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Intestinal, intestinal-type and intestine-localized metastatic adenocarcinoma. Immunohistochemical approach to the differential diagnosis

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Abstract. The pathologist is often called to define the origin of tumors through the help of ancillary studies, mainly immunohistochemical stainings. In this setting, the differential diagnosis between intestinal adenocarcinomas, other tumors with intestinal-type morphology, and adenocarcinomas metastatic to the bowel can be particularly difficult. In such cases, an accurate assessment of the disease is required to address the patients to the optimal treatment. Immunohistochemistry offers the use of multiple antibodies: the integrated evaluation of specific stainings can lead to a correct diagnosis. Particularly, the use of cytokeratins, mucins, and β-catenin could be of great help in most cases. In addition, recently, novel specific markers such as SATB2 and AMACR have been introduced, improving the utility of immunohistochemistry in the differential diagnosis of intestinal-type and intestinal adenocarcinomas.

Key Words:
Intestinal type, Cancer, Prognostic factors, Immunohistochemical.

Introduction

The distinction between primary tumors and metastatic tumors of unknown origin is a frequent challenge in surgical pathology routine practice. In most cases, histological features, combined with clinical and instrumental findings, are enough to identify the origin of a neoplasm. However, in some cases, morphology may not be sufficiently specific since some neoplasms may aberrantly show phenotypical – both morphological and immunohistochemical (IHC) – features that are considered typical of other entities. When this occurs, establishing the site of origin of a tumor, even upon meticulous clinical-pathological correlation, can be extremely difficult, mainly when facing metastatic and disseminated diseases. In this setting, the evaluation of neoplasms with an intestinal-type phenotype is one of the most common issues. Intestinal-type adenocarcinomas are a heterogeneous group of neoplasms mimicking carcinomas or adenomas of intestinal origin. Intestinal phenotype is morphologically characterized by columnar cells, hyperchromatic, cigar-shaped, and pseudostratified nuclei, and dense eosinophilic cytoplasms; cells are arranged in glandular structures, often containing cellular debris and inflammatory cells, the so-called "dirty necrosis". These morphological features are conventionally seen in colorectal and small intestine adenocarcinomas, as well as in a proportion of gastric cancers. The same holds true for tumors with a mucinous phenotype, which can be considered a sort of variant of the intestinal phenotype, given its higher frequency in neoplasms of gastrointestinal origin as compared to neoplasms of other origins. Intestinal- and mucinous-type tumors, however, may arise in almost every other anatomic location, including head and neck, lung, ovary, urinary bladder and others. Conversely, although regarded as a rare occurrence, the gastrointestinal tract can be site of metastatic adenocarcinomas from other organs; in addition, other primitive tumors arising in the gastrointestinal tract, such as gastrointestinal stromal tumors or neuroendocrine tumors, could show features resembling those of conventional adenocarcinomas.

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In all these cases, the correct identification and subtyping of the neoplasm is mandatory and can dramatically influence the therapeutic choices, as specific biological treatments may apply only to specific neoplasms. Numerous IHC markers could aid to identify the origin of the tumors of uncertain derivation. Particularly, intestinal-type tumors arising away from the gastrointestinal tract could offer most problems. Nowadays, it has been clearly established that intestinal-type tumors of different origin classically show at least a partial enteric immunophenotype, defined by positivity for cytokeratin 20 and CDX2. As a consequence, these markers cannot be considered specific for intestinal origin and may not be sufficient for differential diagnostic purposes[1]. Other useful markers in intestinal-type tumors are mucins – a group of high molecular weight glycoproteins produced by epithelial cells, which are heterogeneously expressed in the digestive tract, being MUC2 typically positive in intestinal mucosa[2]. Unfortunately, neither mucins expression profiles are specific enough to reliably identify the exact origin of an intestinal-type tumor. Considering the so-far discussed difficulties in diagnosing tumor with an enteric phenotype and the limits of traditional immunohistochemistry, the aim of the current work is to analyze the IHC features of adenocarcinomas arising in the gastrointestinal tract and to review the most recent and promising IHC markers of diagnostic utility for neoplasms with an intestinal-type phenotype arising from different organs.

Overview of Gastrointestinal Tract Tumors

Gastrointestinal adenocarcinomas: histological variants and immunophenotypes

Several tumors, with different histogenesis, can develop in the gastrointestinal (GI) tract. Adenocarcinomas (ACs) represent the most frequently encountered histotype in the GI tract[3]. Conventional adenocarcinomas could show some peculiarities according to the site of origin, from the stomach to the rectum, but some common histological variants could be recognized throughout the entire digestive system. For example, tumors with pure mucinous differentiation represent a histological variant of classic AC, characterized by abundant mucin production, constituting > 50% of the neoplastic mass[4]. The incidence of this histotype varies by location in the digestive tract, with the highest frequency found in the appendix, where it represents more of 50% of tumors[5], followed in descending order by colon, rectum, small intestine, stomach and esophagus[6]. Another characteristic histotype is Signet Ring Cell Carcinoma (SRCC), defined by the presence of > 50% tumor cells with a signet-ring morphology[7]. SRCC occurs more frequently in the stomach, but it can localize throughout the digestive tract as well as in other different anatomic locations[8].

Stomach

Gastric adenocarcinomas include distal carcinomas located in the corpus or in the antrum-pyloric region, and carcinomas of esophageal-gastric junction[9]. In clinical practice, this topographic distinction does not usually produce diagnostic challenges and, from a molecular standpoint, important immunophenotype differences between distal and junctional tumors do not exist.

Microscopically, these entities are classified as Intestinal-type and Diffuse-type adenocarcinomas according to Lauren Classification[10].

Intestinal- and diffuse- type adenocarcinomas show variable expression of low molecular weight cytokeratins (CKs), with prevalence of CK7 over CK20 and CK19[11]. CDX2 expression, as well as HepPar-1, is more prominent in diffuse gastric carcinomas rather than in intestinal-type cancers[3], but with lower expression rates than those observed in the colorectal cancer (Figure 1). In addition, mucins are characteristically expressed by gastric adenocarcinomas with the following profile: MUC1+, MUC2-, MUC5AC+/-, while diffuse-type carcinomas and SRCCs show a MUC1-, MUC2+/-, MUC5AC+, MUC6+ phenotype[12]. Moreover, gastric SRRCs demonstrate higher EMA expression levels than their colorectal counterpart[8].

