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# Variants of Gastric Carcinoma: Morphologic and Theranostic Importance

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Sun-Mi Lee, Kyoung-Mee Kim and Jae Y. Ro

Additional information is available at the end of the chapter

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## 1. Introduction

Variants of gastric cancer account for approximately 5% of all carcinomas of the stomach. Some variant carcinomas, such as lymphoepithelioma-like carcinoma, hepatoid carcinoma with or without  $\alpha$ -fetoprotein (AFP) production, small cell or neuroendocrine carcinoma, adenosquamous and squamous carcinoma, choriocarcinoma, sarcomatoid carcinoma, parietal cell or oncocytic carcinoma, micropapillary carcinoma, mucoepidermoid carcinoma, chief cell carcinoma, and Paneth cell carcinoma have been described, and recognition of the specific subtype is important due to not only their correlation with a distinct clinical course and prognosis but also differential diagnosis from metastasis from the outside of the stomach and different therapeutic modalities, particularly in the era of targeted treatment. Gastric lymphoepithelioma-like carcinoma and parietal cell or oncocytic carcinoma have been found to have a lower risk of lymph node metastasis and better prognosis. However, other variants such as hepatoid carcinoma, small cell or neuroendocrine carcinoma, adenosquamous and squamous carcinoma, choriocarcinoma, sarcomatoid carcinoma, and micropapillary carcinoma have shown to be associated with a poorer prognosis and a higher risk of metastasis to the lymph node and other organs, compared to conventional intestinal or diffuse type of gastric adenocarcinomas.

In recent years, early detection, endoscopic mucosal resection (EMR) for early gastric cancer, and neoadjuvant therapy have made a remarkable progress in the management and prognosis of gastric cancers. Thus, the prediction of aggressive behavior and accurate risk stratification in the variants of gastric cancer has become more important than ever. The World Health Organization (WHO) classification and the degree of differentiation have not been applied to some variants of gastric carcinoma. Considering that EMR and neoadjuvant therapy are selectively applied to patients with gastric carcinoma based on the tumor size, WHO classifi-

cation, and degree of differentiation, further specific subclassification for each variant should be discussed to allow treatment to be directed to appropriate patient groups..

Recently, Giuffre et al analyzed the HER2 status in a cohort of rare histologic variants of advanced gastric adenocarcinoma such as hepatoid adenocarcinoma and oncocytic adenocarcinoma [1]. This series demonstrated that one of rare variants of gastric carcinoma, hepatoid adenocarcinoma, has shown an increased HER2 overexpression in up to 42.86% of cases compared to the intestinal (31.25%) and diffuse (3.45%) types of gastric adenocarcinoma. Trastuzumab has been known as an additional useful therapeutic standard option for patients with HER2-positive advanced gastric cancer. Therefore, this result and further studies may bring a significant progress in clinical course and prognosis in patients with aggressive variants of gastric carcinoma such as hepatoid adenocarcinoma. However, future studies are needed to evaluate overexpression of HER2 in other variants of gastric carcinoma. The variants of gastric carcinoma are listed in Table 1.

## **2. Epstein-Barr virus associated lymphoepithelioma-like carcinoma**

Lymphoepithelioma-like carcinoma of the stomach (LELCS), also known as gastric carcinoma with lymphoid stroma, undifferentiated carcinoma with lymphoid stroma or medullary carcinoma, is a unique variant of gastric adenocarcinoma which is highly associated with Epstein-Barr virus (EBV) infection. This variant was described originally by Watanabe et al in 1976 and accounts for approximately 4% of all gastric carcinomas [2-4]. It has recently been emphasized that the role of EBV infection in the carcinogenesis of LELCS. The incidence of EBV-associated gastric adenocarcinoma varies from 1.3% to 20.1% in different areas, with an average of 10% worldwide [5, 6]. The prevalence of EBV infection has been found approximately 75 % of LELCS and 16% of conventional gastric adenocarcinoma in North America by EBV-encoded ribonucleic acids in situ hybridization (EBER-ISH) [7].

The clinicopathologic and molecular characteristics of EBV-associated LELCSs are quite different from those of conventional gastric carcinoma, such as a male predominance (male to female ratio: 2-3.4:1), predisposition to proximal stomach, frequent association with multiple and remnant gastric cancers, a lower frequency of lymph node metastasis, a relatively favorable prognosis, and aberrant concordant methylation of multiple genes [4, 8-10]. The mean age of diagnosis is 54.8 years, younger than conventional gastric carcinomas [11]. The clinical symptoms of LELCS are similar with conventional gastric adenocarcinoma, and patients with EBV-associated gastric carcinoma are known for elevated antibodies against EBV-related antigens. Levine et al reported that patients with EBV-associated gastric carcinoma have significantly high IgG and IgA antibody titer to EBV viral capsid antigen more than 5 years preceding their first diagnoses [12].

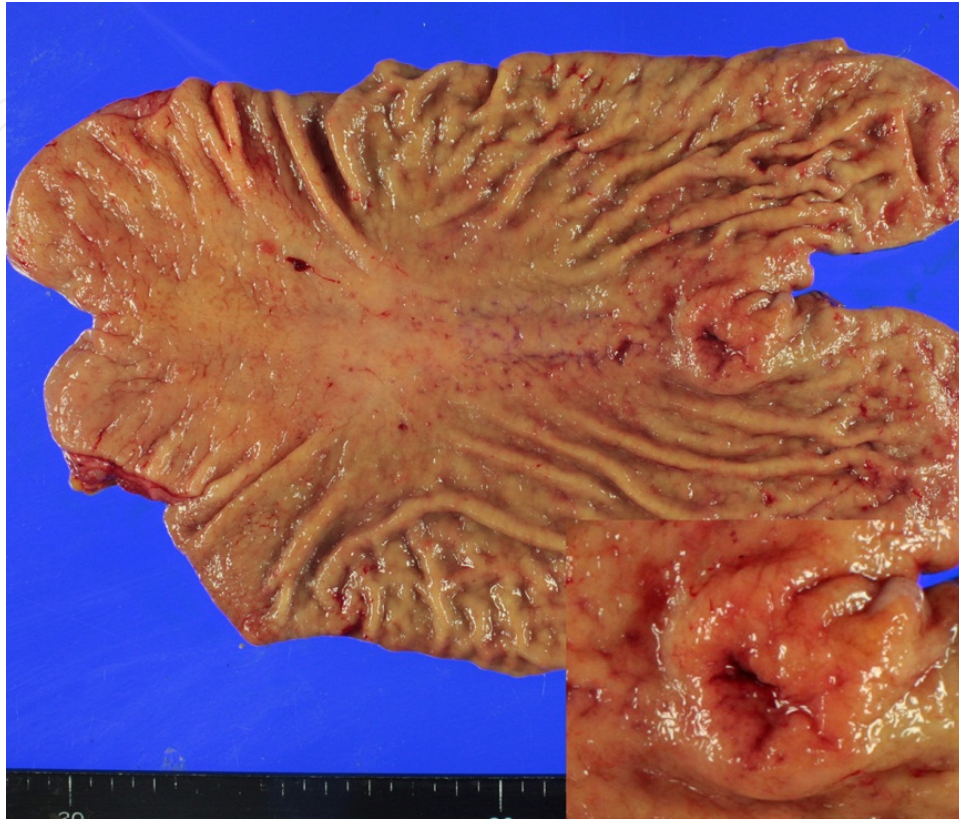
Watanabe and Yanai et al had reported the specific endoscopic findings of EBV-related LELCS in early and advanced lesions [4, 8]. In their series, approximately 80 % of LELCS appear to be a superficial depressed type, such as IIc, IIc+III, and IIa+IIc, frequently combined with ulcer in an early stage. Endoscopic ultrasonography of this variant demonstrates a hypoechoic

Histologic type	Incidence	Mean age	Sex	Clinical importance	Morphologic feature	Prognosis
<b>EBV-associated lymphoepithelioma-like carcinoma</b>	4%	54.8 yrs	M:F= 2-3.4:1	Possible good candidate for EMR and DNA methyltransferase inhibitor	Undifferentiated tumor cells embedded within a lymphoid stroma	Better prognosis compared to CoA (5-YSR: 71.4%)
<b>Hepatoid adenocarcinoma</b>	0.4-0.7%	64.5 yrs	M:F=3.5:1	Possible good candidate for anti-HER2 therapy (HER2 overexpression)	Tumor showing hepatoid differentiation with an immunoreactivity of AFP and glycan3	Worse prognosis compared to CoA (5-YSR: 9%)
<b>Neuroendocrine cell carcinoma</b>	0.1-0.6%	65 yrs	M:F=2.9:1	Response well to chemotherapy	Monotonous polygonal cells having fine granular chromatin and inconspicuous nucleoli with an immunoreactivity of neuroendocrine markers	Unfavorable prognosis (median survival: 1.7 years)
<b>Squamous and adenosquamous carcinoma</b>	0.04-0.9%	64 yrs	M:F=5:1	Differentiation from squamous or adenosquamous cell carcinoma arising from distal esophagus	Tumors with definite squamous differentiation including keratinization, squamous pearl formation, and intercellular bridges with or without a glandular component	Unfavorable prognosis (mean survival: 1.6 years)
<b>Choriocarcinoma</b>	0.08%	58.6 yrs	M:F=2.3:1	Elevated serum $\beta$ -HCG Frequent cause of gastrointestinal bleeding and some hormone effects	Tumor with an admixture of cytotrophoblasts and syncytiotrophoblasts	Unfavorable prognosis (maximum survival: one year)
<b>Sarcomatoid carcinoma</b>	50 cases reported	45 yrs	M:F=2.3:1	Diagnosed at an advance stage with lymph node and liver metastasis	Tumor with a high grade sarcomatous component	Unfavorable prognosis (mean survival: 10 months)
<b>Acinar cell carcinoma</b>	10 cases reported	64.8 yrs	M:F=1:1	Tumor arising from pancreatic heterotopias or de novo acinar metaplasia	Tumor with acinar cell differentiation and pancreatic exocrine enzyme production confirmed by immunohistochemistry	Undetermined
<b>Invasive micropapillary carcinoma</b>	0.07%	66.2 yrs	M:F=2.5-3:1	High incidence of lymphovascular invasion and lymph node metastasis	Tumor with papillary clusters devoid of fibrovascular cores within lacunar spaces	Worse prognosis compared to CoA (5-YSR:30%)
<b>Gastric adenocarcinoma of fundic gland type (chief cell predominant)</b>	A few cases reported	65 yrs	M:F=1:1	Differentiation from a fundic gland polyp	Well differentiated adenocarcinoma admixed with predominantly chief cells and scattered parietal cells	Favorable prognosis expected but limited data
<b>Parietal cell carcinoma and oncocytic carcinoma</b>	Less than 30 cases reported	70.2 yrs	M:F=9:1	Occurs in an older population with a favorable prognosis	Tumors showing parietal cell differentiation with or without an immunoreactivity of H+/K+ ATPase	Favorable prognosis but limited data

M:F indicates male to female ratio; EMR: endoscopic mucosal resection; CA: conventional adenocarcinoma; AFP: Alpha-fetoprotein; 5-YSR: 5-year survival rate

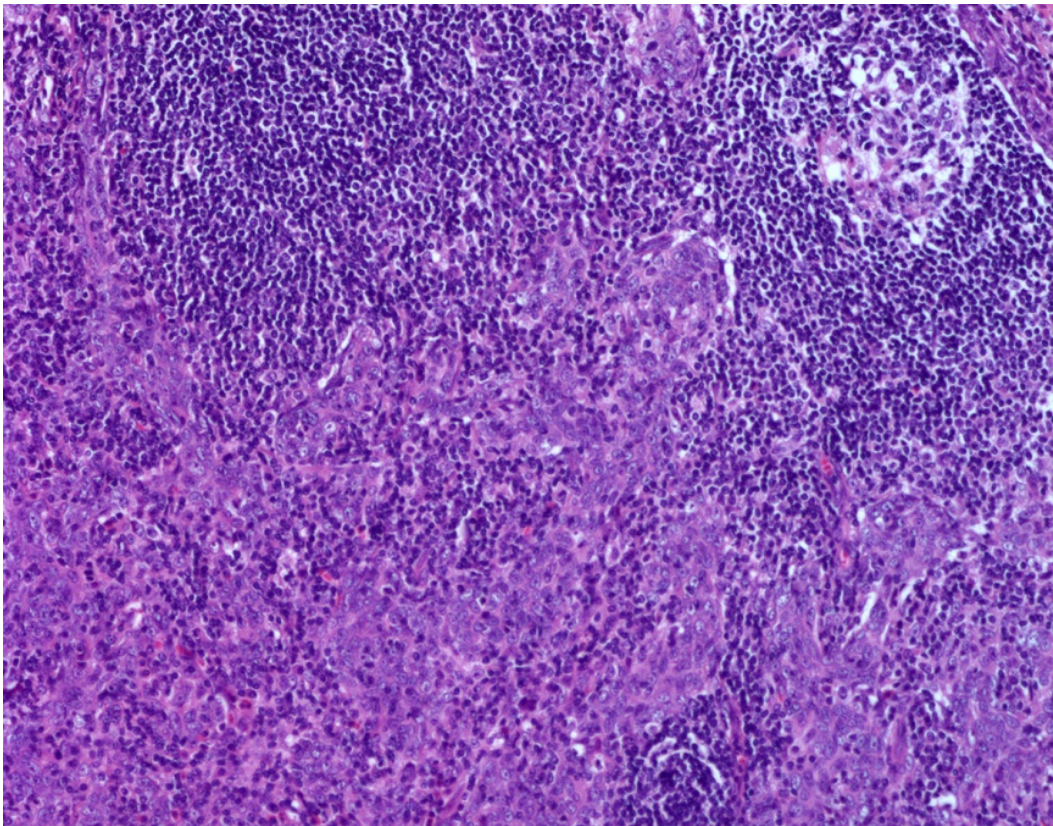
**Table 1.** Variants of Gastric carcinoma

submucosal tumor-like protrusion with a large thickness compared to the length in an early lesion. Most LELCSs appear as a fungating mass (Bormann type II) accompanied by marked thickening of the gastric wall in an advanced stage (Fig. 1).



**Figure 1.** Gross photograph of EBV-associated lymphoepithelioma-like carcinoma in an advance stage. This tumor usually presents as a fungating mass (Bormann type II).

