J Gastric Cancer. 2024 Jan;24(1):69-88
https://doi.org/10.5230/jgc.2024.24.e7
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Review Article

Unusual or Uncommon Histology of Gastric Cancer

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Received: Nov 29, 2023
Revised: Dec 6, 2023
Accepted: Dec 7, 2023
Published online: Dec 28, 2023

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: P.Y.S., S.J.; Data curation: P.Y.S., S.J.; Investigation: P.Y.S., S.J.; Methodology: P.Y.S., S.J.; Project administration: P.Y.S.; Resources: P.Y.S.; Writing – original draft: P.Y.S., S.J.; Writing – review & editing: P.Y.S., S.J.

ABSTRACT

This review comprehensively examines the diverse spectrum of gastric cancers, focusing on unusual or uncommon histology that presents significant diagnostic and therapeutic challenges. While the predominant form, tubular adenocarcinoma, is well-characterized, this review focuses on lesser-known variants, including papillary adenocarcinoma, micropapillary carcinoma, adenosquamous carcinoma, squamous cell carcinoma (SCC), hepatoid adenocarcinoma, gastric choriocarcinoma, gastric carcinoma with lymphoid stroma, carcinosarcoma, gastroblastoma, parietal cell carcinoma, oncocytic adenocarcinoma, Paneth cell carcinoma, gastric adenocarcinoma of the fundic gland type, undifferentiated carcinoma, and extremely well-differentiated adenocarcinoma. Although these diseases have different nomenclatures characterized by distinct histopathological features, these phenotypes often overlap, making it difficult to draw clear boundaries. Furthermore, the number of cases was limited, and the unique histopathological nature and potential pathogenic mechanisms were not well defined. This review highlights the importance of understanding these rare variants for accurate diagnosis, effective treatment planning, and improving patient outcomes. This review emphasizes the need for ongoing research and case studies to enhance our knowledge of these uncommon forms of gastric cancer, which will ultimately contribute to more effective treatments and better prognostic assessments. This review aimed to broaden the pathological narrative by acknowledging and addressing the intricacies of all cancer types, regardless of their rarity, to advance patient care and improve prognosis.

Keywords: Pathology; Classification; Diagnosis

INTRODUCTION

Gastric cancer remains a significant clinical and diagnostic challenge and is characterized by various histological types and the occasional occurrence of metastases from other malignancies. The most prevalent form of stomach cancer is tubular adenocarcinoma, which accounts for over half of all cases and has been reported to be as high as 72% in South Korea [1,2]. This histological type is well characterized in terms of epidemiology, pathogenesis, and clinical management. However, within the spectrum of gastric malignancies, there is a subset of unusual gastric cancers that exhibit unique pathological features that defy the typical presentation patterns. These rare entities often present diagnostic conundrums and therapeutic challenges due to their atypical presentation and sometimes aggressive nature.

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However, the unusual forms of gastric cancers are poorly understood. This type of cancer includes papillary adenocarcinoma, micropapillary carcinoma, adenosquamous carcinoma, SCC, hepatoid adenocarcinoma, gastric choriocarcinoma, gastric carcinoma with lymphoid stroma (GCLS), carcinosarcoma, gastroblastoma, parietal cell carcinoma, oncocytic adenocarcinoma, Paneth cell carcinoma, gastric adenocarcinoma of the fundic gland, undifferentiated carcinoma, and extremely well-differentiated adenocarcinoma. Each unusual form of stomach cancer has distinct histopathological characteristics, potentially unique pathogenic mechanisms, and molecular profiles.

This review aimed to synthesize the current knowledge and case reports regarding unusual and uncommon gastric cancers, providing insight into their histology and diagnostic challenges.

By shedding light on these lesser-known facets of gastric cancer, this review contributes to a broader oncological narrative that acknowledges and addresses the intricacies of all cancer types, regardless of their rarity, to advance patient care and improve prognosis.

PAPILLARY ADENOCARCINOMA

Papillary adenocarcinoma of the stomach is a distinct and relatively rare subtype, accounting for 2.7%–9.9% of cases [3]. Grossly, these tumors appear as exophytic polypoid masses. Tumor cells form well-differentiated, elongated, finger-like, or papillary processes lined with columnar or cuboidal epithelial cells, maintaining their polarity (**Fig. 1**). These cells are supported by fibrovascular connective tissue cores that sometimes contain tubular structures in a tubulopapillary configuration.