Mucinous gastric carcinoma represents a histotype with a specific molecular profile and distinctive immunophenotype[13]. It shows higher CK20 and CDX2 immunohistochemical expression than conventional adenocarcinomas and mucins profile shows intense and diffuse positivity for MUC2 and MUC5AC and negativity for MUC1[12]. Finally, an interesting marker whose expression has been studied on both the upper and lower digestive tract is Alpha-methylacyl-CoA racemase (AMACR). Particularly, in the stomach, AMACR is negative in gastric normal and reactive mucosa, whereas IHC positivity is observed in the dysplastic epithelium. Moreover, both intestinal- and diffuse-type carcinomas show expression of AMACR, with lower rates in the latter[14].

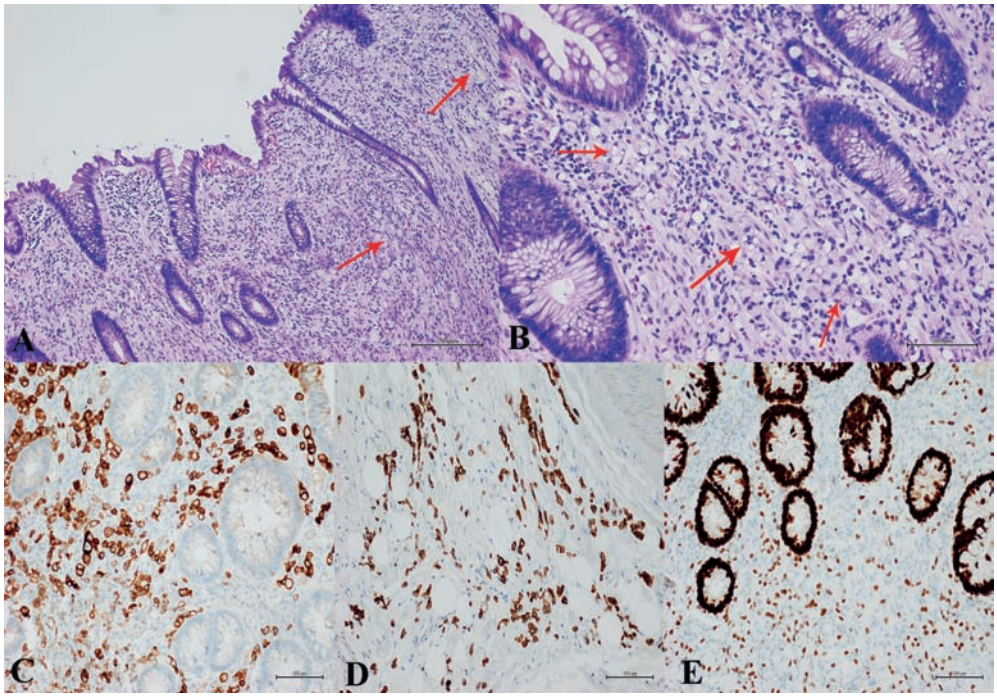

Figure 1. A 68-year-old woman with a previous diagnosis of diffuse-type gastric adenocarcinoma. The patient was hospitalized for intestinal obstruction and underwent transverse colon resection surgery. Histological examination showed full-thickness infiltration of the intestinal wall by a neoplastic signet ring cells admixed with normal colonic glands (**A**-**B**, *red arrows*). Immunohistochemical stains showed positivity for CK7 (**C**), for CK20 (**D**) and positivity for CDX2 (**E**) with lower intensity of staining than that of surrounding colonic glands. A diagnosis of colonic infiltration by signet ring cell adenocarcinoma was rendered. **A**, 10x magnification; **B**-**C**-**D**-**E**, 20x magnification.

Small Intestine

Neoplasms originating in the small intestine are very rare and constitute about 0.4% of total cancers in United States[15]. They can be located along all segments of the small intestine, but the most frequent are represented by adenocarcinomas of the ampulla of Vater in the duodenum[3]. Ampullary neoplasms include two major histologic subtypes: intestinal-type and pancreatobiliary-type. These two entities are morphologically very similar but have a different immunophenotype[16]. Intestinal-type tumors show positivity for CK7, CK20, CDX2, and MUC2, whereas pancreatobiliary-type tumors are positive for CK7, CK17, and MUC1[17]. The differential diagnosis between the two subtypes has a considerable clinical impact, because intestinal-type neoplasms have a significantly better prognosis.

In general, adenocarcinomas of the small intestine, in contrast with those of the large intestine, show diffuse positivity for CK7 and lower rates of CK20 and CDX2 expression[18].

Another IHC marker, showing positivity in almost 100% of small intestine adenocarcinomas, is Villin, a cytoskeletal protein expressed in small intestinal microvilli[19]. AMACR shows lower rates than those seen in colorectal cancer[20] (Figure 2).

Large Intestine

Adenocarcinomas of the large intestine are divided in conventional type-adenocarcinomas, pure mucinous adenocarcinomas and primitive SRCCs of proximal colon and colorectal region. Some interesting differences regarding the immunophenotype have been observed.

According to the literature, usual IHC profile of large intestine adenocarcinomas is CK20+, CDX2+, CK7-[3]. Nevertheless, up to 70% of primary rectal adenocarcinomas and 27% of proximal adenocarcinomas express CK7[21].

