1): 24-29.
5. Bayrak R, Haltas H, Yenidunya S. The value of CDX2 and cytokeratins 7 and 20 expression in differentiating colorectal adenocarcinomas from extraintestinal gastrointestinal adenocarcinomas: cytokeratin 7-/20+ phenotype is more specific than CDX2 antibody. Diag Pathol 2012; 7: 1- 9.
6. Selves J, Long-Mira E, Mathieu MC, Rochaix P, Ilie M. Immunohistochemistry for diagnosis of metastatic carcinomas of unknown primary site. Cancers 2018;10(4):108.
7. Park SY, Kim BH, Kim JH, Lee S, Kang GH. Panels of immunohistochemical markers help determine primary sites of metastatic adenocarcinoma. Arch Pathol Lab Med 2007; 131(10):1561-1567.
8. Chandan V.S. Metastatic Tumors. In: Mounajjed T, Chandan V, Torbenson M. Surgical pathology of liver tumors. Springer 2015; 435-464
9. Park JH, Kim JH. Pathologic differential diagnosis of metastatic carcinoma in the liver. Clin Mol Hepatol 2019; 25(1):12-20.
10. de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V, Nagtegaal I. Incidence, origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. Oncotarget 2016; 7(34): 55368- 55376.
11. Ordóñez NG. Broad-spectrum immunohistochemical epithelial markers: a review. Hum Pathol 2013; 44(7):1195-1215.
12. Bae JM, Lee TH, Cho NY, Kim TY, Kang GH. Loss of CDX2 expression is associated with poor prognosis in colorectal cancer patients. World J Gastroenterol 2015; 21(5):1457-1467.
13. Pavlidis N and Pentheroudakis G. Cancer of unknown primary site. Lancet 2012; 379(9824):1428-1435.
14. Moh M, Krings G, Ates D, Aysal A, Kim GE, Rabban JT. SATB2 expression distinguishes ovarian metastases of colorectal, appendiceal origin from primary ovarian tumors of mucinous or endometrioid type. Am J Surg Pathol 2016; 40(3):419-432.
15. Bosman FT, Carneiro F, Hruban RH. Theise ND.WHO classification of tumors of the digestive system. World Health Organization 2010; 4th Ed.