Moreover, papillary adenocarcinomas are associated with a higher risk of adverse outcomes [4,5]. This is highlighted by their tendency to metastasize to the liver and the resulting poor survival rates linked to this subtype.

Clear cell variants have been reported in papillary adenocarcinoma, which share basic histologic features with papillary carcinoma, including a glycogen-rich clear cytoplasm and frequent tubulopapillary patterns [6,7]. However, this subtype continues to be reported as the alpha-fetoprotein (AFP)-producing tumor and designated as gastric adenocarcinoma with enteroblastic differentiation (GAED) [8] (discussed in “Hepatoid adenocarcinoma”).

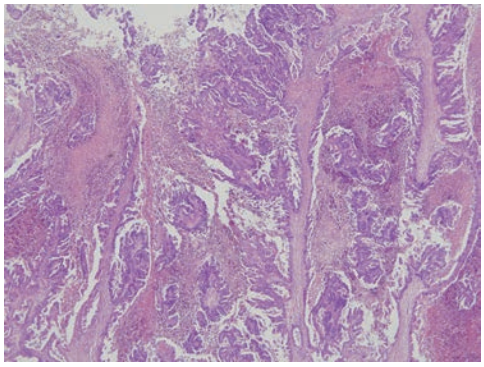

Fig. 1. Papillary adenocarcinoma. The tumor cells form well-differentiated, elongated, finger-like, or papillary processes that are lined by columnar or cuboidal epithelial cells maintaining their polarity (hematoxylin and eosin, original magnification ×40). Image courtesy of Dr. Jihun Kim.

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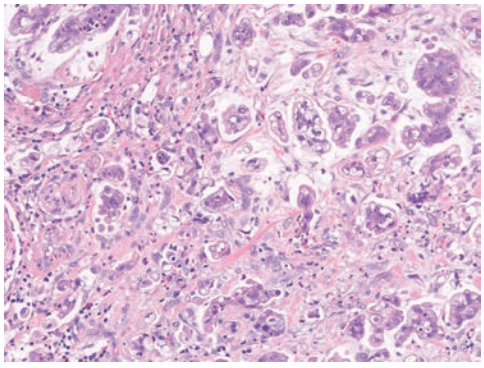

Fig. 2. Micropapillary carcinoma. Small nests of tumor cells show the absence of fibrovascular cores within transparent lacunar spaces that mimic the architecture of lymphatic or vascular channels (hematoxylin and eosin, original magnification ×100). Image courtesy of Dr. Soomin Ahn.

MICROPAPILLARY CARCINOMA

Micropapillary adenocarcinoma is rare and has a worse prognosis due to higher lymphovascular invasion and lymph node metastasis rates [9,10], and it is characterized by the presence of small tumor cell nests without fibrovascular cores within transparent lacunar spaces that mimic the architecture of lymphatic or vascular channels (**Fig. 2**), micropapillary adenocarcinoma arises in conventional tumors, including tubular or papillary adenocarcinoma, and its proportion varies from 5% to 90% [9,11].

ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma of the stomach forms 0.25%–2% of all cases [12,13]. It is a primary carcinoma that exhibits both glandular and squamous cell elements, with the latter accounting for approximately 25% of the tumor volume [14]. Clinically, these tumors often present as large masses and are most frequently located in the lower third of the stomach, although they can occur throughout the organ [15].

Histopathologically, adenosquamous carcinoma demonstrates a distinct squamous component characterized by keratin pearl formation and intercellular bridges along with the glandular element of adenocarcinoma (**Fig. 3A**) [16]. The transition between these 2