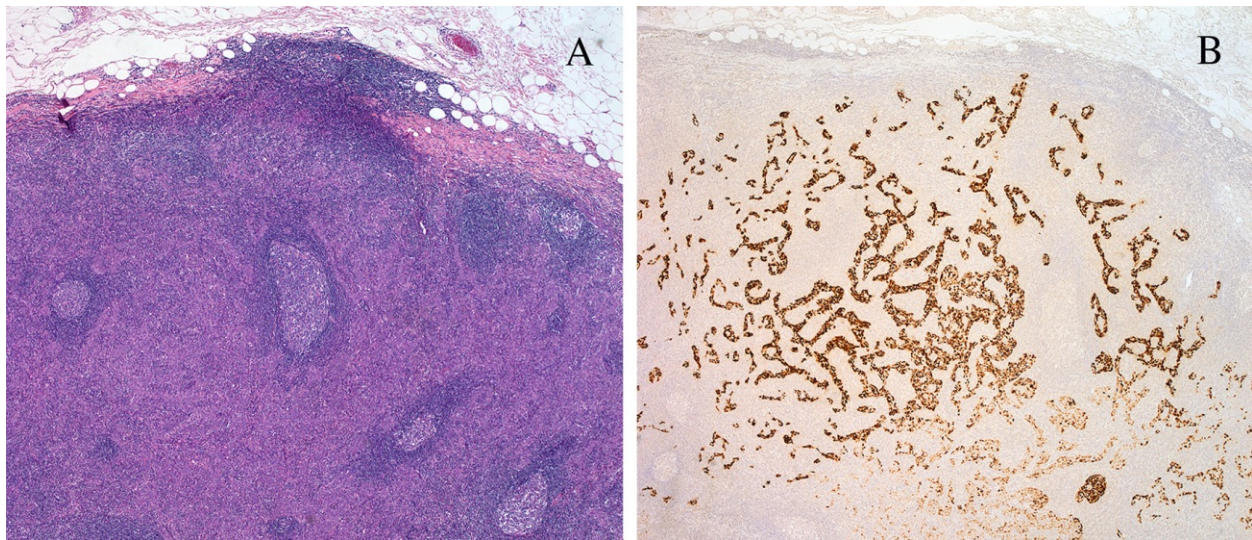
Histologically, LELCS has a well demarcated and pushing border and nests of poorly or undifferentiated tumor cells embedded within a lymphoid stroma. The tumor cells are arranged in syncytia, microalveolar, thin trabecular, or primitive tubular patterns. Also, they contain vesicular to clear nuclei, prominent nucleoli, and abundant eosinophilic polygonal cytoplasm with poorly defined cell borders (Fig 2). Generally, tumor cells grow in a diffuse manner intermixed with lymphocytes and plasma cells, mimicking malignant lymphoma (Schmincke type). However, a sharp demarcation between the tumor nests and lymphocyte stroma that is composed of variable amounts of lymphocytic infiltration, sometimes with lymphoid follicles, is noted (Regaud type) but no desmoplastic reaction is identified. Rarely, giant cells and epithelioid granulomas are observed within the lymphoid stroma [13, 14]. In the early lesion, LELCS shows a “lace pattern”, which consists of columnar arrangement and intercolumnar fusion of neoplastic glands between dense lymphocytic infiltration at the intermediate zone of lamina propria [15]. This tumor is usually accompanied with severe atrophic gastritis in the background but not associated with intestinal metaplasia or *Helicobacter pylori* infection that are often observed in usual gastric adenocarcinoma [16].



**Figure 2.** High magnification view of LELCS shows syncytial and solid nests of undifferentiated tumor cells with vesicular nuclei and prominent nucleoli surrounded by dense lymphocytic infiltration on H&E stain

The epithelial cell component of this variant is positive for keratins. Also HLA-DR expression of tumor cells associated with dense lymphocytic infiltrates can be detected in some cases of EBV-associated LELCS [17]. Increased dendritic cells within a lymphocyte stroma are also seen, which are positive for S100 and CD83. CD8<sup>+</sup> T lymphocytes are the predominant cells infiltrating into tumor cell nests in EBV-associated LELCS, many of which express perforin and granzyme B [18]. Florid proliferation of CD8<sup>+</sup> T lymphocytes within tumor cells seems to be associated with the host immune response to remove EBV antigen or cellular EBV-induced antigen [19].

EBV has specific latency expression patterns in different EBV-associated malignancies. EBV-associated LELCS can express viral latent genes and related products, not only EBV-encoded small ribonucleic acids (EBER) but also EBV-determined nuclear antigen type 1, BamHI A region rightward transcripts, and variable latent membrane protein 2A and 2B [20]. Polymerase chain reaction (PCR) to amplify EBV deoxyribonucleic acid fragments and EBER-ISH techniques could be used to detect EBV in tumor tissues; however, as a PCR test for amplifying EBV DNA is very sensitive and may cause a false positivity, and EBERs are always abundantly expressed in nearly 100% of tumor cell tissues (Fig.3), EBER-ISH technique is a gold standard test to detect EBV in paraffin-embedded tissues [21].



**Figure 3.** Microscope and EBV-ISH photographs of EBV-associated lymphoepithelioma-like carcinoma. **A.** A relatively well circumscribed mass with focal infiltration into subserosa. Reactive lymphoid follicles are scattered between tumor nests combined with dense lymphocytic infiltration. **B.** EBV-ISH highlights solid nests of EBV-infected tumor cells with cytoplasmic staining pattern in lymphoepithelioma-like carcinoma.

Previous studies of conventional gastric adenocarcinoma have been shown 34-60% of p53 overexpression. Some studies showed the frequency of p53 immunoreactivity, approximately 14%, was much lower in patients with EBV-associated LELCS compared to conventional gastric carcinoma [22]. However, other studies have almost same frequency of p53 expression with conventional gastric adenocarcinoma [23, 24]. The role of p53 mutation in the development of EBV-associated gastric carcinoma is still unclear.

If an accompanying lymphoid stroma contains multiple reactive follicles and intense lymphocytic infiltration in LELCS can be mistaken as a pseudolymphoma or lymphoma. It is important to examine the presence of malignant epithelial cell component carefully. Immunohistochemical markers for the cytokeratins, AE1/AE3 and CAM5.2, should be essential to detect in which only scarce undifferentiated malignant epithelial cells are present.

EBV is a ubiquitous  $\gamma$ -1 herpes virus usually acquired during childhood via salivary transmission, which establishes a life-long persistent infection of B cells in over 90% of adults [20]. EBV has been linked to the pathogenesis of several mesenchymal and epithelial neoplasms including nasopharyngeal carcinoma, B and T cell lymphomas, NK cell malignancies, and a subset of smooth muscle tumors [25]. The role of EBV in gastric carcinoma is considered to be directly oncogenic, but is still largely unknown. The infection of EBV is assumed to be occurred in the very early stage of carcinogenesis [23]. However, there is still a controversy over whether EBV infects gastric epithelial cells before or after the development of invasive gastric carcinoma [9].

Studies for genetic abnormality for EBV-associated gastric carcinoma are still limited and sparse. Several previous studies had failed to demonstrate any significant chromosomal loss or gain in comparative genome hybridization, changes of DNA copy number and microsatellite clearly. In contrast to inconsistent and negative results in genetic alteration, epigenet-

ic alterations such as promoter hypermethylation, which bring in chromatin remodeling and silencing of tumor-related genes, plays a key role in the carcinogenesis of EBV-associated gastric carcinoma [26]. Kusano et al demonstrated that EBV-associated gastric carcinomas were strongly associated with high CpG-island methylation (CpG-island methylator phenotype- high, CIMP-H) by using methylation-specific polymerase chain method [27]. Other epigenetic series about EBV-associated gastric carcinoma have shown simultaneous methylation of multiple genes, including cell cycle regulation (p14, p15, p16, and cox2), DNA repair and protection (HMLH1, MGMT,GSTP1), cell adherence and metastasis (E-cadherin, TIMP3), angiogenesis (THBS1), apoptosis (DAP-kinase, bcl-2, p73), and signal transduction (APC, PTEN, RASSF1A) [28, 29]. Higher frequencies of hypermethylation of cancer-related genes found in EBV-associated gastric carcinoma suggest a close relationship between EBV infection and aberrant methylation of this variant during its carcinogenesis. Also, these findings suggest that DNA methyltransferase inhibitors such as 5-aza-2'-deoxycytidine (5-aza-CdR) or trichostatin A (TSA), which can induce the lytic phase of EBV infection in EBV positive gastric cancer cell lines, can be a promising therapeutic agent specially for EBV-associated gastric carcinoma [30].

Another interesting characteristic of EBV-associated gastric carcinoma is its higher occurrence among gastric remnant carcinomas, ranging from 27% to 42% [31-33]. Chen et al hypothesizes that the injuries of gastric mucosa and/or changes of the microenvironment within the remnant stomach may be involved in the development of EBV-associated gastric carcinoma [34].

EBV-associated LELCS has known to have a low risk of lymph node metastasis [35]. Interestingly, whether the presence of tumor metastasis within the regional lymph nodes or not, perigastric lymph nodes frequently show reactive hyperplasia that represents a host immune response against LELCS [4]. EBV-associated LELCS shows a very low rate of regional lymph node metastasis especially if the tumor involves in the mucosa and submucosa as an early gastric cancer [4]. The patients with this variant tumor can be good candidates for EMR in regard to a lower frequency of lymph node metastasis and a relative well circumscribed tumor margin that can be easily assessed endoscopically. Some clinical trials to remove EBV-associated LELCS in an early stage have been reported using an endoscopic resection such as EMR or submucosal dissection [36, 37]. The patients treated with endoscopic resection have shown a benign clinical course without recurrence or metastasis. The prognosis of EBV-associated gastric carcinoma has been considered better than conventional gastric carcinoma. Song et al reported that 5-year overall survival rate of EBV-associated gastric carcinoma was 71.4%, and disease-free survival rate was 67.5% compared to 56.1% and 55.2% of those usual gastric carcinoma and suggested the prognosis of EBV-associated gastric carcinoma depends on the patient's inflammatory response (tumor-infiltrating lymphocyte counts) [11].

### 3. Hepatoid adenocarcinoma

Hepatoid adenocarcinoma of the stomach (HACS) was first described by Ishikura et al in 1985 as a subtype of AFP producing gastric carcinoma, which has a histologic similarity with

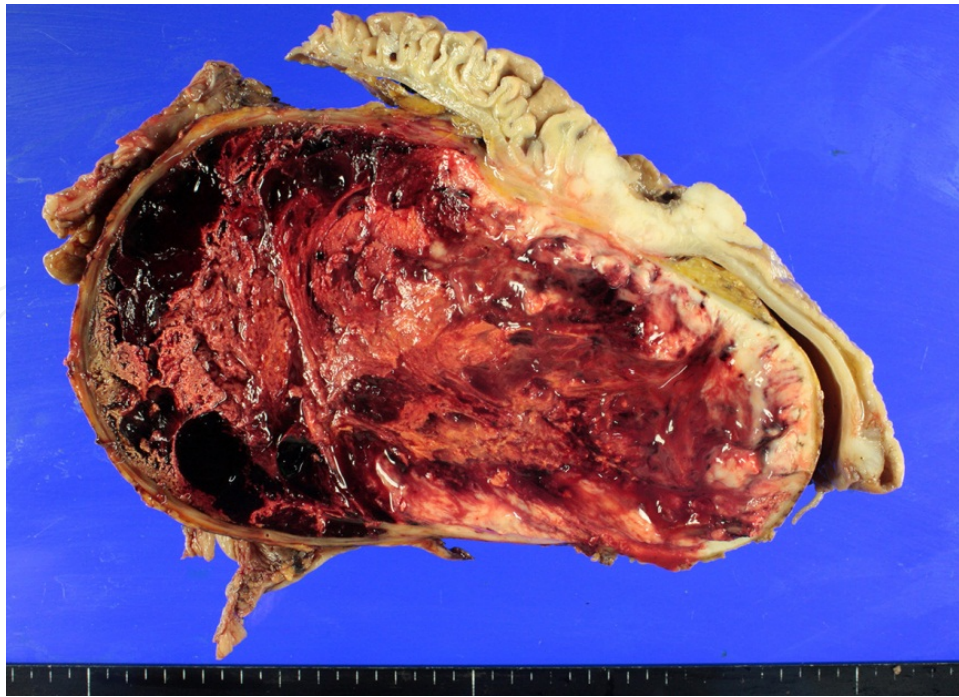


hepatocellular carcinoma and distinct clinicopathological properties [38]. The incidence of this variant ranges from 0.38% to 0.73% of all gastric cancer [39, 40]. The mean age of diagnosis is 64.5 years (range from 49 to 78 years), similar to that of conventional gastric carcinomas. The clinical symptoms are similar to those seen in patients with conventional gastric adenocarcinoma except marked elevated serum level of AFP in most patients. Characteristically, earlier studies demonstrated that HACS frequently combined with vascular invasion, liver metastasis, and a higher incidence of lymph node metastasis which result in a poorer prognosis than other common types of gastric adenocarcinoma [41, 42].

AFP is a serum protein produced by fetal liver, yolk sac cells, and some fetal gastrointestinal cells [43]. HACS is characterized by distinct hepatoid differentiation histologically and the production of liver specific proteins including AFP confirmed by immunohistochemistry. However, not all HACSs produce hepatic specific protein. Approximately 54 % of HACSs express AFP by immunohistochemistry and 63% of patients with HACS show an elevated serum AFP level [39, 44]. In addition, there are some histologic types of carcinoma other than HACS, tubular/papillary adenocarcinomas, poorly differentiated medullary carcinoma, and enteroblastic adenocarcinoma, also can produce and secrete AFP [38, 45-48].