As regards mucins profile, different patterns of expression depending on the histotype are recognized. Indeed, MUC2 is positive in the majority of the large intestine adenocarcinomas, especially in mucinous tumors[22], whereas MUC1 and MUC5AC show variable expression in conventional adenocarcinomas, however with lower rates than in the upper digestive tract tumors[12]. Moreover, mucins profile could help distinguishing a primitive colonic SRCC from a gastric metastasis. In

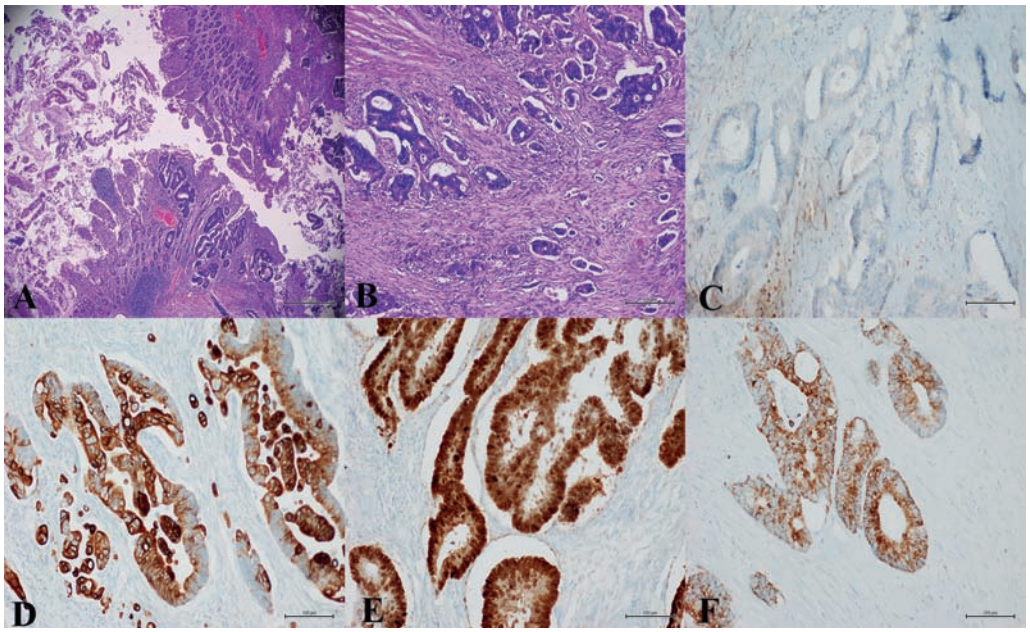

Figure 2. A 49-year-old male with previous history of rectal adenocarcinoma treated with surgery was admitted at the hospital with severe abdominal pain and diagnosed with ileal bowel obstruction. Bowel resection showed an intramural mass with mucosal ulceration. Microscopic examination showed adenocarcinoma ulcerating the ileal mucosa (**A**) with full-thickness wall invasion and diffuse lymphovascular embolization (**B**). Immunohistochemical analysis highlighted negativity for CK7 (**C**) and positivity for CK20 (**D**); CDX2 (**E**) and AMACR (**F**) were positive. The diagnosis was ileal metastasis from rectal adenocarcinoma. **A**, 10x magnification; **B-C-D-E-F**, 20x magnification.

fact, primitive colonic tumors show higher expression of MUC1 and MUC2, whereas gastric SRCCs tend to express MUC5AC and MUC6[23].

As previously mentioned, AMACR is positive in large intestine adenocarcinomas, where higher expression rates are observed in the left-sided tumors than in right-sided ones[24]. Moreover, AMACR expression is associated with more favourable tumor grade and is more frequent in conventional adenocarcinomas than in mucinous carcinomas[25].

A marker to be considered for its usefulness in distinguishing colorectal tumors is the nuclear expression of β-catenin. Indeed, β-catenin translocation to the nucleus, resulting from APC inactivation or direct β-catenin mutations, is an essential step in colorectal carcinogenesis. β-catenin nuclear immunostaining is seen in virtually 100% of conventional colorectal adenocarcinomas, while it is usually absent (or very rare) in other CK20-positive adenocarcinomas or carcinomas arising at other levels in the GI tract[26,27].

Recently, a novel marker, SATB2, has been introduced, being selectively expressed by colonic and appendiceal neoplasms[28]. SATB2 is negative in neoplasms with an intestinal phenotype arising from other organs, such as ovary, uterine cervix, pancreas, and biliary tract[29]. It seems to be superior to CDX2 in distinguishing metastatic SRCCs of the lower GI tract from those of the upper GI tract[30].

Expression profiles of cytokeratins, mucins, and other markers of diagnostic utility in gastrointestinal carcinomas are summarized in Tables I, II, and III, respectively.

The Differential Diagnosis Between Primary Adenocarcinomas and Other Primary Tumors of the GI Tract

Epithelium-derived tumors other than adenocarcinomas in the GI tract mainly include neuroendocrine tumors (NETs), arising from enterochromaffin/neuroendocrine cells dispersed throughout the stomach, small and large intestine. In the colorectal tract, NETs may show a pseudoglandular architecture. Of note, NETs usually express cytokeratins alongside with neuroendocrine markers (including chromogranin, synaptophysin, NSE and CD56). On the other hand, the expression of neuroendocrine markers in colorectal adenocarcinomas has also been described[31,32]. Consequently, in exceptional case, the differential diagnosis from primary GI adenocarcinoma and NET may be problematic. Insulino-

Table I. Cytokeratins expression profiles in gastrointestinal adenocarcinomas.

	Gastric Intestinal ADC	Gastric Diffuse ADC & SRCC	Gastric Mucinous ADC	Intestinal Ampullary ADC	PB Ampullary ADC	Colon Conventional ADC	Colon Mucinous ADC	Colon SRCC
CK7	+	+	+	+	+	-*	-	-
CK20	±	±	+	∓	-	+	+	+
CK19	±	∓	-		+	±	∓	±
CK17	-	-	-	-	+	-	-	-

+ positive, - negative, ± variable expression, more frequently positive ∓ variable expression, more frequently negative; ADC = adenocarcinoma; SRCC = signet ring cell carcinoma; PB = pancreatobiliary. * Variable expression only in distal/rectal adenocarcinomas

Table II. Cytokeratins expression profiles in gastrointestinal adenocarcinomas.

	Gastric Intestinal ADC	Gastric Diffuse ADC & SRCC	Gastric Mucinous ADC	Intestinal Ampullary ADC	PB Ampullary ADC	Colon Conventional ADC	Colon Mucinous ADC	Colon SRCC
MUC1	+	∓	-	-	+	±	+	±
MUC2	∓	∓	+	+	-	+	+	+
MUC5AC	±	+	+	-	±	±	-	∓
MUC6	+	+	±	-	-	-	-	-

+ positive; - negative; ± variable expression, more frequently positive; ∓ variable expression, more frequently negative; ADC = adenocarcinoma; SRCC = signet ring cell carcinoma; PB = pancreatobiliary.