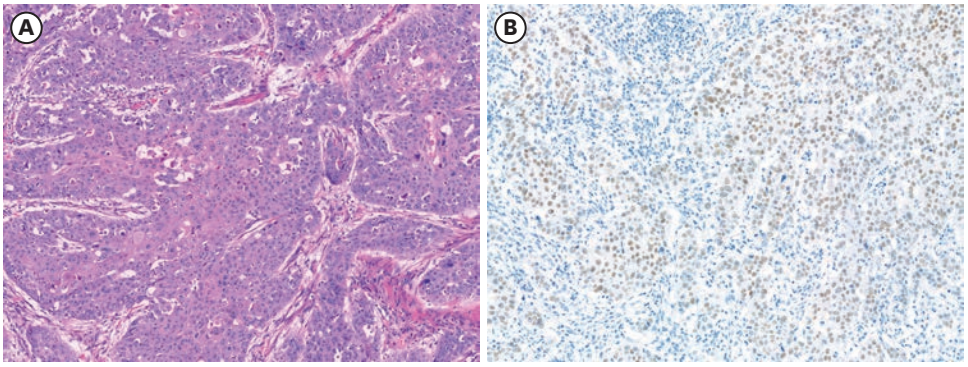

Fig. 3. (A) Adenosquamous carcinoma shows a distinct squamous component alongside the glandular element of adenocarcinoma (hematoxylin and eosin, original magnification, ×40). (B) Squamous components of the tumor are positive in p40 immunohistochemistry (p40, original magnification, ×40). Case courtesy of Dr. Su-Jin Shin.

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components can be abrupt or intermingled, suggesting a potential origin for multipotentially common stem cells [17]. The squamous cell component exhibited features similar to those observed in esophageal SCC, and p63/p40 immunohistochemistry confirmed squamous differentiation (**Fig. 3B**). These tumors have a poor prognosis owing to their deep penetration and high propensity for lymphovascular invasion, which often results in an advanced stage at diagnosis and a higher likelihood of metastasis [18,19].

SCC

Gastric SCC is even rarer than adenosquamous carcinoma, accounting for 0.04%–0.07% of gastric cancers, with under 100 cases reported in the literature [20-25]. It is characterized by the presence of keratinocyte-type cells with features such as intercellular bridges and keratinization and lacks the glandular components observed in adenosquamous carcinomas (**Fig. 4**).

The origin of gastric SCC is not definitively known; however, it has been hypothesized to arise from squamous metaplasia within adenocarcinomas, ectopic squamous nests, or multipotent stem cells in the gastric mucosa capable of bidirectional differentiation [24,26,27]. Gastric SCC is typically diagnosed at an advanced stage, and its prognosis is generally poor, although certain case reports have demonstrated better responses to chemotherapy than their adenocarcinoma counterparts [28,29].

HEPATOID ADENOCARCINOMA

Hepatoid adenocarcinoma is characterized by the presence of tumor cells that exhibit features reminiscent of hepatocellular carcinoma (HCC), notable for eosinophilic polygonal tumor cells (**Fig. 5A**), and AFP production, a biomarker typically associated with HCC and fetal hepatic differentiation, detectable both serologically and immunohistochemically (**Fig. 5B**) in tumor tissues [30,31].

Hepatoid adenocarcinoma typically affects patients aged >50 years and is predominantly located in the stomach [32]. Morphologically, hepatoid adenocarcinoma exhibits large polygonal cells with eosinophilic cytoplasm, often arranged in trabecular or acinar

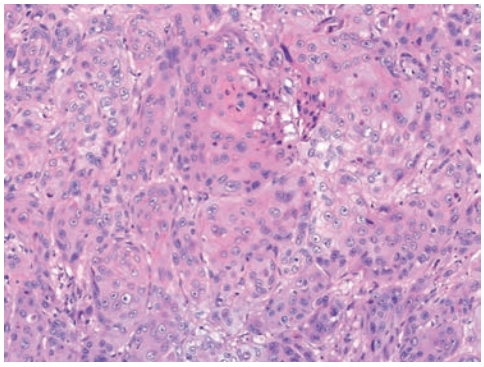

Fig. 4. Squamous cell carcinoma. This cancer is characterized by the presence of keratinocyte-type cells, with features such as intercellular bridges and keratinization, and lacks glandular components (hematoxylin and eosin, original magnification, ×100). Image courtesy of Dr. Soomin Ahn.