The most commonly found macroscopic type of HACS is 0-IIc (superficial depressed type) in an early lesion [49]. This tumor can occur as a circumscribed mass, Bormann type II (fungating type) or III (ulceroinfiltrative type) as an advanced cancer in the antrum and lower body of the stomach (Fig.4) [44, 49]. Microscopically, this variant contains areas of hepatoid differentiation showing structural mimicry of liver tissue such as sheet-like or trabecular arrangement of tumor cells with sinusoid-like vasculature and bile canaliculus-like structure [50]. This tumor consists of cuboidal or polygonal cells with centrally located nuclei and abundant eosinophilic cytoplasm (Fig.5). However, there is no consensus for quantification of the proportion of hepatocellular differentiated component yet to accept as HACS. The proportion of hepatoid component ranges from 10 to 90% in reported cases of HACS [51]. The glandular component such as well-differentiated tubular or papillary adenocarcinoma frequently intermingles with the hepatoid component. The transition between glandular and hepatoid components of HACS can be gradual or abrupt. Occasionally, bile and periodic acid-Schiff-positive/diastase-resistant hyaline globules may be observed in intracellular and extracellular sites. In addition to the production of liver-specific proteins such as AFP as well as prealbumin, albumin, and transferrin, Proteins Induced by Vitamin K Absence - II (PIVKA-II) and Hep-par1 antigen can be detected in tumor cells [38, 52, 53]. Some HACSs exhibit extensive lymphovascular invasion, extending to veins with tumor emboli, which results in early metastasize to other organs, predominantly to the liver [39].

Immunohistochemically, the tumor cells are positive for CK8, CK18, CK19, CK20, but negative for CK7. Also this variant can express the canalicular pattern of polyclonal carcinoembryonic antigen (CEA),  $\alpha$ -1 antitrypsin, and  $\alpha$ -1 antichymotrypsin [54]. The immunoreactivity of PIVKA-II and Hep-par1 are variably observed. Glypican-3 is a cell surface heparin sulfate proteoglycan considered to be an oncofetal protein because of its presence in fetal liver and liver tumors (hepatocellular cell carcinoma and hepatoblastoma) [55]. The immunohistochemical staining pattern of glypican-3 is strongly positive in membrane and cytoplasm of hepatoid

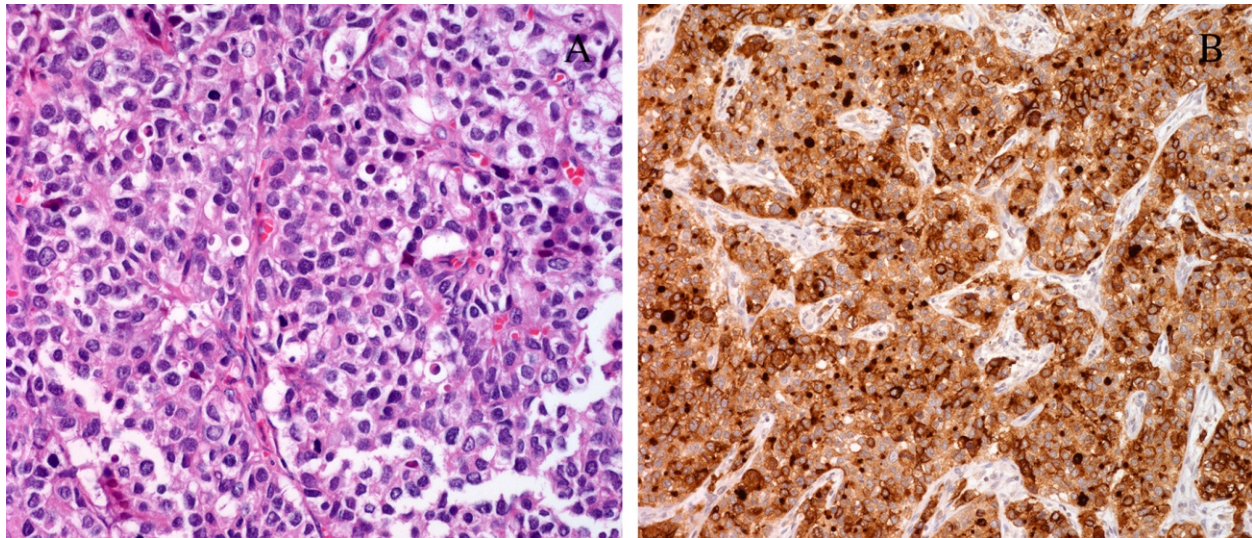


**Figure 4.** Gross photograph of hepatoid adenocarcinoma. The tumor presents as a fungating mass (Bormann type II) in the lower body of the stomach which projects exophytically into the abdominal cavity. The subserosal lesion shows extensive necrosis and hemorrhage on the cut surface.

tumor cells (Fig. 5). Hishinuma et al reported that glypican 3 is more sensitive (100% sensitivity) than either Hep-par1 or AFP but Hep-par1 is more specific as an immunohistochemical marker for HACS [51]. In a series by Kinjo et al showed that AFP has 81.1% of sensitivity and 46.1% of specificity and glypican-3 has 90.5% of sensitivity and 63.2% of specificity [49]. These studies support both AFP and glypican-3 could be useful markers to make a diagnosis of HACS.

Many cytogenetic and molecular studies had been undertaken to investigate pathogenesis and biological behavior of this variant. However, the histogenesis of HACS is still unclear. Kishimoto et al proposed that gastric carcinoma might acquire hepatic differentiation during the tumor progression, “HACS transdifferentiation” [56]. Akiyama et al demonstrated that the hepatoid component exhibited exactly same patterns of chromosome X inactivation, p53 gene mutation, the level of p53 expression, and loss of heterozygosity with conventional adenocarcinomatous component of HACS [57]. These findings suggest a monoclonal origin of both glandular and hepatoid elements of HACS and support “HACS transdifferentiation” as the most accepted histogenesis.

Differential diagnoses of HACS include other similar-appearing tumors (lung, pancreas, esophagus so on) and hepatocellular cell carcinoma. Particularly, the metastatic HACS to the liver may be almost indistinguishable from hepatocellular cell carcinoma due to overlapping clinicopathologic features such as elevated AFP level, hepatoid morphology, and immunoexpressions of AFP, polyclonal CEA, and alpha-1 antitrypsin. Moreover, the hepatoid component of HACS can be more prominent in metastatic lesions to perigastric lymph nodes or liver [45, 58]. The presence of underlying disease such as liver cirrhosis and the presence of primary



**Figure 5.** Microscopic photograph of hepatadenocarcinoma and its immunostaining pattern of glycan-3. **A.** Solid nests of tumor cells are incompletely surrounded by sinusoid-like microvascular structure. This tumor is composed of polygonal cells with centrally located polymorphic nuclei and pale pinkish relatively abundant cytoplasm, resembling hepatocytes. **B.** The glycan-3 immunostain shows membranous and cytoplasmic staining pattern of tumor cells.

lesion detected by screening modalities such as endoscopy and abdominal computerized tomography scan would be useful to differentiate metastatic HACS and primary hepatocellular carcinoma. Although hepatocellular carcinoma arising in non-cirrhotic liver and without known risk factors is rare, this tumor has been reported to appear as a single nodule with pseudo-adenomatous or sclerosing pattern histologically [59, 60].

In recent clinical series by Baek et al, approximately 77% of patients with HACS at presentation were diagnosed as an advanced stage, stage III or IV [44]. Median overall survival and progression free survival of these patients after gastrectomy and/or palliative chemotherapy were 8.03 months (95% CI: 6.59-9.47) and 3.47 months (95% CI: 0.65-6.29), respectively. The incidence of liver metastasis of HACS is significantly higher than that of conventional gastric adenocarcinoma. Liu et al reported the overall incidence of liver metastasis was 75.6% including 8.9% synchronous and 73.2% metachronous liver metastasis in HACSs compared to 11.6%, including 1.8% synchronous and 9.9% metachronous liver metastasis in conventional gastric adenocarcinoma [50]. The overall 5-year survival rate of HACS was 9% compared to 44% in conventional gastric adenocarcinoma [50]. Most of HACS cases clinically appear to chemoresistant and curative resections are limited due to advanced lesions at diagnosis. Kamata et al demonstrated multiple ATP-binding cassette transporters related with multidrug resistance of tumor such as multidrug resistant-associated proteins 1,2, and 6 were expressed frequently in HACS [61]. This finding suggested that ATP-binding cassette transporters participated in the mechanism of multidrug resistance in HACS.

HER2 gene amplification and protein overexpression have been introduced as the target therapy with anti-HER2 humanized monoclonal antibody (trastuzumab) in various cancers including gastric cancer in an advanced stage. Although reported rates of HER2 overexpres-

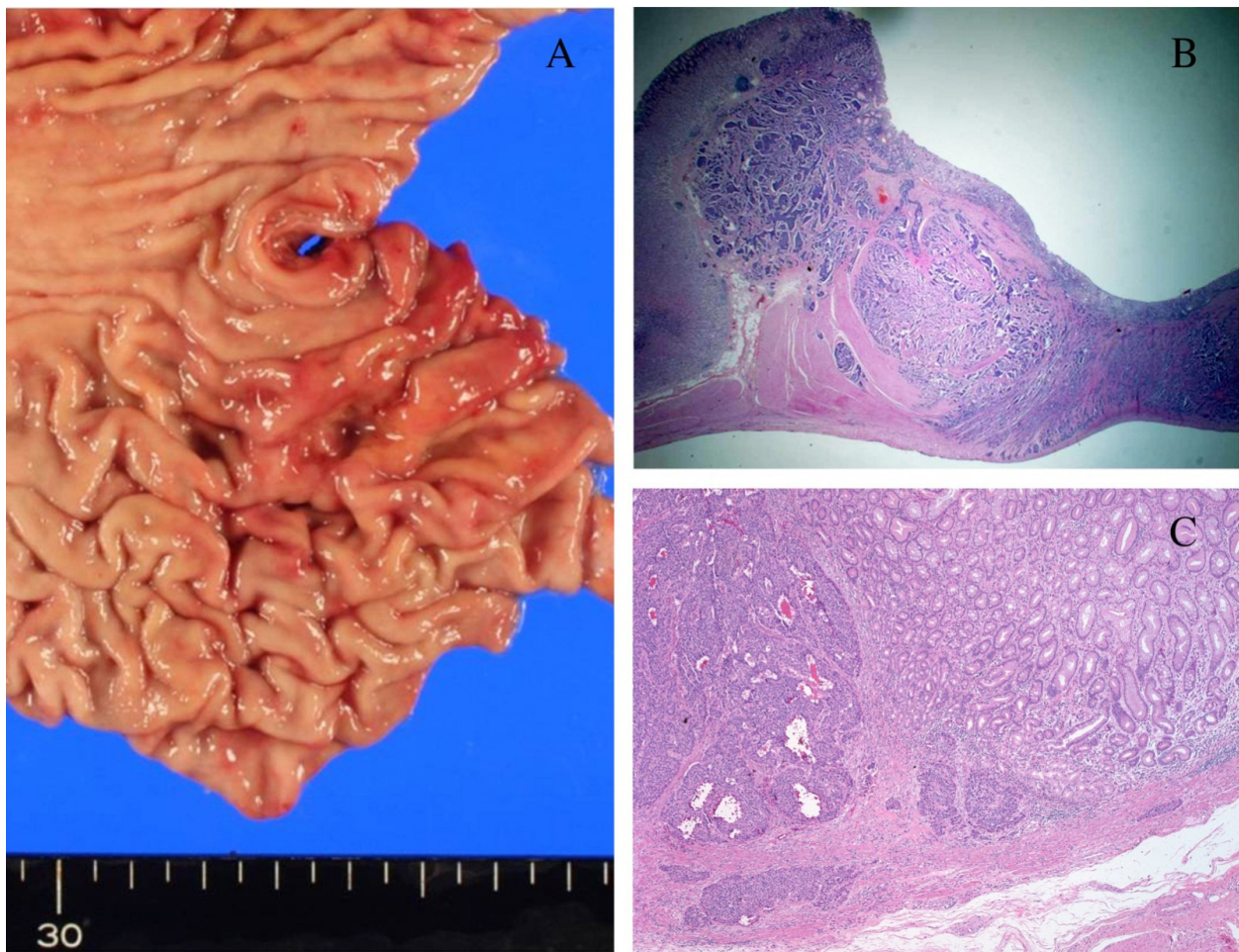
sion have been variable, it accounts for approximately 20 % of all gastric carcinomas. Recently, Giuffre et al reported that a markedly increased HER2 amplification was more frequent in HACS (42.9%) than that seen in tubular gastric adenocarcinomas (31.3%) [1]. This finding shows trastuzumab can be a useful therapeutic standard option not only for patients with advanced gastric cancer but also in aggressive variants like HACS.

#### 4. Neuroendocrine cell carcinoma

Primary small cell carcinoma of the stomach (PSCCS) is an exceedingly aggressive variant of gastric carcinoma with neuroendocrine differentiation. Since Matsusaka et al described this variant first in 1976, less than 230 cases have been reported in the literature [62]. This tumor also has been referred to “oat cell carcinoma” and “atypical carcinoid” and accounts for 0.1 - 0.6% of total gastric cancers [63, 64]. The mean age of presentation is 65 years (range, 42 to 84 years) and it commonly affects males [65]. The clinical presentation is similar to those seen in patients with conventional gastric adenocarcinoma in an advanced stage. PSCCS may rarely secrete hormones such as vasoactive intestinal peptide, neuron-specific enolase, pro-gastrin-releasing peptide, antidiuretic hormone, and adrenocorticotrophic hormone [66-68]. A few cases of PSCCS have been reported in association with paraneoplastic syndromes including paraneoplastic neurological syndrome and Cushing syndrome by ectopic production of ACTH [69, 70].

PSCCS tends to metastasize early to regional lymph nodes and liver and extends to surrounding organs including liver, transverse colon, pancreas, and diaphragm at the presentation [71-74]. In the largest retrospective series, Chiba et al demonstrated that PSCCSs have a higher incidence rate of lymphatic invasion (88.9% vs. 56.6%), vascular invasion (75.6% vs. 31.6%), and lymph node metastasis (82.1% vs. 58.8%) compared to those of conventional gastric carcinoma [75].

Neuroendocrine cell carcinomas of the gastrointestinal tract are usually responded well to the chemotherapy. Although there has been no established chemotherapy regimen for PSCCS due to its rarity, generally it has been recognized that surgical resection alone may not be sufficient treatment and emphasize the importance of adjuvant chemotherapy, especially for advanced disease. Fukuda et al insisted that intensive chemotherapy with or without surgical resection should be recommended for this tumor at any stage [76]. Recently, some studies have reported good response of some chemoregimens routinely used for lung SCC such as etoposide/cisplatin, irinotecan/cisplatin, and S1/cisplatin [65, 68, 77, 78]. The 5-year survival rate of patients with gastric neuroendocrine carcinoma has been reported to be 22.1%- 43.8% and the median survival time is 19 month [68, 79, 80]. However, long-term survival up to 3 years was reported in a patient with aggressive adjuvant chemotherapy [68].