16. Al-Maghrabi J, Emam E, Gomaa W. Immunohistochemical staining of cytokeratin 20, cytokeratin 7 in colorectal carcinomas: Four different immunostaining profiles. Saudi J Gastroenterol 2018; 24(2):129-34.
17. Lin F, Liu H. Immunohistochemistry in undifferentiated neoplasm/tumor of uncertain origin. Arch Pathol Lab Med 2014; 138(12):1583-1610.
18. Stelow EB, Yaziji H. Immunohistochemistry,carcinomas of unknown primary, incidence rates. Semin Diagn Pathol 2018; 35(2):143-152.
19. Li Z, Rock JB, Roth R, Lehman A, Marsh WL, Suarez A, et al. Dual stain with SATB2, CK20/Villin is useful to distinguish colorectal carcinomas from other tumors. Am J Surg Pathol 2018; 149(3): 241-246.
20. Saad RS, Silverman JF, Khalifa MA, Rowsell C. CDX2, cytokeratins 7, 20 immunoreactivity in rectal adenocarcinoma. Appl Immunohistochem Mol Morphol 2009;17(3):196-201
21. Perysinakis I, Minaidou E, LeontaraV, Mantas D, Sotiropoulos GC, Tsipras H, et al., Differential expression of β-catenin, EGFR, CK7, CK20, MUC1, MUC2, CDX2in intestinal, pancreatobiliary-type ampullary carcinomas. Inter J surg pathol 2017; 25(1): 31-40.
22. Bensaada FZ, Cadi HO, Sahraoui T, El Kebir FZ. Colorectal Cancer: Epidemiological Study, Clinical, Histological, Immunohistochemistry Examination in Patient of West Algeria. JCT 2017; 8: 26-36.
23. Oue N, Sentani K, Sakamoto N, Yasui W. Clinicopathologic, molecular characteristics of gastric cancer showing gastric, intestinal mucin phenotype. Cancer sci 2015; 106(8):951-958.
24. Ugras N, Atalay FO, Yerci GO. Cytokeratin 7/20 expression patterns, association with prognostic variables in gastric adenocarcinomas. Acta Medica 2014; 30:1041.
25. Park S, Kim H, Hong EK, Kim WH. Expression of cytokeratins 7, 20 in primary carcinomas of the stomach, colorectum, their value in the differential diagnosis of metastatic carcinomas to the ovary. Hum pathol 2002: 33(11):1078-1085.
26. Tot T. Cytokeratins 20, 7 as biomarkers: usefulness in discriminating primary from metastatic adenocarcinoma. Eur J Cancer 2002; 38(6):758-763.
27. Kandalaft PL, Gown AM. Practical applications in immunohistochemistry: carcinomas of unknown primary site. Arch pathol lab med 2015; 140(6): 508-523.
28. Duval JV, Savas L, Banner BF. Expression of cytokeratins 7, 20 in carcinomas of the extrahepatic biliary tract, pancreas, gallbladder. Arch pathol lab med 2000; 124(8): 1196-1200.
29. Dalerba P, Sahoo D, Paik S, Guo X, Yothers G, Song N, et al., CDX2 as a prognostic biomarker in stage II, stage III colon cancer. N Engl J Med 2016; 374(3): 211-222.
30. Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: its utility, limitations. World J gastrointest surg 2011; 3(11):159-166.
31. Logani S, Oliva E, Arnell PM, Amin MB, Young RH. Use of novel immunohistochemical markers expressed in colonic adenocarcinoma to distinguish primary ovarian tumors from metastatic colorectal carcinoma. Mod pathol 2005; 18(1):19-25.
32. Yang Z, Klimstra DS, Hruban RH, Tang LH. Immunohistochemical characterization of the origins of metastatic well-differentiated neuroendocrine tumors to the liver. Am J surg pathol 2017; 41(7): 915-922.
33. Moskaluk CA, Zhang H, Powell SM, Cerilli LA, Hampton GM, Frierson Jr HF. CDX2 protein expression in normal, malignant human tissues: an immunohistochemical survey using tissue microarrays. Mod pathol 2003; 16(9): 913-919.
34. Altree-Tacha D, Tyrrell J, Haas T. CDH17 is a more sensitive marker for gastric adenocarcinoma than CK20, CDX2. Arch Pathol lab med 2016; 141(1): 144-150.
35. Barbareschi M, Murer B, Colby TV, Chilosi M, Macri E, Loda M et al., CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. Am J surg pathol 2003; 27(2): 141-149.
36. Zhang Y, Wang H, Bi C, Xiao Y, Liu Z. Expression of CDX2in gastric cardia adenocarcinoma, its correlation with H. pylori, cell proliferation. Oncotarget 2016; 7: 54973-54982.
37. Kaimaktchiev V, Terracciano L, Tornillo L, Spichtin H, Stoios D, Bundi M et al. The homeobox intestinal differentiation factor CDX2 is selectively expressed in gastrointestinal adenocarcinomas. Mod pathol 2004; 17: 1392- 1399.
38. Chu PG, Schwarz RE, Lau SK, Yen Y, Weiss LM. Immunohistochemical staining in the diagnosis of pancreatobiliary, ampulla of Vater adenocarcinoma: application of CDX2, CK17, MUC1, MUC2. Am J surg pathol 2005; 29: 359-367.
39. Xiao W, Hong H, Awadallah A, Zhou L, Xin W. Utilization of CDX2 expression in diagnosing pancreatic ductal adenocarcinoma, predicting prognosis. PloS ONE 2014; 9(1): e86853.
40. Liu H, Shi J, Anandan V, Wang HL, Diehl D, et al. Reevaluation, identification of the best immunohistochemical panel (pVHL, Maspin, S100P, IMP-3) for ductal adenocarcinoma of the pancreas. Arch Pathol lab Med 2012; 136: 601–609.

To Cite:

latif, A., Abd Elwahab, R, Abd Elhamid, N, Salem, A., The Diagnostic Utility of Immunohistochemical expression of CDX2, CK7 and CK20 in Colorectal Adenocarcinoma. Zagazig *University Medical Journal*, 2023; (368-375): -.doi: 10.21608/zumj.2019.16509.1479.