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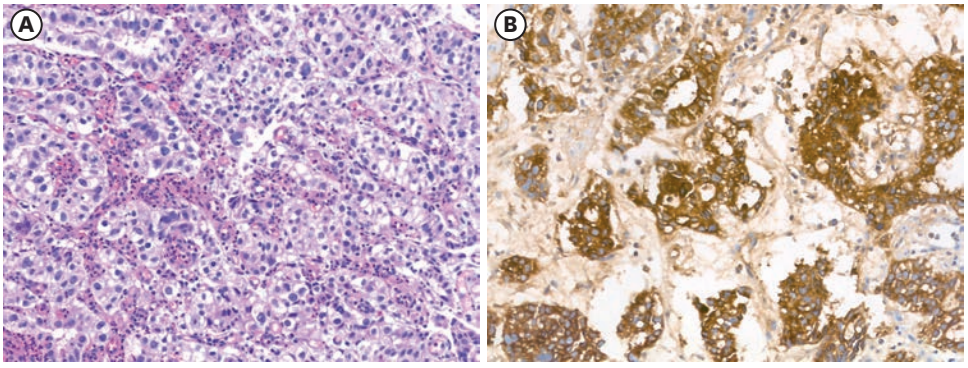

Fig. 5. (A) Hepatoid adenocarcinoma is characterized by the presence of tumor cells that exhibit features reminiscent of hepatocellular carcinoma, notable for eosinophilic polygonal tumor cells (hematoxylin and eosin, original magnification, ×100). (B) Tumor cells are positive for alpha-fetoprotein immunohistochemistry (alpha-fetoprotein, original magnification, ×200). Images courtesy of Dr. Soomin Ahn.

structures, similar to those seen in HCC [31,32]. Hepatoid adenocarcinoma is known for its Periodic acid-Schiff-diastase-resistant intracytoplasmic hyaline globules and may exhibit less differentiated regions with bizarre giant and spindle cells [32,33]. These tumors frequently exhibit mixed histological features of hepatoid areas with traditional tubulopapillary adenocarcinomatous patterns.

The disease is aggressive, often infiltrating the venous and lymphatic vessels, leading to a high incidence of liver and lymph node metastases and culminating in a poorer prognosis, regardless of AFP production [32,34-36]. Diagnosing hepatoid adenocarcinoma with multiple liver metastases can be challenging. Cases with multiple hepatic mass lesions with high serum AFP levels and the absence of background chronic liver disease should raise the possibility of hepatoid adenocarcinoma [37].

Immunohistochemically, hepatoid adenocarcinoma can be differentiated from HCC by the expression of markers such as Hep-Par-1, which typically shows extensive staining in HCC, but only focal staining in hepatoid adenocarcinoma [38]. In addition, significant presence of cytokeratin (CK) 19 and CK20 were detected in hepatoid carcinomas (HACs) at rates of 94% and 47%, respectively. These rates are considerably higher than those of HCCs, which suggests that CK19 is present in 0%–50% and CK20 in 0%–42% [39-41].

AFP-expressing carcinomas appear in 2.6%–5.4% of gastric cancers [42,43]. They include GAED, well-differentiated papillary/tubular adenocarcinoma with a clear cytoplasm, and yolk sac tumor-like carcinoma [44-46]. GAED is characterized by a tubular papillary structure and columnar cancer cells with clear cytoplasm. This differentiation is reminiscent of the early developmental stages of fetal gastrointestinal epithelium in fetuses [8,47]. These morphological features lead to the expression of several fetal gut markers, including SALL4, claudin-6, and glypican-3, which are useful for differentiating them from HCC [47,48]. GAED has a relatively favorable prognosis compared to HAC [45,49].

CHORIOCARCINOMA

Gastric choriocarcinoma exhibits adenocarcinomatous variable degrees of differentiation and germ cell elements with syncytiotrophoblasts and cytotrophoblasts (**Fig. 6A**) [50,51].

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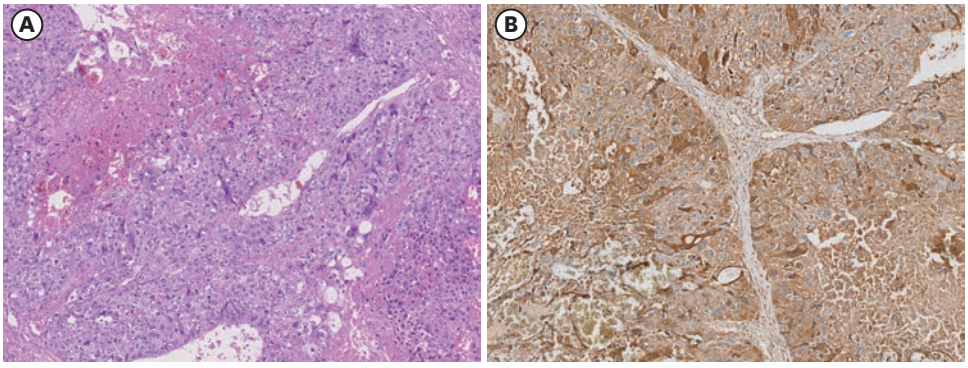