Table III. CDX2, AMACR, Villin and SATB2 expression in gastrointestinal adenocarcinomas.

	Gastric Intestinal ADC	Gastric Diffuse ADC & SRCC	Gastric Mucinous ADC	Intestinal Ampullary ADC	PB Ampullary ADC	Colon Conventional ADC	Colon Mucinous ADC	Colon SRCC
CDX2	±	±	±	+	-	+	+	+
AMACR	+	±	∓	-	-	+	∓	-
Villin	-	-	-	+	-	±	-	-
SATB2	-	∓	-	-	-	+	+	+

+ positive, - negative, ± variable expression, more frequently positive ∓ variable expression, more frequently negative; ADC = adenocarcinoma; SRCC = signet ring cell carcinoma; PB = pancreatobiliary.

ma-associated protein 1 (INSM1) is a novel IHC marker, showing high specificity and sensitivity for neuroendocrine neoplasms in several anatomic sites[33,34,35,36]. INSM1 has recently been tested in colorectal NETs, demonstrating a specificity of 95.7%, higher than that of Chromogranin, Synaptophysin, and CD56[37].

Other primary GI tumors include mesenchymal neoplasms. Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms in the GI tract. They can arise anywhere in the digestive system but most frequently affect the stomach followed by the small bowel and the colon-rectum.

Generally, the distinct morphology of GISTs allows to easily differentiate them from intestinal adenocarcinomas. However, when the morphological diagnosis is not straightforward (undifferentiated adenocarcinoma VS epithelioid GIST), immunohistochemistry is mandatory: c-Kit and DOG-1 are the markers of highest specificity for a diagnosis of GIST[38] while their aberrant expression is regarded as a rare event in intestinal adenocarcinomas[39]. The IHC profile of GIST is completed with CD34 (+/-), a-SMA (-/+), S100 (-), and desmin (-) that allow the differential diagnosis between GIST and other GI mesenchymal tumors[40].

The Differential Diagnosis Between Primary Adenocarcinomas of the GI Tract and GI Metastasis From Other Neoplasms

The stomach and the bowel are an infrequent target of metastases from extraintestinal neoplasms, representing less than 1% of all colorectal tumors [41]. Metastases to GI tract can derive from primitive neoplasms of lung[42], skin (melanoma)[43], gynecological system[44], breast[45] and many others. Most patients present with multiple lesions causing obstruction, anemia, bleeding and weight loss[41]. Nevertheless, metastases may be asymptomatic and discovered as incidental findings in up to one third of cases.

Lung cancers, mainly adenocarcinomas or squamous cell carcinomas, are the most common cause of GI metastases[46]. Excluding rare subtypes, the immunophenotype of primary lung malignancies easily allows their recognition from GI adenocarcinomas. Conventional lung cancers do not usually express the previously discussed markers with high specificity for gastrointestinal origin, such as AMACR, villin, nuclear β-catenin and SATB2. Moreover, unlike primary GI adenocarcinomas, lung adenocarcinomas are TTF-1+, napsin A+, CK7, and CK20 -[47].

Melanoma metastases may need to be distinguished from an undifferentiated intestinal carcinoma. Although morphology alone often leads to the diagnosis, an IHC support is of vital importance. Metastatic melanoma may lose the expression of melanocytic markers, like HMB45 and Melan-A. In this setting, more sensitive, although less specific, melanoma markers include S100 and SOX10[48].

An invasive lobular breast carcinoma (BC) metastatic to the bowel may be challenging to distinguish from a primitive signet ring cell carcinoma[49]. Immunohistochemistry can reveal the expression of estrogen and/or progesteron receptors but it must be borne in mind that estrogen receptors are expressed by a proportion of gastric cancers[50]. Other useful markers include MUC1 (positive in BC, negative in GI adenocarcinomas), MUC2 and MUC5AC (negative in BC) gross cystic disease fluid protein 15 (GCDFP-15) and mammoglobin (positive in BC, negative in GI adenocarcinomas)[51,52].

Endometrial carcinomas metastases to the bowel have been described, but they are rare, with less than ten published cases (Figure 3). An endo-