**Figure 6.** Gross and microscopic photographs of neuroendocrine carcinoma in the stomach. **A.** It forms an ulceroinfiltrative solid mass (Bormann type III) in the upper body of the stomach. **B.** At lower magnification, this solid tumor invades into the subserosa. **C.** Dark purple solid nests of poorly differentiated neuroendocrine carcinoma invades into the muscularis mucosa accompanied by desmoplastic reaction in the surrounding tissue.

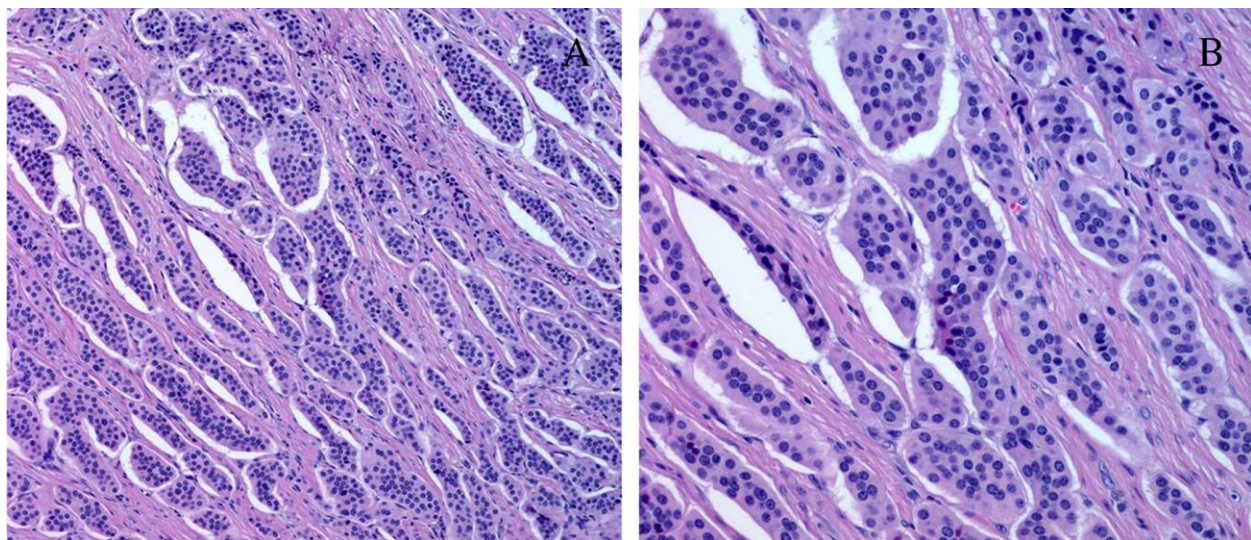
Macroscopically, the average size of the tumor is approximately 6.3 cm [65]. This tumor is an ulcerative or protruding mass (70% of cases) with frequent invasion to subserosa (Fig.6) [65, 81]. PSCCS can be classified as pure (Fig.7) or mixed (composite) SCC (Fig.8) depending on the proportion of neuroendocrine cell component. However, regardless of the proportion of neuroendocrine carcinoma in total volume of gastric carcinoma, its presence has been correlated with a poor prognosis. Approximately 60% of PSCCS cases are associated with conventional gastric adenocarcinoma, and rare cases with sarcomatoid carcinoma, adenosquamous, and squamous carcinoma variants have been reported [82-85]. Histologically, diagnostic criteria for PSCCS are identical with those for pulmonary neuroendocrine tumors by the WHO/International association for the Study of Lung Cancer [86]. First of all, the SCC histology is

defined as having a markedly high nuclear/cytoplasmic ratio and hyperchromatic small nuclei (less than 3 resting lymphocytes) with finely granular chromatin and inconspicuous or rarely conspicuous nucleoli. Frequent nuclear molding might be present. Focal or extensive necrosis can be seen. The typical organoid architecture pattern of low grade neuroendocrine neoplasm (eg. carcinoid) is rarely present in PSCCS. As a high grade tumor, their proliferative rate is high, and all exhibit more than 10 mitoses per 10 high power fields, with a mean of 40 to 50 mitoses [87]. Intestinal metaplasia may be seen in the background of gastric mucosa. In cases with classic histologic features of neuroendocrine tumors, positive staining for neuroendocrine markers is not a requirement for a diagnosis [87].

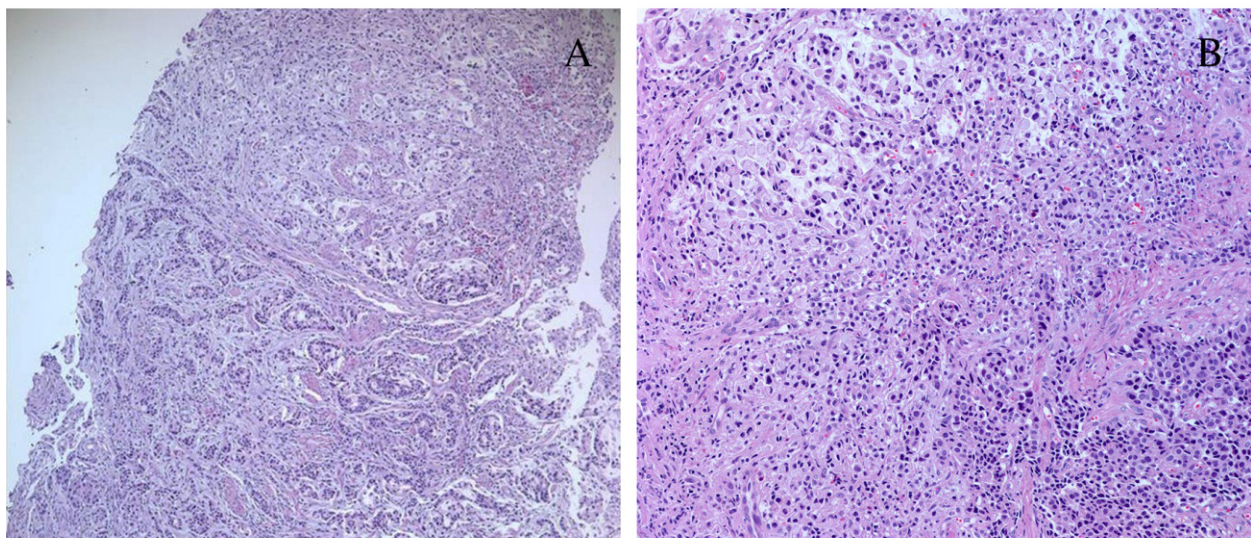
The pathogenesis of neuroendocrine carcinoma of the stomach is unknown. The most commonly accepted hypothesis is the presence of a “pluripotent stem cell” that has a potential to grow and differentiate into other cell types producing mucin or keratin [88]. This hypothesis has been supported by some cases of composite neuroendocrine carcinomas with other glandular or squamous cell components [89, 90]. Other suggested theory is that neuroendocrine carcinoma of the stomach arises from neuroendocrine precursor cells in gastric adenocarcinoma during its genetic progression [91].

Since PSCCS could be occasionally misdiagnosed as poorly differentiated adenocarcinoma or malignant lymphoma due to accompanying crush artifact in small biopsies, Grimelius stain and immunohistochemistry would be useful to differentiate morphologic mimickers. Immunohistochemical staining for neuroendocrine markers, including chromogranin, synaptophysin, and CD56, is usually positive (Fig.9) [81, 92, 93]. Its intensity and distribution can vary, with most examples showing patchy and moderately intense immunoreactivity. Also, most PSCCSs show an immunoreactivity for keratin AE1/AE3 and CEA but not for high molecular cytokeratin CK34 $\beta$ E [87]. Recently, Li et al demonstrated the low molecular weight cytokeratin, CK8 (CAM 5.2), is more commonly expressed in SCC in gastrointestinal tract including PSCCS than is the expression of AE1/AE3 or epithelial membrane antigen, suggesting CK8 as a sensitive marker for SCCs of the gastrointestinal tract [94]. The proliferation index for Ki-67 is high, usually more than 25 % positive nuclei. Rindi et al have reported that angioinvasion, tumor size, clinicopathological type, mitotic count, and Ki-67 proliferation index are predictors of tumor malignancy and patient outcome in neuroendocrine tumors of the stomach [79].

At the current time, neuroendocrine carcinomas in the gastrointestinal tract are classified into neuroendocrine carcinoma (small and large cell subtypes) and mixed adenoneuroendocrine carcinoma by World Health Organization (WHO) [95]. Large cell neuroendocrine carcinoma of the stomach (LCNECS) is defined as a high grade or poorly differentiated malignant neuroendocrine tumor of non-small cell type. In the largest series by Jiang et al, LCNECSs account for at least 1.5% of all gastric cancer [96]. In this series, the mean age of the patients with LCNECS is 62.7 years (range, 47 to 79 years) and it mostly affects males.



**Figure 7.** Pure well differentiated neuroendocrine carcinoma of the stomach. **A.** Well differentiated neuroendocrine carcinoma shows a typical organoid or solid nest growth pattern. **B.** At higher magnification, the tumor cells display characteristic cytologic features of neuroendocrine cells including hyperchromatic small nuclei with finely granular chromatin ("salt and pepper" nuclei) and inconspicuous nucleoli.



**Figure 8.** Mixed small cell carcinoma reveals an admixture of poorly differentiated adenocarcinoma with signet ring cell features and small cell carcinoma. **A.** In a small biopsy, neuroendocrine carcinoma component can be misled as a part of poorly differentiated adenocarcinoma. **B.** At high magnification, the upper part of this picture shows rounded aggregates of signet ring cell carcinoma with mucin. Adjacent to signet ring cell carcinoma, solid nests of poorly differentiated neuroendocrine tumor cells with a high nuclear to cytoplasmic ratio are present in the lower part of this picture.

Grossly, the mean size of the tumor is 6.4 cm (range 1.1 to 13.0 cm) and 66% of cases are Bormann type II or III in an advanced stage [96]. The diagnostic criteria for LCNECS is defined

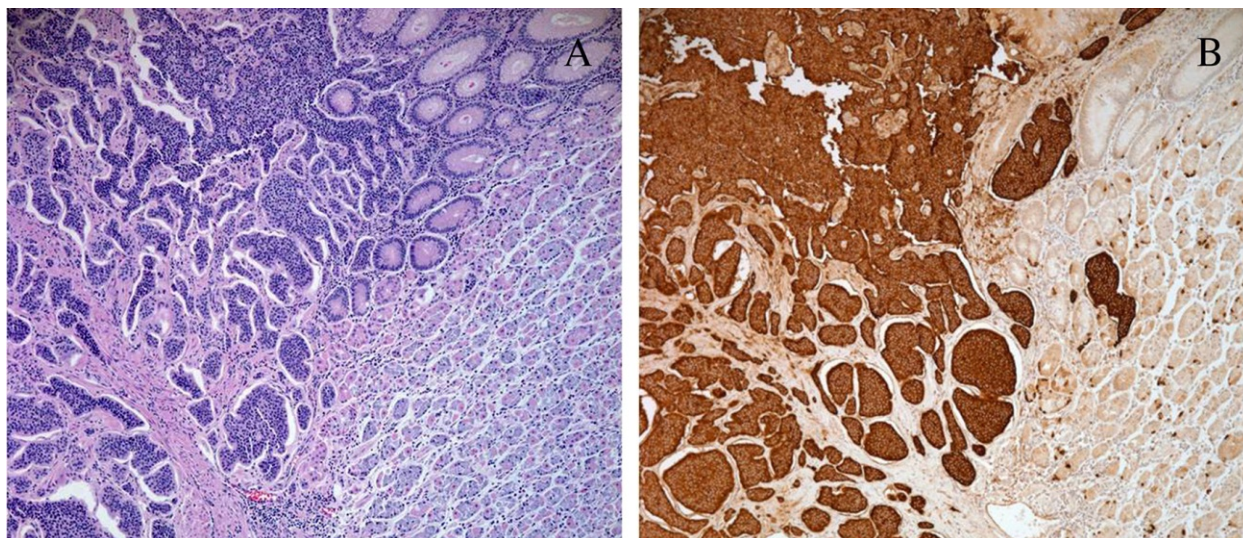
as having the following features: a diffuse growth pattern or “neuroendocrine architecture” (organoid, nesting, palisading, rosettes, or trabeculae), monotonous polygonal or round to oval cells with moderate amounts of slightly eosinophilic cytoplasm and ill defined cell border, granular or vesicular nuclei with evenly distributed granular chromatin, and with or without visible nucleoli [97]. Focal lumen formation or focal intracytoplasmic mucin might be seen, and are not feature for exclusion. LCNECSs usually combine with other common adenocarcinoma components. Immunohistochemical evidence of neuroendocrine differentiation is defined as positive staining for one of three neuroendocrine markers, chromogranin, synaptophysin, and CD56, in > 20% of the tumor cells [97]. In a relatively large study to compare LCNECS and PSCCS by Matsui et al, they demonstrated LCNECSs reveal a higher mitotic count, larger polygonal cells, a lower nuclear-cytoplasmic ratio, coarser nuclear chromatin, and more frequent conspicuous nucleoli than PSCCSs [81].

The main difficulty with the diagnosis of gastric neuroendocrine carcinoma is to distinguish them from poorly differentiated adenocarcinoma with solid growth pattern and malignant lymphoma. Preoperative diagnosis of neuroendocrine carcinoma from gastric endoscopic biopsy specimens would be challenging for the pathologists due to its histologic heterogeneity as well as the propensity of neuroendocrine tumor that mainly proliferates under the mucosal layer [65, 71]. Also, neuroendocrine carcinoma of the stomach cannot be easily recognizable due to less prominent neuroendocrine histologic features in high grade tumor cells. These factors can result in limited and demanding biopsy specimens for making a diagnosis of PSCCS preoperatively. However, careful evaluation for hidden or faint neuroendocrine architecture, cytologic features of neuroendocrine cells, and comparable immunohistochemical profiles would be useful to differentiate two disease entities. Sometimes ultrastructural study can help to demonstrate accumulation of electron-dense core neurosecretory granules measuring 200 nm in diameter in these tumors [98].