Fig. 6. (A) Gastric choriocarcinomas exhibit both adenocarcinomatous of variable degrees of differentiation and germ cell elements with syncytiotrophoblasts and cytotrophoblasts (hematoxylin and eosin, original magnification, ×100). (B) Tumor cells are positive for beta-hCG. (beta-hCG, original magnification, ×100). Case courtesy of Dr. Jihun Kim.
hCG = human chorionic gonadotropin.

The pathogenesis of gastric choriocarcinoma is thought to involve the choriocarcinomatous transformation of conventional adenocarcinoma [51]. Macroscopically, the lesion typically presents as an exophytic mass with significant necrosis and hemorrhage [52,53]. Immunohistochemistry often revealed human chorionic gonadotropin (hCG) expression within the trophoblastic components of the tumor (**Fig. 6B**), and patients typically exhibited markedly elevated circulating hCG levels. Serum hCG serves as both a prognostic indicator and a postoperative marker of potential tumor recurrence [52,54-56].

The management of gastric choriocarcinoma is challenging owing to its rarity, aggressive behavior, and complex histological presentation. With a high metastatic disease rate at the time of diagnosis, therapeutic approaches are often limited, and overall treatment outcomes remain poor. Their propensity to metastasize hematogenously often leads to hepatic failure due to extensive liver metastasis. Metastatic spread is rapid and widespread, significantly affecting prognosis, with most patients surviving for only a few months post-diagnosis [51,52,57].

Other germ cell tumor elements may present alongside embryonal carcinoma, yolk sac tumors, and hepatoid adenocarcinoma [58,59]. Only a few cases involving pure gastric yolk sac tumors have been documented [60-63].

GCLS

GCLS, also known as lymphoepithelioma-like carcinoma or medullary carcinoma, is an uncommon subtype, accounting for approximately 1%–8% of gastric cancers [64,65]. Typically, GCLS are histologically diverse, with patterns ranging from well-defined cellular trabeculae to less-organized syncytial structures (**Fig. 7A**). They are marked by dense lymphoid cell infiltration within the tumor architecture, mainly comprising cytotoxic CD8-positive T cells, although other immune cells contribute to dense infiltration [66,67].

Epstein-Barr virus (EBV) infection causes an interplay between carcinoma cells and immune elements within the gastric tissue. EBV positivity rates vary from 22.5% to 100% depending on the report, and it is worth noting that studies reporting rates as high as 80% or more used

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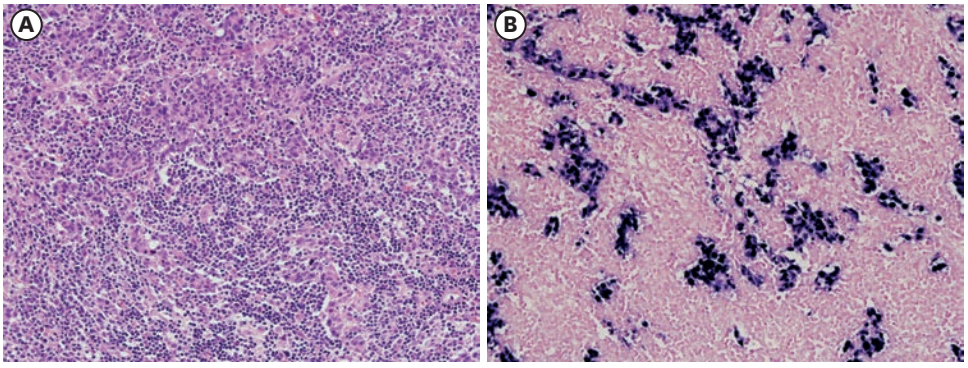

Fig. 7. (A) Gastric carcinoma with lymphoid stroma. Typically, these cases are histologically diverse, with a range of patterns from well-defined cellular trabeculae to less organized syncytial structures. They are marked by dense infiltration of lymphoid cells within the tumor architecture (hematoxylin and eosin, original magnification, ×200). (B) The tumor cells, not the tumor-infiltrating lymphocytes, are positive in EBER *in situ* hybridization (EBER *in situ*, original magnification, ×200).
EBER = Epstein-Barr virus-encoded small RNA.