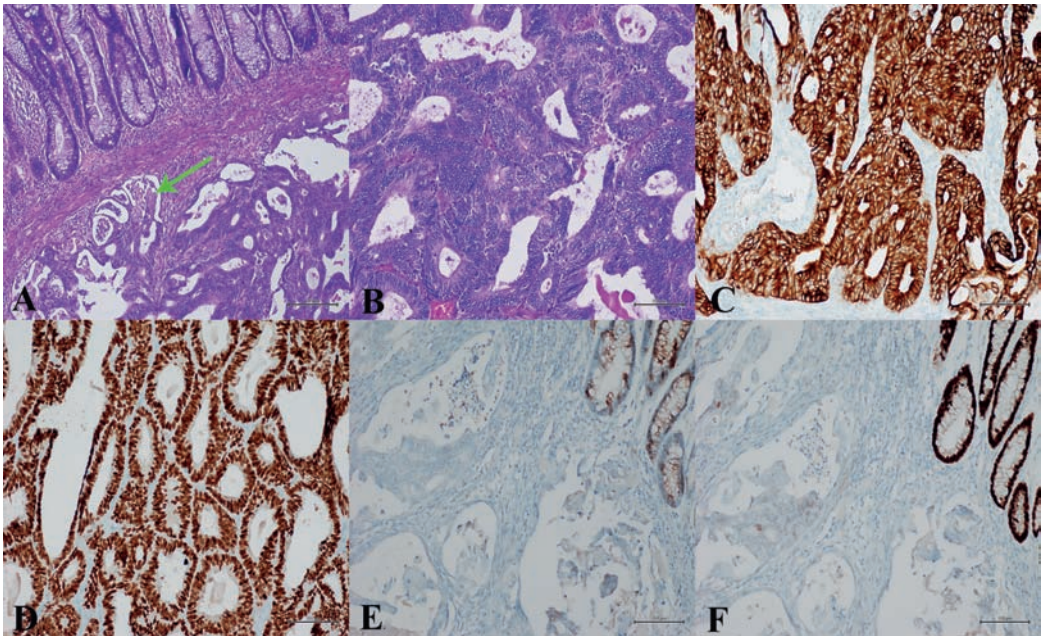

Figure 3. A 65-year-old woman with a previous diagnosis of endometrioid adenocarcinoma of the uterine body came to the attention of health care professionals for episodes of rectorrhagia. A colonoscopy revealed a sigmoid mass compatible with adenocarcinoma. The patient underwent colon resection. Microscopic examination of the specimen showed an intramural neoplastic proliferation with glandular architecture and focal ulceration of the mucosa. This neoplasm showed areas of squamous metaplasia (**A**, *green arrow*) and "back to back" growth pattern of glands (**B**). Immunohistochemical stainings revealed widespread positivity for CK7 (**C**) and for estrogen receptor (**D**). CK20 (**E**) and CDX2 (**F**) stains were negative, with the internal positive control of the colonic glands (on the right side of the images). Therefore, a diagnosis of colonic metastasis from endometrioid adenocarcinoma of the uterus was performed. **A**, 10x magnification; **B-C-D-E-F**, 20x magnification.

Table IV. Main tumours giving metastases to the gastrointestinal tract.

	Morphology	Immunphenotype
Lung Cancer	Glandular/solid nests (ADC); Solid nests with squamous appearance (SCC); Solid nests of small cell with poor cytoplasm (SCLC)	CK7+, CK20±,TTF1+ SATB4- (ADC) p63+, p40+, CK20-, SAT-B4- (SCC) CD56+, Synaptphisin+, Cromogranin+, TTF1±, CK20-, SAT-B4- (SCLC)
Melanoma	Solid nests of epithelioid/spindled cells	S100+, MelanA+, HMB45+, SOX10+, CK20-, SATB4-
Breast Cancer	Medium cells arranged in cords or small clusters; sometimes signet ring cell	ER+, PgR+, CK7+, CK20+, MUC1+, GCFPD-15+, Mammoglobulin+
Endometrial Cancer	Glandular structures	CK7+, CK20−, ER+, PgR+

+ positive; - negative; ± variable expression, more frequently positive; ∓ variable expression, more ADC = adenocarcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer.

metrioid carcinoma may mimic a well differentiated GI-adenocarcinoma. The expression of cytokeratins 7 and 20 (CK7 and CK20) can be quite helpful, because endometrial cancers are CK7+ and CK20− while almost all cases of colorectal carcinoma are CK7− and CK20+, alongside with expression of hormone receptors (ER and PgR), usually expressed by endometrial carcinoma[44,53].

To summarize, the detection of metastatic lesions to the GI tract may be a difficult issue to solve principally because of their rarity. Therefore, great awareness is needed during their investigation and a complete clinical workup is critical. The main tumors metastatic to GI tract and their IHC profile are listed in Table IV.

Intestinal Type Tumors Outside the GI Tract

Intestinal-type adenocarcinoma of the lung

Primary pulmonary neoplasms with intestinal phenotype are named Primary enteric adenocarcinoma (PEAC)[54] (Figure 4). By definition, PEAC is composed of more than 50% of tall columnar cells with eosinophilic cytoplasm arranged in glandular or cribriform pattern. Dirty necrosis in the glandular lumens and prominent nuclear debris are variably present[54]. Of course, the differential diagnosis between PEAC and colorectal adenocarcinoma metastatic to lung (L-CRC) has critical implications[55]. Immunohistochemically, PEAC usually expresses at least one of the enteric differentiation markers (CDX2, CK20, and MUC2)[56]. If tumor cells are negative for all intestinal markers, the neoplasm should be termed as "lung adenocarcinoma with enteric morphology" rather than as "enteric carcinoma of the lung"[57].

Lung adenocarcinoma markers expression, as CK7, Napsin-A and TTF-1, is retained in about half of the cases[55]. In a series published by Chen et al, CK7 and CDX2 resulted the most frequently expressed markers in PEAC, with high sensitivity (71.3, 95%, CI 63.5-79.1%) and specificity (82, 95%, CI 71.4-92.6%)[58]. Expression of TTF1 and Napsin-A is less common, ranging from 30% and 23.0% to 35.7% and 25.0%, respectively[59,60]. However, some PEACs may have a pure intestinal immunophenotype, being CK20-positive, CK7-negative, and TTF-1-negative. In these cases, the differential diagnosis between PEAC and L-CRC can become troublesome. Useful markers to solve such a diagnostic dilemma include SATB2 and β-catenin. In fact, in a recent study the positive rates for SATB2 and β-catenin in lung metastases from L-CRC were 100% and 55%, respectively while they resulted 13% and 0% in PEAC[61]. Furthermore, Bian et al[62] have investigated the diagnostic role of SATB2 in combination with another marker, cadherin 17 (CDH17), demonstrating significantly different positive rates in PEAC and L-CRC (15.4% and 7.7% *versus* 74.1% and 74.1%).

It is noteworthy to remember that PEACs can also show Villin expression. Zhao et al analyzed 28 cases of PEAC showing Villin as the most frequently expressed marker (89.2%), followed by CK7 (66.6%), CDX2 (57.1%), CK20 (36.0%), TTF1 (35.7%) and Napsin-A (23.0%)[59]. However, Villin expression resulted lower in other studies, ranging from 66.7% to 80%[57,60,63].

The immunohistochemical markers allowing the differential diagnosis between PEAC and gastrointestinal carcinomas metastatic to lung, with special reference to the more common colorectal adenocarcinomas, are recapitulated in Table V.