Primary gastric malignant lymphoma can be distinguished by immunoreactivity of CD45 and lack of cytokeratins. SCC of the lung metastatic to the stomach should always be considered in the differential diagnosis of PSCCS. With limited data, staining for the lung marker, thyroid transcription factor-1 (TTF1), seems to be almost always negative in neuroendocrine tumors of the gastrointestinal tract [99]. So TTF1 can be helpful to differentiate a metastatic lesion from SCC of the lung.

Another subtype of neuroendocrine carcinoma is a mixed neuroendocrine carcinoma. Although localized endocrine cell differentiation in benign or malignant glandular neoplasm of the gastrointestinal tract is relatively common, truly mixed glandular-endocrine neoplasms (adenoneuroendocrine carcinoma) are rare. These tumors are composed of both glandular component like conventional adenocarcinoma and recognizable neuroendocrine component of small or large cell type that comprises substantial proportions of the tumor volume with each component at least 30% of the lesion [100]. Most of mixed glandular-neuroendocrine neoplasms of the stomach are malignant tumors arising in the background of atrophic gastritis.





**Figure 9. A.** Small cell carcinoma of stomach forms solid nests or sheets of tumor cells that invades into the gastric mucosa. **B.** This variant shows a strong positivity for one of neuroendocrine markers, chromogranin.

## 5. Squamous and adenosquamous carcinoma

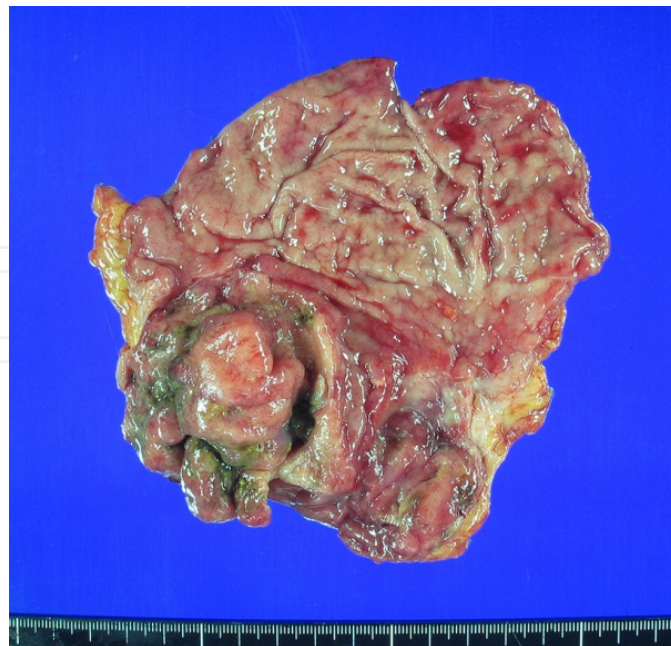
Primary squamous and adenosquamous carcinoma of the stomach is an extremely rare and aggressive variant of the stomach cancer that accounts for 0.04 to 0.9 % of all gastric carcinoma [101, 102]. Although clinical manifestation of the patients with primary squamous and adenosquamous carcinoma of the stomach is similar with patients with conventional gastric adenocarcinoma, it has been reported a mildly elevated serum level of squamous cell carcinoma antigen and a long history of smoking and alcohol abuse in some patients [103-105]. The mean age of presentation is 64 years (range, 17 to 89 years) and men are affected about five times as often as women [104]. Patients with primary squamous or adenosquamous carcinoma of the stomach frequently present with advanced stage disease (pT3 or T4) with or without metastases or involvement of other organs (stage III or IV) [106]. It has known that these variants do not response well to the routine chemoregimen for conventional gastric carcinoma. There is no established standard adjuvant chemoradiation therapy for patients with primary squamous and adenosquamous carcinoma in the stomach. However, one isolated case suggested that low-dose 5-fluorouracil plus cisplatin would be an effective preoperative chemoregimen to shrink the size of tumors and lower postoperative complications [106].

Although there is no specific macroscopic feature for primary squamous carcinoma of the stomach, recently Oono et al demonstrated a well demarcated, white superficial depressed area of primary squamous carcinoma as an early lesion which is not stained by 3.0% lugol solution on chromoendoscopy [107]. Main differential diagnosis of primary squamous carcinoma of the stomach is primary squamous carcinoma of the esophagus that involves the proximal stomach. Parks et al have proposed the diagnostic criteria for primary squamous carcinoma of the stomach based on not only histologically definite squamous features but also

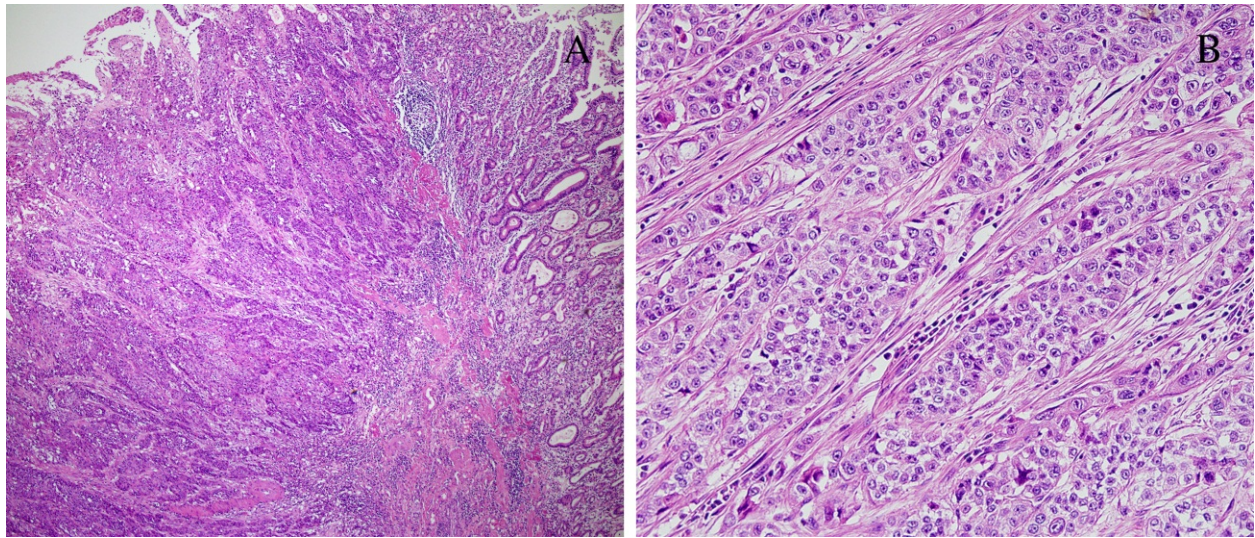
in regard to clinical findings as follows: (1) the tumor must not be located in the cardia; (2) the tumor must not extend into the esophagus; (3) there should be no evidence of squamous carcinoma in any other part of the body [108] (Fig.10). Another criteria for primary squamous carcinoma of the stomach by the Japanese Classification of Gastric Carcinoma are as follows: (1) the tumor must consist of only squamous carcinoma without any component of adenocarcinoma (pure squamous component only) (Fig.11) and (2) any tumor near esophagogastric junction must be excluded unless evidence for supporting the tumor originated from the stomach exists [109].

The origin of primary squamous carcinoma of the stomach is unclear, but four hypotheses concerning its development have been proposed, including (1) nests of ectopic squamous cells in gastric mucosa; (2) squamous metaplasia of the gastric mucosa before malignant transformation; (3) squamous differentiation in a preexisting adenocarcinoma; and (4) multipotential stem cells in the gastric mucosa [110-112].

Focal squamous differentiation in the intestinal-type adenocarcinoma is relatively common. Therefore, Straus et al established a diagnostic criteria for adenosquamous carcinoma of the stomach that the squamous component should be present in more than 25 percent of the resected tumor (Fig.12 and 13) [111]. Its biological behavior is usually determined by the adenocarcinoma component. Also the diagnostic criteria by Parks should be applied for the final diagnosis of primary gastric adenosquamous carcinoma to exclude primary esophageal cancer and metastatic lesion.



**Figure 10.** Gross photograph of pure squamous carcinoma. Gastrectomy specimen displays a large, fungating solid mass with surface ulceration and necrosis.



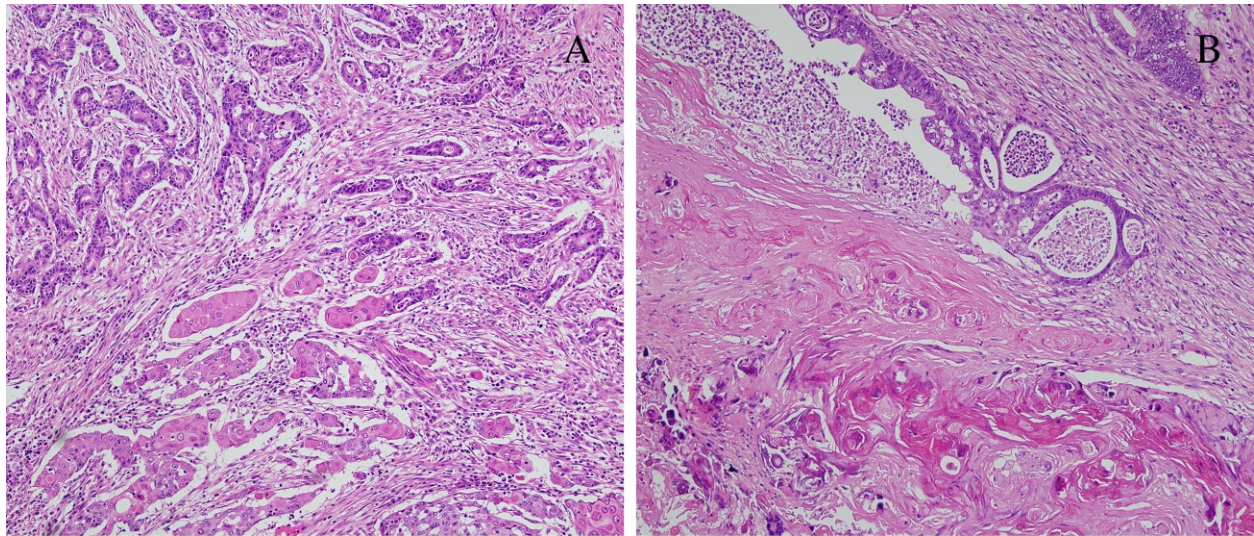
**Figure 11. A.** Dense solid sheets of squamous carcinoma invade into the submucosa. **B.** At high magnification, infiltrating solid nests of tumor cells show marked pleomorphism, intercellular bridges, and high mitotic counts.



**Figure 12.** Gross photograph of adenosquamous carcinoma. Adenosquamous carcinoma with a pale yellow solid cut surface that involves all the gastric wall and an attached lymph node.

Differential diagnosis of primary squamous and adenosquamous carcinoma of the stomach include (1) gastric adenocarcinoma, intestinal type, with squamous differentiation; (2) chronic gastritis or ulcer with squamous metaplasia; (3) esophageal squamous carcinoma arising from the esophagogastric junction; (4) metastatic squamous carcinoma to the stomach. Most of reported cases of primary squamous and adenosquamous carcinoma of the stomach have demonstrated a poorer clinical course and prognosis than conventional gastric adenocarcino-

ma. The mean survival after surgery is less than 12 months (1-16 months) [113]. Radical surgical excision is the only option for localized disease. For advanced-stage disease, surgery plus adjuvant radio-and/or chemotherapy appears to achieve a better outcome than surgery alone in terms of longer survival, although experience is limited due to the rarity of this variant.



**Figure 13.** **A.** A mixed area of both glandular and squamous carcinoma. **B.** At high magnification, a mixed area of squamous carcinoma with prominent keratin formation and adjacent adenocarcinoma with intraluminal abscess is seen.

## 6. Choriocarcinoma

Primary choriocarcinoma of the stomach (PCCS) is a highly aggressive variant of gastric carcinoma that was described for the first time by Davidsohn in 1905 [114]. This variant represents approximately 0.08 % of all the gastric cancers [115]. Pure gastric choriocarcinomas are extremely rare and only less than twenty cases were reported [116-118]. Most of primary gastric choriocarcinomas have been reported as a composite or mixed tumor with a combination of predominant choriocarcinoma component and a variable degree of adenocarcinoma. Transitions between adenocarcinoma and choriocarcinoma component may be clear or not. Yolk sac tumor, small cell carcinoma, and hepatoid carcinoma components may be seen as well [119-122]. In the study by Kobayashi et al, the average age of the patients with PCCS is 62.4 years in men and 54.8 years in women with a male predominance (male: female ratio=2.3:1) [123]. The clinical presentation of this variant is similar to that of gastric adenocarcinoma, however, it is a frequent cause of gastrointestinal bleeding and may have some hormonal effects such as gynecomastia in men, precocious puberty, pregnancy mimicking symptoms including amenorrhea, nausea and vomiting in women [124, 125].

PCCS behaves more like gestational choriocarcinoma because it shows extensive hematogenous dissemination or metastasis by mixed or pure components of choriocarcinoma as

opposed to the routine lymphatic spreading of gastric adenocarcinoma. Kobayashi et al analyzed previously reported 53 cases of PCCS and concluded that the most common cause of death in patients with PCCS is hepatic failure caused by liver metastasis followed by massive cancerous hemorrhage [123]. Untreated patients with PCCS have an average survival of several months [126]. Although no standard therapy has been established, complete surgical resection with neoadjuvant chemotherapy for non-gestational choriocarcinoma has been used in most of cases. Noguchi et al have reported a good response with the combination chemotherapy of 5-fluouracil and cisplatin after surgery [127]. However, radiotherapy did not show any improvement for clinical course and outcome [126]. Basically, accurate diagnosis by initial biopsy, curative resection, early and appropriate intervention by chemotherapy, and the absence of combined liver metastasis are favorable prognostic factors for patients with PCCS.