EBV-encoded small RNA (EBER) (**Fig. 7B**) [64,68-72]. The role of EBV in GCLS carcinogenesis is multifaceted, with evidence suggesting that the virus contributes to carcinogenesis through a cascade of molecular events [73,74]. These include the induction of CpG island methylation and alterations in signaling pathways potentially mediated by viral gene products [75,76].

A subset of EBV-negative GCLS cases has been identified as microsatellite instability-high (MSI-H) [77]. MSI-H tumors are characterized by a significant number of alterations in DNA microsatellite sequences. This instability can arise because of defects in the DNA mismatch repair (MMR) system, which is responsible for correcting errors in DNA replication. This type of cancer can be detected by immunolabeling with MMR protein heterodimers (loss of MLH1/PMS2 vs. MSH2/MSH6 expression).

Predominantly occurring in the proximal stomach, GCLS demonstrates a male predominance and is often diagnosed at an earlier stage than other gastric cancers [75,78]. Early detection and the associated immune response may contribute to a comparatively improved prognosis in patients with GCLS [70,79].

The management of GCLS may benefit from the targeted application of checkpoint inhibitors due to the frequent overexpression of immunomodulatory molecules such as programmed cell death ligand 1/2 in these tumors [80-82], suggesting that GCLC is a possible immune checkpoint inhibitor and opens up a new treatment option.

CARCINOSARCOMA

Carcinosarcoma of the stomach is a biphasic malignancy that represents a distinct histological subtype characterized by the coexistence of adenocarcinoma and sarcoma components within the same tumor. These tumors exhibit striking heterogeneity in their histological composition, often incorporating sarcomatous elements. The sarcomatous component commonly displays spindle-cell morphology and frequently exhibits features of various types of sarcomas, including osteosarcoma, chondrosarcoma, rhabdomyosarcoma, and leiomyosarcoma [83-86]. Reported cases have demonstrated neuroendocrine or adenosquamous differentiation, underscoring the remarkable heterogeneity within these tumors [87-90].

https://doi.org/10.5230/jgc.2024.24.e7

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Most gastric carcinosarcomas typically manifest as large polypoid or fungating masses and are associated with poor prognosis, partly due to their aggressive behavior and advanced stage at diagnosis in many cases [91].

It is crucial to distinguish true gastric carcinosarcomas from benign ossification or osteoid production, which occasionally occurs in gastric carcinomas [92]. The presence of mature bone or osteoids in the tumor stroma must be carefully evaluated to rule out true carcinosarcoma.

GASTROBLASTOMA

Gastroblastoma is a biphasic tumor that primarily affects children and young adults, with a male predominance. This unique neoplasm is composed of mixed spindle and epithelial cellular elements, both of which lack sufficient atypia to be diagnosed as carcinosarcoma [93-97].

Most commonly, these tumors are located in the antrum of the stomach and present as submucosal tumors centered in the proper muscle layer [96,97]. Clinical symptoms often include abdominal pain, epigastric discomfort, fatigue, or gastrointestinal bleeding [93-97]. Physical examination revealed a mass in the epigastric area.

A gastroblastoma hallmark is its biphasic histology, which is characterized by the presence of 2 distinct cellular components: spindle cells and nests of epithelial cells. Epithelial cells in gastroblastomas exhibit specific features, including scant pale cytoplasm, round nuclei, and inconspicuous nucleoli. The spindle cell component was monotonous, with long, slender cells often observed in the myxoid background (**Fig. 8**). Importantly, mitotic activity in these tumors is generally low; however, a case demonstrating up to 30 mitoses per 50 high-power fields has been reported [93].