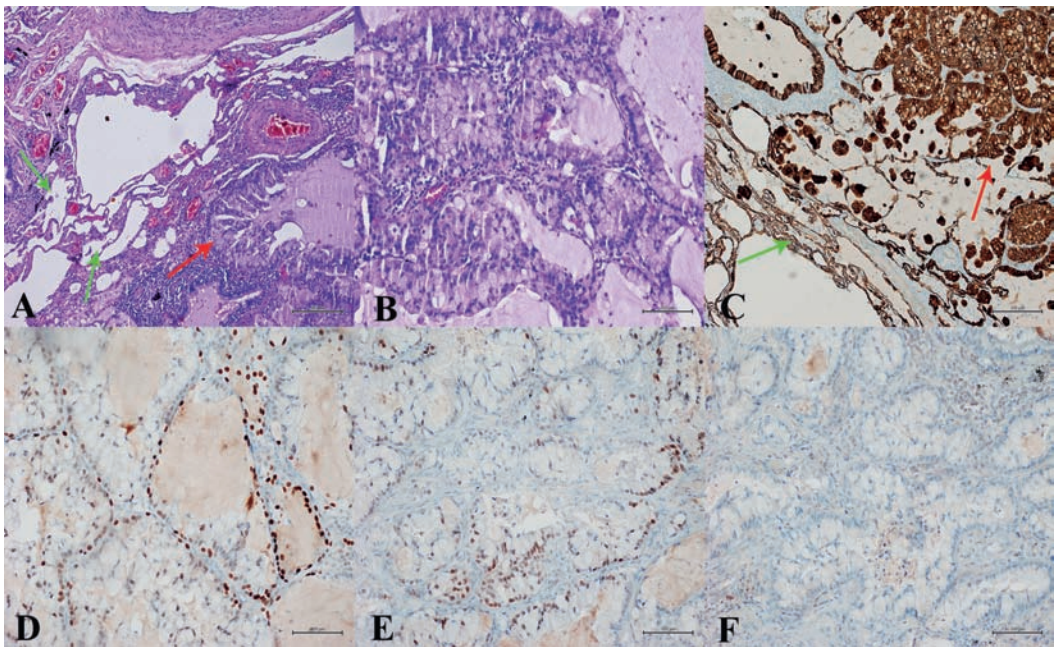

Figure 4. A 58-year-old woman was diagnosed with rectal adenocarcinoma and treated with surgery. During follow-up, computed tomography (CT) showed a nodular mass in the lower lobe of the right lung. Lung metastasis from colonic adenocarcinoma was suspected and pulmonary lobectomy surgery was performed. Microscopic examination showed lung parenchyma (**A**, *green arrow*) partially occupied by a glandular neoplasm composed of columnar cells admixed with mucinous goblet cells (**A**, *red arrow* and **B**). CK7 (C, red arrow indicates the neoplasm, the green arrow the lung parenchyma) was found to be diffusely positive. TTF-1 (**D**) was also positive while CDX2 (**E**) showed focal and weak positivity. CK20 (**F**) was negative. Therefore, the final diagnosis was primary enteric adenocarcinoma (PEAC) of lung. **A**, 10x magnification; **B-C-D-E-F**, 20x magnification.

Intestinal-type tumor in the female reproductive tract

Mucinous ovarian tumors

Primary Mucinous Ovarian Carcinoma (MOC) are characterized by the presence of epithelial cells containing mucin, organized in a glandular growth pattern[64] and can show intestinal-type or, less frequently, endocervical-type differentiation[65]. Histologically, the intestinal-type is characterized by the presence of goblet cells, resembling gastric or pancreatic epithelia, organized in glandular structures[66]. Advanced primary MOCs generally show poor response to therapy[67]. Most MOCs, however, are metastases from the gastrointestinal tract, appendix, pancreas, and gallbladder[68,69]. Differential diagnosis between primary and secondary MOCs can be difficult with important therapeutical implications. Some clinical, macroscopical and histological features may be indicative of primary or metastatic origin, but in a significant proportion of cases these features are not sufficient alone[70,71,72]. Generally, the standard IHC profile for primary MOC is CK7 +, CK20 +/−, CDX2 +/−, PAX8 +, WT1 +, ER −, PR − [73]. Immunohistochemistry plays an essential role in distinguishing primary MOC from other possible diagnoses but, unfortunately, a significant overlap of expression patterns exists regarding IHC markers of widespread use such as CK7, CK20, CDX2, CEA and Ca19.9 in primary carcinomas

Table V. Immunohistochemical markers in the differential diagnosis between lung primary intestinal-type adenocarcinomas and intestinal adenocarcinomas.

	Lung Intestinal-type ADC	Intestinal ADC
CK20	±	+
CK7	+	∓
CDX2	±	+
MUC2	±	+
TTF1	±	-
Napsin-A	∓	-
SATB2	-	+
β-catenin	-	±
Villin	±	+

+ positive; - negative; ± variable expression, more frequently positive; ∓ variable expression, more frequently negative; ADC = adenocarcinoma.