The significance of an elevated serum  $\beta$ -human chorionic gonadotropin (HCG) is controversial. Some studies suggested that it is associated with a shorten survival and poorer prognosis [128]. However, other insisted that it does not have any prognostic significance [129].  $\beta$ -HCG can be detected in blood or tissue in about 10% of patients with conventional gastric carcinoma; however, many of these tumors do not show any histologic evidence of the presence of choriocarcinoma component [130-132]. Also, the elevation of serum  $\beta$ -HCG and HCG immunoreactivity on tissue in these patients were usually mild. Most of reported cases of PCCS have been accompanied by markedly elevated serum level of  $\beta$ -HCG level up to 53,000 IU/ml at the presentation preoperatively and it significantly declined to the low level or baseline several months after surgeries. So, monitoring serum  $\beta$ -HCG level may have a role in evaluating response to treatment and tumor recurrence.

Macroscopically, this tumor usually occurs as a large exophytic mass with extensive necrosis and hemorrhage. Radiographically, it is a heterogeneous mass with enhanced vascularity and hemorrhage, mimicking a vascular tumor such as cavernous hemangioma [133]. Microscopically, this variant consists of choriocarcinoma and conventional adenocarcinoma with a variable proportion. Choriocarcinoma exhibits a typical biphasic pattern of admixed cytotrophoblasts and syncytiotrophoblasts. Polygonal cytotrophoblasts are located with a central core and surrounded by a peripheral rim of multinucleated syncytiotrophoblasts. Cytotrophoblasts have large, round hyperchromatic nuclei, abnormal nuclear chromatin, irregular nuclear membranes, occasional prominent nucleoli, and dense eosinophilic to amphophilic cytoplasm. Pleomorphic and multinucleated large cells are syncytiotrophoblasts. The viable tumor cells are found mainly at the lesion's periphery while extensive hemorrhage and necrosis are often in the center of the tumor like gestational choriocarcinoma. Typical and atypical mitotic figures may be frequently found. This tumor can show vascular invasion with tumor thrombi and tumor cells lining vascular spaces occasionally. Adenocarcinoma components would be tubular or papillary type with varying degree of differentiation. This tumor has been frequently misdiagnosed as gastric adenocarcinoma at presentation due to the size of tumor, massive tumor necrosis, and combined adenocarcinoma element. The diagnosis may even more become difficult in a small gastric biopsy from the lesion because it may reveal only scant syncytiotrophoblasts intermixed with recognizable routine adenocarcinoma component. Only 8% of PCCS cases in a pooled analysis of 53 cases were correctly diagnosed as choriocarcinoma in an initial biopsy [123]. Therefore, an extensive and large tissue sampling would be required for a precise diagnosis of

PCCS prior to surgery. In addition, if the biopsy contain any suspicious elements that suggest syncytiotrophoblasts, immunohistochemical biomarkers for trophoblastic cells will help confirming the diagnosis. In most instances, choriocarcinomatous cells are strongly positive for cytokeratin,  $\beta$ -HCG, and weakly positive for human placental lactogen. However, PCCS may not express  $\beta$ -HCG in the tumor tissue by immunohistochemistry [134].

Regarding the pathogenesis of PCCS, several theories have been proposed. The dedifferentiation theory first proposed by Pick in 1926 has been the most accepted explanation for the pathogenesis of choriocarcinoma [135]. Liu et al reported the first interphase cytogenetic study of PCCS, the results of which support this theory that PCCS arises from an alternative differentiation pathway, a dedifferentiation, of primary gastric adenocarcinoma [135, 136]. In this study, PCCSs showed the gain of chromosome 12, which is frequently associated with choriocarcinoma, and other genomic imbalances (gains of function mutations in 2q, 7pq, 8pq, 13q, 17q, 18q, 20pq and deletions in 17p) that are common genomic mutations in conventional gastric adenocarcinoma.

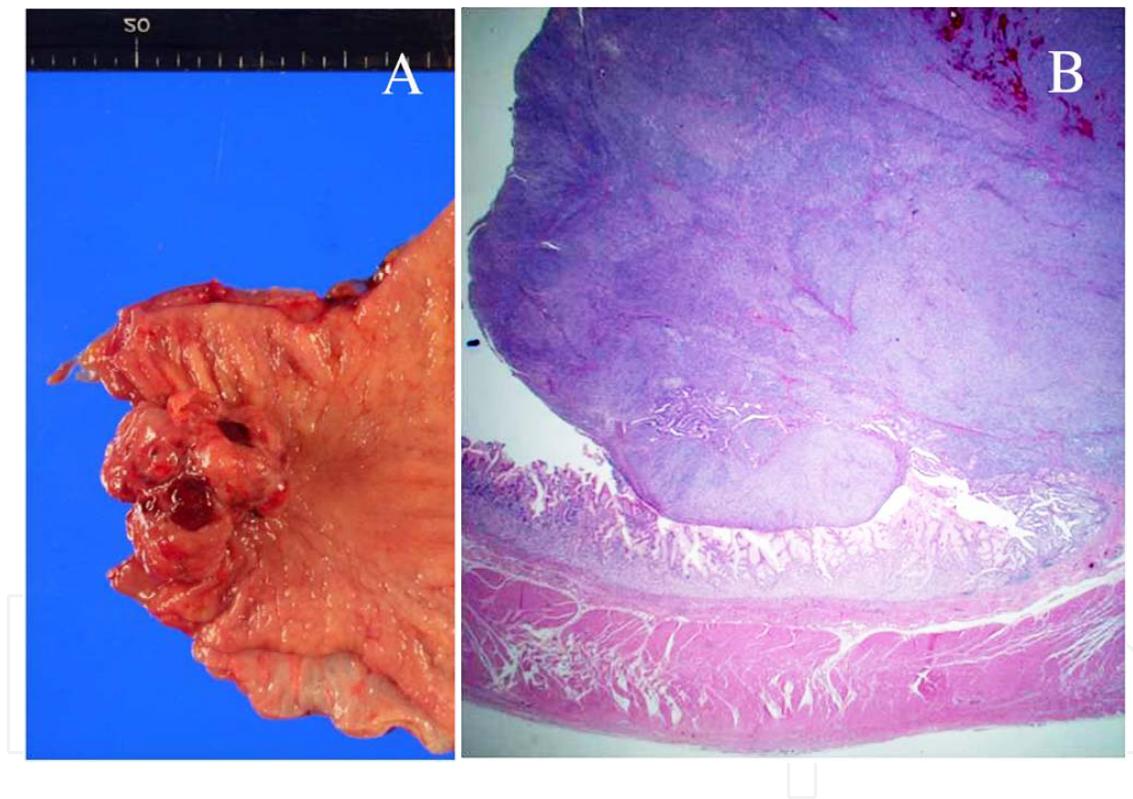
The major differential diagnosis of PCCS is metastatic trophoblastic tumor from other sites, particularly a non-gestational gonadal or extragonadal germ cell tumor from men and intrauterine or extrauterine gestational trophoblastic tumor in reproductive aged women. Extensive radiologic and clinical evaluation is recommended to rule out metastatic trophoblastic tumor from genital tracts in the men and women to make an unequivocal PCCS diagnosis.

## 7. Sarcomatoid carcinoma

Since Queckenstedt described the existence of the sarcomatous component in the gastric adenocarcinoma in 1904, approximately 50 cases of gastric sarcomatoid carcinoma have been reported [137]. Sarcomatoid carcinoma of the stomach (SCS) - also referred to as carcinosarcoma, malignant mixed mesodermal tumor, spindle cell carcinoma, and pseudosarcoma- is an uncommon variant of gastric carcinoma which is a biphasic neoplasm composed of a mixture of malignant epithelial and mesenchymal components. The various terms in use represent the uncertain histogenesis of this tumor, whether sarcomatoid carcinomas represent a single or two separate entities (carcinoma with sarcomatoid differentiation versus collision tumor consisting of carcinoma and sarcoma) remains controversial; however, some stromal tumor cells of SCS showing epithelial features such as staining for cytokeratin favor a monoclonal origin with divergent transformation.

The mean age of presentation is 45 years (range, 27 to 74 years) and males are predominantly affected (2.3:1), with patients frequently having metastasis to regional lymph nodes and liver at the time of diagnosis [138, 139]. Due to this tumor detecting at advance stage and its rapid growth, most of SCSs are associated with a poor clinical outcome. Sato et al reported a mean survival of 10 months in patients with SCS [140]. The current standard therapy for SCS is partial or total gastrectomy with regional lymph node dissection. The effects of chemotherapy or radiotherapy have not been established [141]. SCS may present synchronously with conventional adenocarcinoma. However, there is no case of SCS that develops secondarily in

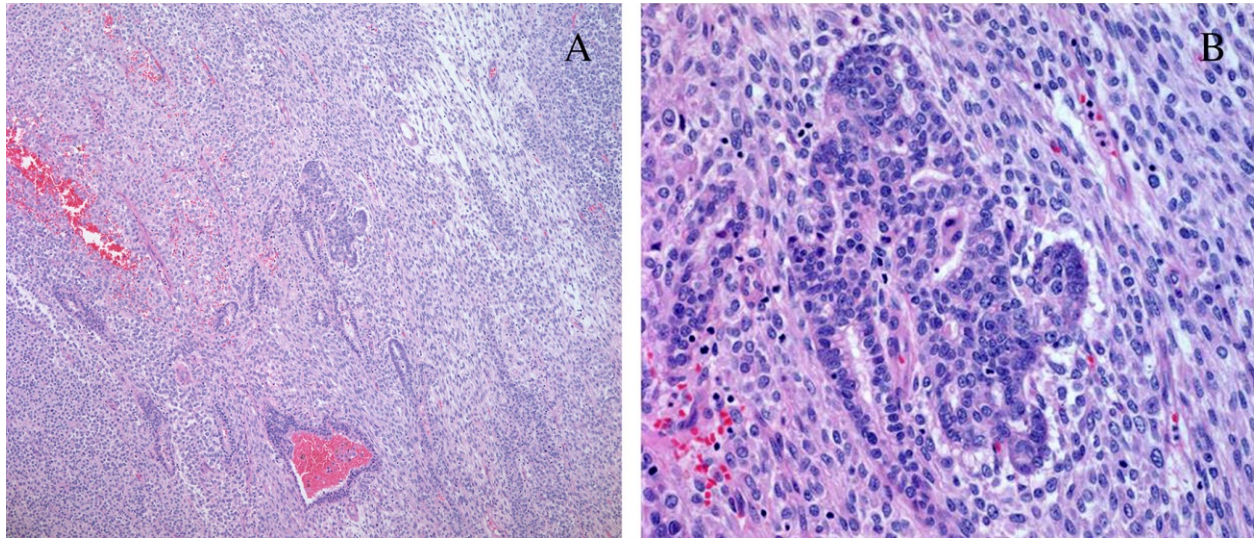
patients with prior chemotherapy, which is different from primary sarcomatoid carcinoma arising from other organs. SCS usually occurs in the antral or pyloric region and infiltrates the gastric wall frequently. Macroscopically, it is a polypoid, exophytic, or endophytic mass with ulceration (Fig.14) [139, 140, 142-146]. Histologically, SCS exhibits an adenocarcinoma component with variable differentiation and a high-grade sarcomatous component composed of spindle cells with high cellularity, frequent mitotic counts with atypical forms and pleomorphism (Fig.15). The spindle cells generally have plump, pleomorphic nuclei with a coarsely stippled chromatin pattern and small nucleoli with a haphazard arrangement. The transition between epithelial and sarcomatoid components can be abrupt but two components may intermix with each other. The epithelial component is predominantly composed of adenocarcinoma but rarely adenosquamous and neuroendocrine cell carcinoma can be accompanied [82, 83, 140]. Some cases represent atrophic gastritis and dysplasia in the background gastric epithelium [142, 145].



**Figure 14.** Gross and microscopic photographs of sarcomatoid carcinoma. **A.** This variant frequently appears as a polypoid or exophytic mass in the antrum. **B.** Low-magnification view shows a relatively well circumscribed dense mass.

The proportion of the sarcomatoid component is highly variable (5 % up to 80 %) [83, 139, 147]. In most instances, the pattern typically resembles that seen in high grade spindle sarcomas which lack specific immunohistochemical markers for identifying the line of differentiation [83, 84, 141, 148]. In some cases, the sarcomatous component can be heterologous, with osteosarcomatous, chondrosarcomatous, and rhabdomyosarcomatous or leiomyosarcomatous differentiation [82, 139, 146, 149, 150]. There have been three cases reported

showing multidirectional differentiation including rhabdomyosarcoma, osteosarcoma, and chondrosarcoma [139, 147, 148].



**Figure 15.** Microscopic photographs of sarcomatoid carcinoma. **A.** Adenocarcinoma component is entrapped by sarcomatoid cell component. **B.** At high magnification, the glandular component showing anastomosing or cribriform pattern is surrounded by dense spindle cells. The spindle cells show compact and hyperchromatic nuclei with marked pleomorphism. This biphasic pattern supports the diagnosis of this variant. The sarcomatous component may display heterologous differentiation toward skeletal and smooth muscle, bone, and cartilage.

The epithelial component is identified by CK, EMA, or Cam 5.2, whereas muscle markers like desmin, myogenin, or myoD1 may confirm rhabdomyoblastic differentiation and when chondrosarcoma or liposarcoma is suspected, S100 protein can be used to confirm the diagnosis. In rare cases such as the epithelial component containing neuroendocrine differentiation, neuroendocrine markers (synaptophysin, chromogranin, and CD56) would be useful.

Differential diagnoses of SCS include other primary gastric sarcomas. If primary gastric sarcoma is suspected based on radiologic and endoscopic findings, multiple and extensive sampling of the lesion should be performed to avoid missing an epithelial component. Another consideration is the extremely rare instance of osseous metaplasia arising in the conventional gastric adenocarcinoma. Unusual bone component in the stomach can be mistaken for a part of SCS element. However, the bone component is histologically benign [151, 152]. Similarly, differentiating SCS from benign, borderline, and malignant spindle cell tumors, such as inflammatory fibroid polyp, calcifying fibrous tumor, gastrointestinal stromal tumor, and plexiform angiomyxoid myofibroblastic tumor need to be considered.