A defining molecular feature is the presence of the MALAT1-GLI1 fusion gene [97,98]. This fusion gene drives GLI1 oncogenic properties and activates the Hh signaling pathway. Immunohistochemical staining revealed that the mesenchymal component of gastroblastoma was positive for CD10, CD56, and vimentin, whereas the epithelial component expressed CK markers (AE1/AE3 and CAM 5.2) and may show focal positivity for

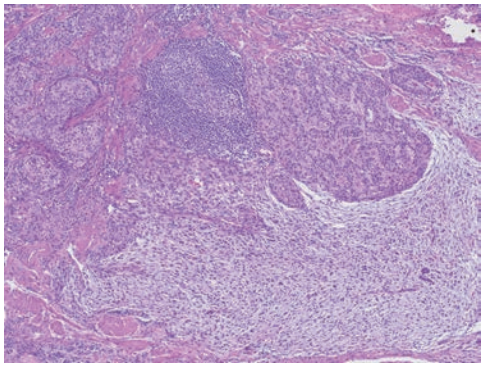

Fig. 8. The hallmark of gastroblastoma is its biphasic histology, characterized by the presence of two distinct cellular components - spindle cells and nests of epithelial cells. The epithelial cells in gastroblastomas exhibit specific features, including scant pale cytoplasm, round nuclei, and inconspicuous nucleoli. The spindle cell component is monotonous, with long and slender cells often observed in a myxoid background (hematoxylin and eosin, original magnification, ×10). Case courtesy of Dr. Jihun Kim.

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CD56 and CD10 [97,99]. Importantly, both components are strongly and diffusely positive for GLI1 immunolabeling [97].

Gastroblastomas are associated with a generally favorable prognosis following surgical resection, which is typically performed as a partial or subtotal gastrectomy. Although regional and distant lymph node metastases and local recurrences are rare, liver and lymph node metastases have been reported [96,97,99].

PARIETAL CELL CARCINOMA AND ONCOCYTIC ADENOCARCINOMA

Parietal cell carcinoma resembles acid-secreting parietal cells, which are normally observed in the gastric lining, with an eosinophilic granular cytoplasm. Histologically, parietal cell carcinomas exhibit an expanding growth pattern and are composed of solids and sheets of cells, a few of which may form small gland-like clefts [100,101]. The characteristic eosinophilic granular cytoplasm can be highlighted by special stains such as phosphotungstic acid-hematoxylin and Luxol fast blue. Furthermore, parietal cell carcinoma cells are positive for specific antibodies associated with parietal cells, including H+/K+ ATPase and human milk fat globule-2. The ultrastructural evaluation of these cells reveals the presence of numerous mitochondria and intracellular canaliculi [100,102].

Although exceedingly rare cases have been reported, it is assumed that parietal cell carcinoma has a more favorable prognosis than typical gastric carcinomas [101,103]. However, because available data are limited, further research is needed to establish a clear prognosis and potential therapeutic strategies.

Besides parietal cell carcinomas, oncocytic adenocarcinomas have been reported. These tumors share features with parietal cell carcinoma, in which both tumors have abundant eosinophilic and granular cytoplasm, numerous mitochondria in their cytoplasm, and occasional intracytoplasmic lumina with associated long microvilli [104]. However, these tumors do not express parietal cell-specific anti-H+/K+-ATPase antibodies, and the authors suggested the term oncocytic adenocarcinoma [104]. Caruso et al. [105] analyzed 9 gastric adenocarcinoma cases and demonstrated an abundance of eosinophilic cytoplasm. They proposed the term mitochondrion-rich carcinoma. They assumed that the tumors were similar to those of thyroid follicular carcinomas. The characteristics of these cases included small tumor size, infrequent lymph node metastasis, early-stage diagnosis, and favorable prognosis. The classification of parietal cell carcinomas, oncocytic adenocarcinomas, and mitochondria-rich carcinomas remains unclear [106]. More cases are required to clarify the terminology and classifications.

Notably, adenocarcinomas of the fundic-gland type, in which parietal cells predominate, are distinct from both parietal cell carcinomas and oncocytic carcinomas. These adenocarcinomas are typically small, well differentiated, and lack the solid sheet-like growth pattern observed in parietal cell carcinoma.

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PANETH CELL CARCINOMA

Paneth cell carcinoma is characterized by the predominance of Paneth cells, demonstrating eosinophilic cytoplasmic granules that are positive for specific markers such as lysozyme and defensin-5 on immunohistochemistry [107,108].

Paneth cells, primarily located at the base crypt of the small intestine and proximal colon, secrete antimicrobial peptides, such as alpha defensin, lysozyme, and phospholipase A2, and play a significant role in defending against intestinal microbes and regulating host immunity [109]. Since Paneth cells may be present in areas of gastric intestinal metaplasia (IM), it can be assumed that Paneth cell carcinoma develops into a preneoplastic lesion with IM [110]. Paneth cell carcinomas are extremely rare, making our understanding of their clinical presentation limited. Clinical data on the effect of Paneth cell carcinomas on patient survival are scarce.