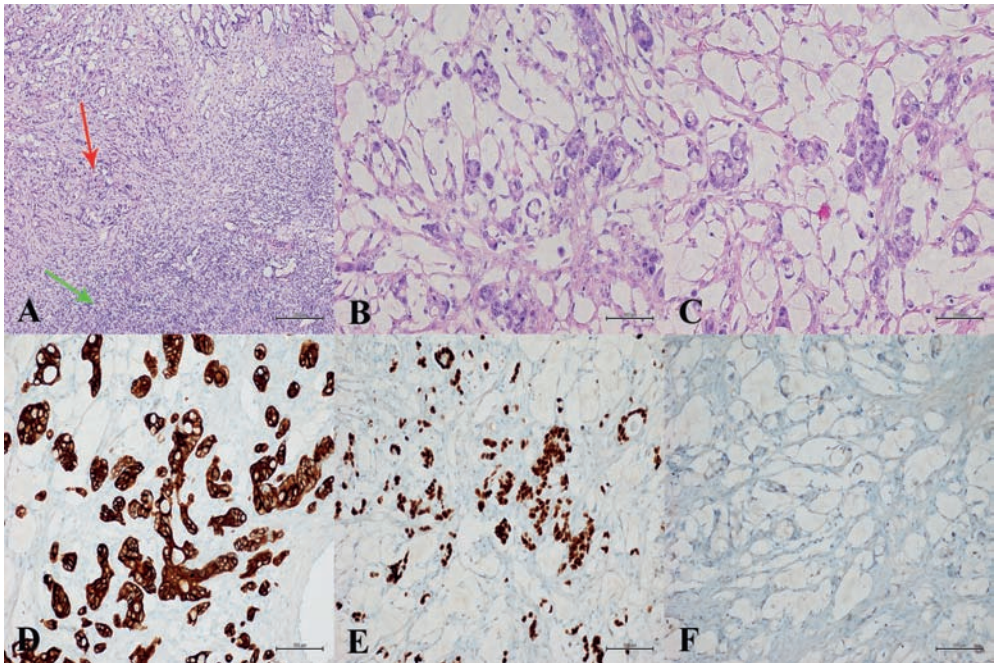

Figure 5. A 39-year-old woman underwent right oophorectomy surgery due to the presence of a large mass of over 10 cm associated with compression symptoms. Histological examination of the mass revealed a mucinous neoplasm (**A**, *red arrow*) infiltrating the ovarian parenchyma (**A**, *green arrow*). At greater magnification (**B**, **C**), the neoplasm appears to consist of mucus lakes containing small groups and isolated cells with mucinous cytological features. Immunohistochemical profile showed positivity for CK20 (**C**) and CDX2 (**D**), whereas CK7 (**E**) was negative. Therefore, a diagnosis of suspected ovarian metastasis from colonic mucinous carcinoma was performed. Based on this diagnosis, the patient underwent a colonoscopic examination which showed the presence of a neoformation in the ascending colon. **A**, 10x magnification; **B**-**C**-**D**-**E**, 20x magnification.

and carcinomas metastatic to the ovaries, depending on their origin[74,75]. Ji et al[76] evaluated the IHC expression of CK7, CK20, Dpc4 and MUC5AC in 57 primary and 46 metastatic MOCs. Primary MOCs were always diffusely positive for CK7 (98%), Dpc4 (100%) and MUC5AC (98%) and often showed focal to diffuse positivity for CK20 (68%). Metastatic colorectal mucinous carcinomas were diffusely positive for CK20 (100%) and Dpc4 (89%) and showed negativity for CK7 and MUC5AC (in 67% of cases) (Figure 5). Appendiceal mucinous carcinoma were largely positive for CK20 (100%) and often negative for CK7 (71%) and often positive for MUC5AC (86%) and Dpc4 (100%). In the cases where primary MOC and colorectal or appendiceal mucinous metastases shared expression of both CK7 and CK20, they could usually be distinguished by pattern of positivity (diffuse CK7/patchy CK20 in ovarian tumors and patchy CK7/diffuse CK20 in colorectal and appendiceal ones). Pancreatic cancers shared the same pattern of diffuse positivity for CK7 (100%) and MUC5AC (92%) and focal to diffuse positivity for CK20 (71%) as primary MOC, but Dpc4 was negative (46%), defining it as a useful element in distinguishing metastatic pancreatic carcinomas from both primary ovarian mucinous tumors and metastatic mucinous carcinomas derived from other sites.

Recently, some novel markers have been introduced, such as SATB2, which appear to have a high specificity for lower gastrointestinal origin[77,78]. Aldaoud et al[79] have demonstrated for SATB2 a 98.0% specificity for metastatic mucinous tumors arising from the colon and appendix, whereas the most specific markers for ovarian origin resulted to be PAX8, recommending that both these markers are included in the IHC panel for the differential diagnosis between primary ovarian mucinous tumors and metastatic mucinous neoplasms from the lower gastrointestinal tract.

All these findings are summarised in Table VI.

Mucinous adenocarcinoma of the cervix, intestinal type

Intestinal-type changes may be found diffusely or focally as a component of mucinous adenocarcinoma, a cervical adenocarcinoma histotype

Table VI. Immunohistochemical markers in the differential diagnosis between primary ovarian mucinous carcinomas and intestinal adenocarcinomas.

	Mucinous ovarian carcinoma	Intestinal ADC
CK7	+	∓
CK20	±	+
CDX2	±	+
PAX8	+	-
WT1	+	-
ER	-	-
PR	-	-
SATB2	-	+
Dpc4	+	+
MUC5AC	+	±

+ positive; - negative; ± variable expression, more frequently positive; ∓ variable expression, more frequently negative; ADC = adenocarcinoma.

usually arising in association with high-risk HPV infection[73]. Intestinal-type cervical adenocarcinomas show an enteric-like immunophenotype, with expression of CDX2 and, in some cases, positive staining for cytokeratin 20. However, expression of cervical markers such as cytokeratin 7, CEA and p16 is usually retained and can be useful in the distinction between primary cervical tumors and cervical involvement by a colorectal carcinoma[80-82].

Intestinal-type differentiation in endometrioid carcinoma, vaginal and vulvar adenocarcinoma

When compared to its frequency in ovarian and cervical cancers, intestinal-type or mucinous differentiation in carcinomas arising from endometrium is an extremely rare occurrence, with only sporadic cases reported in literature[83,84]. Similarly, primary vaginal adenocarcinomas are rare, with few described cases[85-87]. They are far more uncommon than vaginal metastases from colorectal carcinomas or other gynecologic malignancies. According to the WHO classification of Tumours of Female Reproductive Organs[73], they comprise, in order of frequency: 1) clear cell adenocarcinomas; 2) endometrioid-type adenocarcinomas; 3) mucinous adenocarcinomas, further subclassified in endocervical- and intestinal-type cancers. The histogenesis of intestinal-type vaginal adenocarcinomas is not fully understood but they are likely to derive from cloacal renmants[66], from intestinal metaplasia of Skene ducts or other vaginal structures[88,89].

Also called primary villoglandular mucinous adenocarcinoma or cloacogenic adenocarcinoma of the vulva, vulvar adenocarcinoma of intestinal-type is an exceedingly infrequent neoplasm[90]. As for vaginal adenocarcinoma, origin from embryonal vestigial, from Bartholin's glands or from ectopic tissues has been proposed[91-93]. Obviously, given the rarity of these neoplasms, large studies to assess their IHC profile, with particular reference to recently introduced markers, are lacking but their immunophenotypic features resemble those of other intestinal-type malignancies, with common expression of CK20 and CDX2. Consequently, a careful clinical-pathological correlation to establish the exact location of the lesion and to exclude the presence of other primary synchronous or metachronous tumors is more than ever mandatory for the diagnosis. Markers such as SATB2 and β-catenin may supposedly be useful in ruling out a metastasis from a colorectal primary.