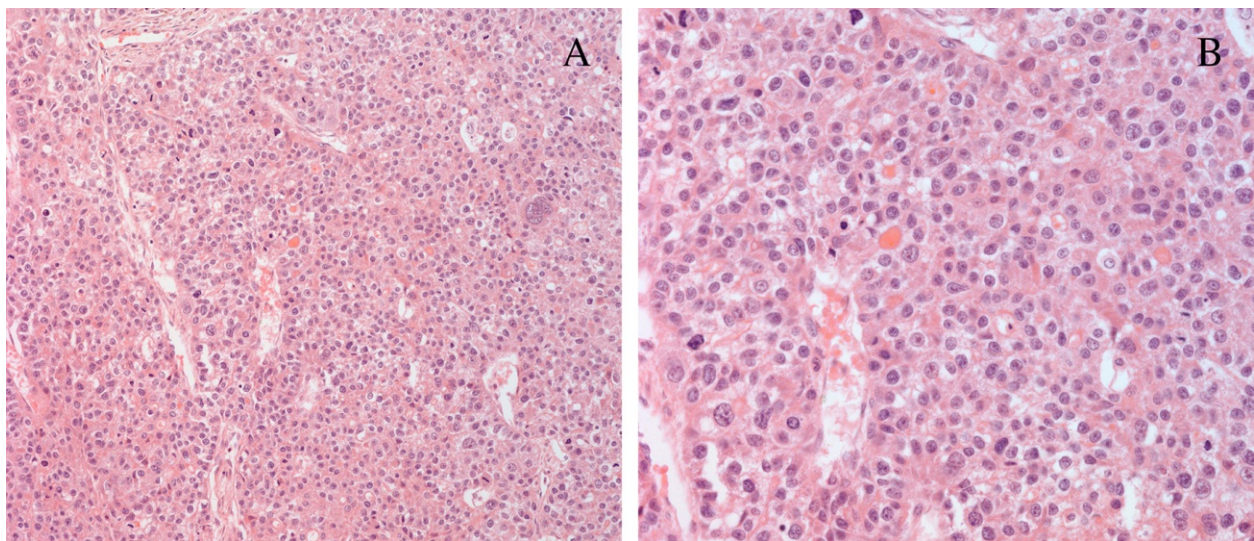
## 8. Acinar cell carcinoma

Acinar cell carcinoma of the stomach (ACCS) defined to have immunohistochemical evidence of pancreatic exocrine enzyme production, is an uncommon variant of gastric adenocarcinoma



that is morphologically resemble to primary pancreatic acinar cell carcinoma. Pure ACCS is extremely rare and only two cases had been reported [153, 154]. Most of reported ACCS are mixed tumors which combine with glandular and/or neuroendocrine carcinoma components.

Microscopically, this variant demonstrates acinar, solid, glandular/microglandular, and trabecular arrangement of cells forming large, densely cellular tumor nodules containing minimal stroma (Fig.16). Tumor cells forming acini are cuboidal or columnar cells similar to size of normal pancreatic acinar cells with basally located nuclei and apical eosinophilic granular cytoplasm (Fig 17). Nuclei are round to oval, with minimal to mild pleomorphism, indistinct nucleoli or occasional single nucleolus. Mitotic activity is variable. The cytoplasm is moderately abundant, eosinophilic, and granular. The non-neoplastic stomach shows chronic gastritis with intestinal metaplasia. ACCS can exhibit different morphologic features such as focal ductal differentiation and well-formed individual ductal elements with mucin production that are uncommon in primary acinar cell carcinoma of the pancreas [155]. Periodic acid-Schiff reaction after diastase digestion and Grimelius stains demonstrate characteristic positive granules within the cytoplasm of the tumor cells. By immunohistochemistry, the tumor cells express pancreatic exocrine enzymes, predominantly trypsin, and variably lipase,  $\alpha$ -1 anti-trypsin,  $\alpha$ -1 anti-chymotrypsin and chymotrypsin. Among many pancreatic enzymes, trypsin is one of the most common and useful markers for the diagnosis of ACCS. The frequency of trypsin expression in series varied from 71% to 100% (average, 97%), whereas chymotrypsin expression ranged from 39% to 100% (average, 66%) [156]. The antigens  $\alpha$ -1 antitrypsin and  $\alpha$ -1 chymotrypsin can be positive for some tumor cells but not specific for ACCS [153, 157]. Another important diagnostic feature of acinar cell carcinoma is the presence of zymogen granules, which are large (250 to 1000  $\mu$ m) electron-dense, homogeneous granules on electron microscopy [155].

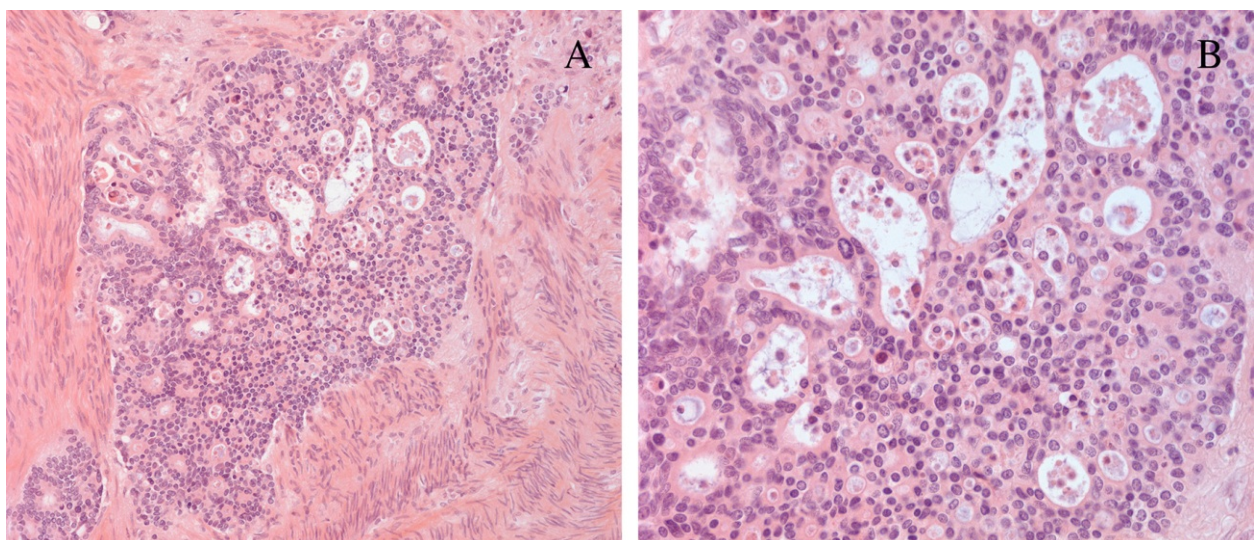


**Figure 16.** Microscopic photographs of acinar cell carcinoma. **A.** This variant shows trabecular and glandular arrangement of tumor cells. **B.** High magnification view demonstrates solid sheets of cuboidal cells with moderate pleomorphism and eosinophilic granular cytoplasm. Occasional mitoses and giant tumor cells are seen.

The histogenesis of ACCS is unclear. There are several hypotheses that may explain the origin of this variant. Because pancreatic heterotopia is relatively common in the stomach, origin in heterotopic pancreatic tissue was proposed first. Some ACCSs arising from heterotopic pancreas have been reported [158-163]. Acinar cell metaplasia is a relatively common finding in the gastric mucosa, either as a congenital abnormality, or in association with chronic gastritis [164-167]. ACCS may arise from this metaplastic process. Ambrosini-Spaltro et al reported an ACCS arising in association with pancreatic metaplasia in the gastric mucosa [168]. The possibility of the presence of “pluripotent stem cells” in the gastric mucosa, which have the potential to grow and differentiate to diverse cell types and neoplasms has been suggested by several studies of gastric composite tumors by morphology, ultrastructural examination, immunohistochemistry, and molecular genetics [157, 169, 170]. Fukunaga reported a gastric carcinoma resembling pancreatic mixed acinar-neuroendocrine carcinoma and proposed the possibility of a primitive multipotent cell with the capacity of divergent differentiation to explain acinar and neuroendocrine differentiation in the tumor [157].

The main differential diagnosis is metastatic lesion from pancreatic neoplasm. Since immunohistochemical expression of this tumor in the stomach and pancreas is exactly same, full clinical and radiographic evaluation would be essential to exclude the possibility of metastasis from pancreas.

The prognosis of primary ACCS is unknown due to the scarcity of reported cases. However, considering 50% of patients with primary pancreatic acinar cell carcinoma having metastases at presentation and a worse prognosis, the recognition of acinar cell component in gastric carcinoma may be important for the patients’ treatment and prognosis.

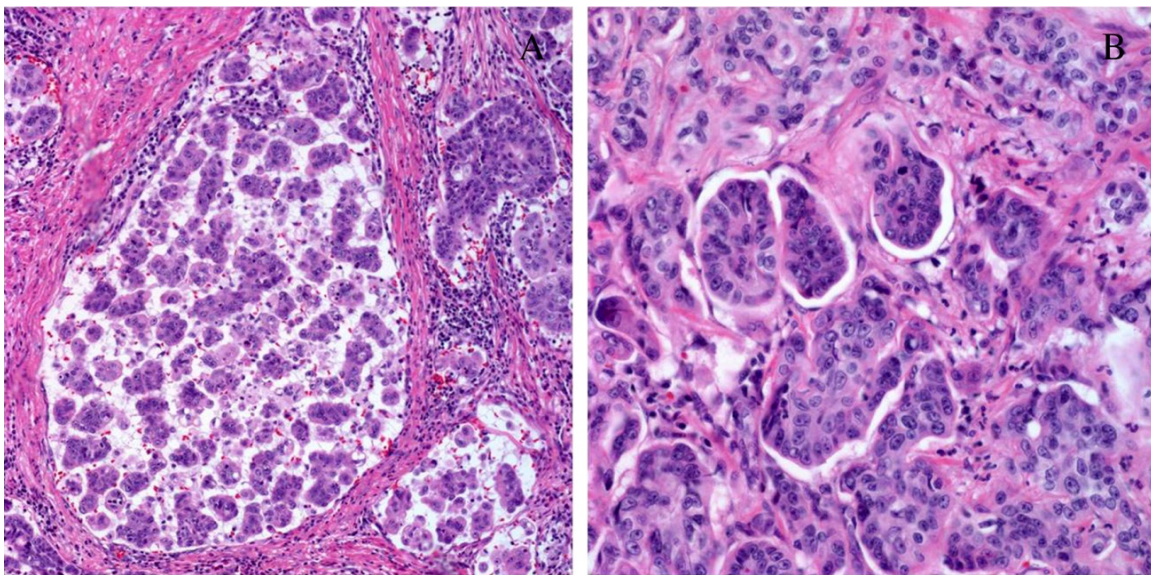


**Figure 17. A and B.** Microscopic photographs of acinar cell carcinoma. This tumor shows a prominent acinar growth pattern mimicking normal pancreatic acinar cells with prominent ductal elements with mucin.

## 9. Invasive micropapillary carcinoma

Recently, an unusual variant of gastric adenocarcinoma called “invasive micropapillary carcinoma of the stomach (IMPCS)” has been described by Shimoda et al in 2008 [171]. In a recent study by Roh et al, IMPCSs were present in up to 0.07% of 1,5254 total or subtotal gastrectomy specimens [172]. The mean age of this variant is 66.2 years (range 36-87 years) with a male predominance (male to female ratio: 2.5-3:1). This rare tumor demonstrates an aggressive behavior associated with a higher incidence of lymphovascular invasion and lymph node metastasis, resulting in a poor prognosis similar to invasive micropapillary carcinomas (IMPCs) of other organs including breast, urinary bladder, ureter, lung, parotid gland, and colon [173-179]. In the reported series to date, patients with IMPCS have an estimated 30% of 5-year overall survival rate compared to those with non-IMPCS having 67% of 5-year survival by Kaplan-Meier method [172].

Histologically, this variant consists of small tight cell clusters of papillary structure devoid of fibrovascular cores within lacunar spaces mimicking lymphatic or vascular channels (Fig.18). The lacunar spaces are artifactual tissue spaces and not lined by an endothelial cell. Several adjunct markers have been introduced to enhance the recognition of IMPCs. IMPCs in most organ systems are characterized by inverted polarity with MUC1 expression with membranous MUC1 staining facing the stroma [180]. Similarly, epithelial membrane antigen shows reverse polarity expression in IMPCs [181]. However, focal or heterogeneous staining pattern of IMPCs by MUC1 and EMA can be seen. Other immunohistochemical expressions of KL-6, CA125, and HER2/neu are frequently increased in IMPCs of the urinary tract but lack of specificity as an ancillary maker [181-184].



**Figure 18.** Invasive micropapillary carcinoma. **A.** Typical pathologic features of micropapillary carcinoma lined by clear spaces without lining cells nor mucin are seen. Papillary adenocarcinoma within lymphatic space is a lesion mimicking micropapillary carcinoma. **B.** In lymphatic spaces, the numbers of papillae are more than two unlike one in micropapillary carcinoma.

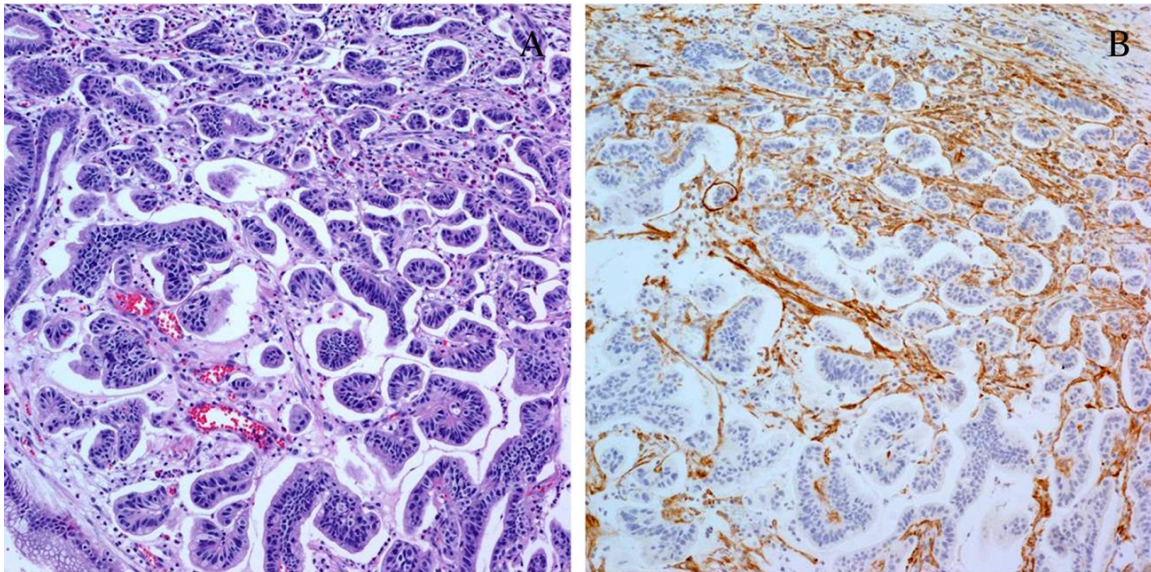
No “pure” form of IMPCS has been reported and all cases of IMPCS reported have been combined with conventional or papillary gastric adenocarcinoma. In the series of 72 IMPCS cases by Eom et al, most of the combined adenocarcinoma components were characterized as intestinal type (64/72 cases, 88.9%) and papillary adenocarcinoma (43/72 cases, 59.7%), and the remaining were classified as diffuse type (8/72 cases, 11.1%) and tubular adenocarcinoma (21/72 cases, 29.2%) [185].

Although IMPC has become increasingly well recognized as a distinct and aggressive variant in stomach as well as other organs from recent vigorous studies. Diagnostic criteria for a diagnosis of IMPCS remain imprecise. In a recent study about interobserver reproducibility in the diagnosis of IMPC of the urinary tract, this study recommended a combination of some histologic features included small tumor cell nests within stromal retraction spaces, back-to-back lacunae, multiple tumor nests within each single retraction space are useful to make a diagnosis for “classic” IMPC that may bring a better reproducibility. Additional associated histologic features to be considered including epithelial ring forms, intracytoplasmic vacuolization, elongated epithelial nests (i.e., micropapillae), and peripherally oriented nuclei. These diagnostic criteria of IMPC in the urinary tract based on a combination of several histologic features would be highly useful to make a diagnosis of IMPCs in other organs including stomach. In addition, the threshold for a diagnosis of IMPCs based on the percentage/volume of IMPC component is undetermined. There has been no validated clinicopathologic data that support the threshold of IMPC proportion in association with a clinical outcome in patients with IMPC. One study of IMPCs in the urinary tract showed a trend towards an association between the proportion of IMPC and survival with >50 % IMPC component imparting a relative mortality risk of 2.4, compared to with < 50% IMPC of those [186]. However, Kim et al suggested that the proportion of IMPC component with respect the whole tumor is not related with the prognosis of the patients with IMPC in the colorectum [187]. In the stomach, Roh et al failed to find any significant clinicopathologic differences between a group with ≤ 20% of IMPC component and another group with > 20% of IMPC component [172]. Some studies suggest an arbitrary cutoff of IMPCS as ≥ 5% of IMPC proportion in total tumor volume but ≥ 10% of IMPC proportion in other studies [172, 185]. Approximately 70% of reported cases in the stomach were found that the proportion of IMPC component to the entire tumor ranged from 10% to 70%. In previous published cases of IMPC of the colorectum, the proportion of IMPC component ranged from 5 % to 80 % but was usually less than 30 % of the entire lesion [178, 187, 188]. Comperat et al analyzed 72 cases of IMPC of the urinary bladder and the proportions of IMPC component are: 10% of cases with less than 10% of IMPC component, 47% of cases with 10%-50% of those, and 43% of cases with more than 50% of these [189]. Further studies are needed to have an established criteria for IMPCS showing a good reproducibility among inter-and intraobservers and to evaluate a diagnostic threshold of IMPC proportion in total volume of the tumor that correlate best with the clinical outcome.

The incidence of metastasis of IMPC from other organs to the stomach is uncommon. The possible metastatic lesions of IMPCs from other organs included urinary bladder, breast, lung, and ovary. Lotan et al investigated immunohistochemical markers to identify the primary site and differentiate metastatic lesions of IMPC [190]. They recommended that an immunohisto-

chemical panel consisting of uroplakin, CK20, TTF-1, ER and WT-1, and/or PAX8, and mammaglobin is the best one for accurately classifying the likely primary site of IMPC. In their studies, urothelial IMPC were usually positive for uroplakin and CK20, whereas p63, high molecular weight cytokeratin, and thrombomodulin were less sensitive and specific. Lung IMPC was uniformly TTF-1 positive. Breast IMPC was ER positive, mammaglobin positive, and PAX8/WT-1 negative, while ovarian IMPC was ER positive, mammaglobin negative, and PAX/WT-1 positive. However, no specific marker has been introduced for verifying specifically IMPCS.

The main differential entity of IMPCS is papillary adenocarcinoma or conventional adenocarcinoma with multiple endolymphatic tumor emboli. Morphologically, when a distinction of IMPC within lacunar spaces from lymphovascular tumor emboli may be difficult, immunohistochemical studies including factor VIII, *Ulex europaeus*, CD31, CD34, and D2-40 as well as FLI1 and Erg nuclear stains would be useful to rule out lymphovascular tumor emboli from other types of adenocarcinoma (Fig.19) [191].



**Figure 19. A.** Invasive micropapillary variant showing tight small clusters of papillary structures within lacunar spaces. **B.** Immunohistochemical stain for D2-40 would be useful to rule out lymphatic tumor emboli.

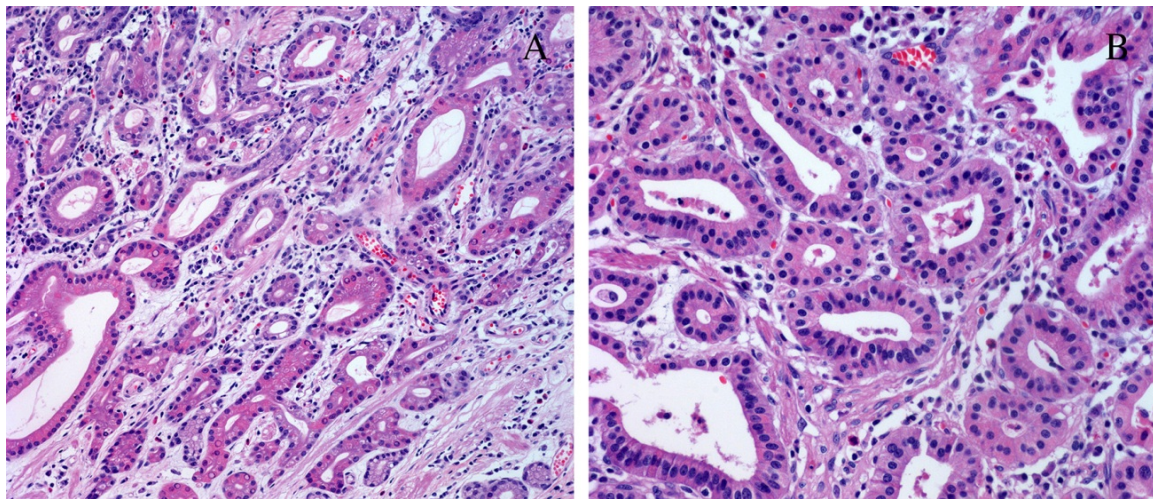
## 10. Gastric adenocarcinoma of fundic gland type (chief cell predominant type)

Recently, Ueyama et al proposed gastric adenocarcinoma of fundic gland type for a new entity of gastric carcinoma [192]. Although gastric adenocarcinomas with foveolar and pyloric gland type differentiation are relatively common, only a few cases of gastric adenocarcinomas with fundic gland differentiation have been reported. This variant is a well differentiated adenocarcinoma composed of mixed chief and parietal cells mimicking fundic glands (Fig.20). In

addition to histologic similarity of chief and parietal cells, immunohistochemical staining with pepsinogen I (a marker for chief cells) and H+/K+ATPase (a marker for parietal cells) exhibit differentiation toward the chief and parietal cells in gastric adenocarcinoma. In the series by Ueyama et al and Singhi et al, the patients' age range from 42 to 79 years (average: 65 years) with a relatively equal sex distribution [192, 193].

Gastric adenocarcinoma of fundic gland type is a relatively small tumor, the maximum diameter of tumors range from 0.2 to 2 cm (average 0.6 cm) [192, 193]. Characteristically, gastric adenocarcinomas of fundic gland type are located in areas with oxyntic mucosa, in the upper third of the stomach, fundus and cardia [192, 193]. Macroscopic findings of this variant in early lesion are the superficial depressed type (type 0-IIc) or superficial elevated type (type 0-IIa) [192]. Histologically, this variant is a well-differentiated adenocarcinoma composed of columnar cells admixed with predominantly chief cells, with pale grey-blue, basophilic cytoplasm, and scattered parietal cells, with coarse granular eosinophilic cytoplasm. Both cells exhibit mildly enlarged and hyperchromatic nuclei with slight pleomorphism. Mitotic activity is absent or very low.

Differential diagnosis includes fundic gland polyps that are small benign mucosal polyps that occur in the gastric fundus. Histologically, they are composed of dilated glands lined by oxyntic mucosa without atypia.



**Figure 20.** Microscopic photographs of gastric adenocarcinoma of fundic gland type. **A.** This variant is a well-differentiated adenocarcinoma mimicking the normal gastric fundic gland with irregular branching and angulated structures that invades in to the lamina propria. **B.** This adenocarcinoma predominantly consists of tumor cells mimicking chief cells with pale basophilic cytoplasm and basally located nuclei and scattered parietal cells with coarse granular eosinophilic cytoplasm.

## 11. Parietal cell carcinoma and oncocytic carcinoma

Since Capella et al originally described in 1984 as “gastric parietal cell carcinoma”, less than 30 cases have been reported to date [194]. The reported mean age of the patients with this

variant is 70.2 years (range 58-84 years) and it exclusively affects men (M:F ratio=9:1). Histologically, parietal cell carcinomas are usually composed of solid sheets of polygonal cells with round nuclei and abundant, finely granular eosinophilic cytoplasm that stain with phosphotungstic acid-hematoxylin and Luxol Fast Blue [194, 195]. Most of gastric parietal cell carcinomas are combined with well to moderately differentiated tubular or papillary adenocarcinoma. Parietal cell differentiation is confirmed by immunoreactivity for antibodies specific for parietal cell biomarkers H<sup>+</sup>/K<sup>+</sup> ATPase and human milk fat globule-2. Ultrastructurally, the granular and eosinophilic cytoplasm, so call “oncocytic cytoplasm” corresponds to the abundance of mitochondria, intracytoplasmic secretory canaliculi, and cytoplasmic tubulovesicles [196, 197]. A few previous studies suggested that this variant of gastric adenocarcinoma is associated with a better prognosis than conventional gastric adenocarcinoma [194, 198-201]. Robey-Cafferty et al reported a case of parietal cell carcinoma with lymphoma-like morphologic features [197]. Takubo et al introduced ten cases of oncocytic adenocarcinoma, which are morphologically similar to parietal cell carcinoma but are negative for anti-parietal antibodies [195].

## 12. Miscellaneous carcinomas

Extremely rare variants of gastric carcinoma have been sporadically reported. Among them are (1) mucoepidermoid carcinoma of the stomach; one case was reported that this variant arose from preexisting ectopic mucous glands of stomach [202]. (2) Paneth cell carcinoma or gastric adenocarcinoma with Paneth cell differentiation; histologically, Paneth cell differentiation is characterized by cytoplasmic distinct coarse eosinophilic granules stained red with periodic acid-Schiff and Masson trichrome reagents and reddish brown with phosphotungstic acid hematoxylin, and electron microscopically by lysozyme in cytoplasmic electron dense granules [203]. Immunohistochemical staining for lysozyme, human defensin-5, and CDX2 is usually positive [204, 205]. and (3) gastric carcinoma with osteoclast-like giant cells; these variants contains a minor component of giant cells that contain 3 to 20 nuclei and are positive for CD68 and vimentin [206]. These findings suggest that giant cells are of monocytic/histiocytic origin and probably represent a host response to the tumor [207]. However, the clinicopathological significance of this variant has not been verified due to its rarity. Salient features of variants gastric adenocarcinoma are listed in Table 2.

HISTOLOGIC TYPE	SALIENT FEATURES OF GASTRIC CANCER VARIANTS
<b>EBV-associated lymphoepithelioma-like carcinoma</b>	EBV infection related tumor with a dense lymphoid stroma, positive EBER-ISH, aberrant methylation, and a better prognosis
<b>Hepatoid adenocarcinoma</b>	Subtype of AFP producing carcinoma resembling hepatocellular carcinoma and showing frequent liver metastasis, and a worse prognosis

HISTOLOGIC TYPE	SALIENT FEATURES OF GASTRIC CANCER VARIANTS
<b>Neuroendocrine cell carcinoma</b>	Aggressive tumor with distinct neuroendocrine cell features and a worse prognosis but good response to chemotherapy
<b>Squamous and adenosquamous carcinoma</b>	Pure or composite tumors with definite squamous features with a very strong male predominance and a worse prognosis
<b>Choriocarcinoma</b>	Tumors with variable choriocarcinomatous components, elevated $\beta$ -HCG in the serum, frequent hematogenous spread and a worse prognosis
<b>Sarcomatoid carcinoma</b>	Biphasic neoplasm composed of a mixture of malignant epithelial and mesenchymal component with a poor prognosis
<b>Acinar cell carcinoma</b>	Adenocarcinoma resembling pancreatic acinar cells with production of pancreatic exocrine enzyme
<b>Invasive micropapillary carcinoma</b>	Adenocarcinoma with micropapillary features showing frequent lymphovascular invasion and lymph node metastasis
<b>Gastric adenocarcinoma of fundic gland type (chief cell predominant)</b>	Well differentiated adenocarcinoma mimicking a fundic gland polyp
<b>Parietal cell carcinoma and oncocytic carcinoma</b>	Well differentiated adenocarcinoma with Parietal cell differentiation and a better diagnosis

Table 2.

## Author details

Sun-Mi Lee<sup>1</sup>, Kyoung-Mee Kim<sup>2</sup> and Jae Y. Ro<sup>3</sup>

1 Departments of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

2 SamSung Medical Center, SungKunkwan University School of Medicine, Seoul, Korea

3 The Methodist Hospital, Weill Medical College of Cornell University, Houston, TX, USA

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