Enteric differentiation in bladder carcinomas

Areas of divergent glandular differentiation, with glands resembling those of colorectal carcinoma, may be seen at various extent in up to 18% of invasive urothelial carcinomas. Urothelium-derived neoplasms characterized by a pure glandular phenotype are named primary bladder adenocarcinomas[94,95]. They account for 0.5-2% of all malignant bladder tumors with well-established risk factors, including bladder exstrophy, schistosomiasis, and other conditions determining a chronic urothelial irritation. Their clinical presentation and cystoscopic aspect are aspecific, overlapping with those of other urothelial tumors. Different histological variants are recognized, namely enteric, mucinous and mixed adenocarcinomas. The enteric variant shows intestinal-type glands lined by pseudostratified columnar cells with variable pleomorphism closely resembling colorectal adenocarcinoma. Mucin production and areas of necrosis are frequent findings. Similarly to primary intestinal tumors, urothelial carcinomas with glandular differentiation and bladder adenocarcinomas express CDX2 and CK20 while typical urothelial markers (p63, GATA3 e high molecular weight cytokeratins) tend to be negative[96] (Figure 6).

Interestingly, however, in most cases urothelial-derived tumors with enteric differentiation lack nuclear expression of β-catenin, a distinctive

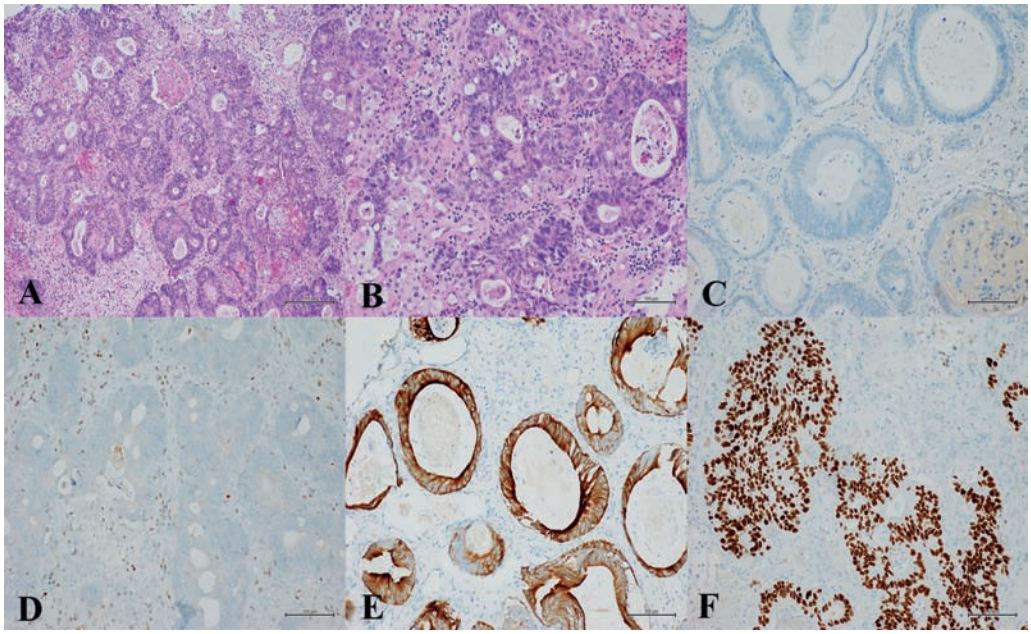

Figure 6. A 73-year-old woman came to medical attention for an episode of hematuria. The patient underwent cystoscopy showing an ulcerated lesion in the posterior wall of the bladder. A transurethral resection (TURB) was performed. Microscopic examination showed bladder wall fragments diffusely infiltrated by a glandular neoplasm (**A**), with dirty intraluminal necrosis (**B**). Immunohistochemical stains demonstrated negativity for CK7 (**C**) and GATA3 (**D**) and positivity for CK20 (**E**) AND CDX2 (**F**). Therefore, a diagnosis of infiltration of the bladder wall from adenocarcinoma of likely colonic origin was performed. Subsequently, the patient underwent computed tomography (CT) examination which revealed a full-thickness infiltrating rectal mass with bladder involvement. **A**, 10x magnification; **B-C-D-E-F**, 20x magnification.

feature of colorectal tumors. Therefore β-catenin immunostaining could help differentiating primary bladder from primary colorectal carcinomas[97,98]. The presence of enteric differentiation in urothelial tumors seems to bear a prognostic significance, predicting a worse outcome and a higher tumor progression and recurrence rate in early stage, non-muscle invasive tumors[99-101].

The immunohistochemical profile of enteric urothelial carcinomas and differences with intestinal adenocarcinomas are highlighted in Table VII.

Conclusions

Intestinal morphology could be observed in primitive tumors originating in several organs. In addition, in the GI tract[102-104], primitive tumors different from adenocarcinomas or metastatic adenocarcinomas could rarely occur. In these clinical settings the differential diagnosis between primitive and metastatic tumors required to the pathologist is of paramount importance for any clinical decision and therapeutic implication. The immunohistochemical approach represents a handy and economic strategy to solve most of these cases, considering the high number of available antibodies[105-107] to differentiate adenocarcinomas of real intestinal origin. Moreover, the use of the immunohistochemical approach represents a crucial step to obtain prognostic and predictive factors information about many cancer, and this kind of approach allows us to customize care in a setting of precision medicine[108-114].

Table VII. Immunohistochemical markers in the differential diagnosis between enteric urothelial carcinomas and intestinal adenocarcinomas.

	Enteric urothelial carcinoma	Intestinal ADC
CK7	+	∓
CK20	±	+
CDX2	±	+
P63	∓	-
GATA3	∓	-
HMWCKs	∓	-
B-Catenin	-	+

+ positive; - negative; ± variable expression, more frequently positive; ∓ variable expression, more frequently negative; ADC = adenocarcinoma.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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