In a few cases, Paneth cells were dispersed in typical gastric adenocarcinomas [111]. This highlights the diversity of cell types encountered within gastric neoplasms and underscores the need for careful histological examination to identify and characterize these rare subtypes.

GASTRIC ADENOCARCINOMA OF FUNDIC-GLAND TYPE (GA-FG)

GA-FG is a well-differentiated neoplasm that develops from an oxyntic gland adenoma [112] According to a single-institute surveillance study, GA-FG accounts for a small percentage (1%) of early gastric adenocarcinomas treated with endoscopic submucosal dissection [113]. Oxyntic gland differentiation, a tumor hallmark, can be further classified into 3 subcategories based on the tumor tissue composition: chief cell-predominant, parietal cell-predominant, and mixed chief and parietal cell types [112]. The chief cell–predominant type constitutes the majority of the reported cases, accounting for approximately 99% of them. The parietal cell-predominant type comprises parietal cells and another type of oxyntic gland cell. A mixed phenotype, containing a combination of chief and parietal cells, was observed within the neoplastic tissues (**Fig. 9**). In cases of the parietal cell-predominant type, differential diagnosis from parietal cell carcinoma is important. GA-FG can be distinguished by its differentiation, whereas parietal cell carcinoma is generally solid with polygonal cell sheets.

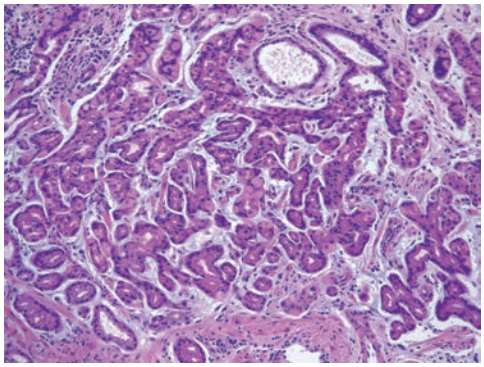

Fig. 9. Gastric adenocarcinoma of fundic-gland type. The tumor cells are composed of well-differentiated columnar cells with pale basophilic cytoplasm and mild nuclear atypia (hematoxylin and eosin, original magnification, ×200).

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Submucosal invasion was observed in a significant proportion (60%) of cases, emphasizing the need for careful histological evaluation. Nevertheless, most lesions appear in the early stages, and lymph node metastasis is rare [112].

These tumors are positive for specific markers including pepsinogen I and MUC6 [114]. Tumor cells exhibiting parietal cell differentiation are positive for H+/K+ ATPase immunolabeling [115].

UNDIFFERENTIATED CARCINOMA (INCLUDES SWI/SNF CHROMATIN-REMODELING COMPLEX MUTATION TYPE)

Undifferentiated carcinomas were characterized by the presence of anaplastic cells lacking specific cytological or architectural differentiation (**Fig. 10A**). These tumors are known for their heterogeneity and can resemble various other malignancies such as lymphomas, metastatic melanoma, germ cell neoplasms, and sarcomas. Undifferentiated carcinoma can manifest as several distinct histological variants, including rhabdoid carcinoma, sarcomatoid carcinoma, carcinoma with osteoclast-like giant cells, and pleomorphic giant cell carcinoma [116-122].

Immunohistochemical analyses often play a critical role in confirming epithelial phenotypes. Positive CK immunolabeling was observed at various intensities and proportions, whereas additional markers such as epithelial membrane antigen immunostaining can be useful, especially in cases with low CK expression. Vimentin, a mesenchymal marker, is consistently expressed in these tumors and often displays a perinuclear dot pattern [123,124].

A few undifferentiated carcinomas may contain areas with glandular components, suggesting that they may have originated through dedifferentiation from other gastric cancer types. The underlying genetic alterations in these tumors are unclear and may involve SWI/SNF chromatin-remodeling complex components. Loss of SMARCB1 (INI1), SMARCA4 (BRG1), and ARID1A, which are associated with chromatin regulation, has been reported in a few cases [123,124].

SMARCB1-deficient undifferentiated carcinoma, previously referred to as malignant rhabdoid tumor, is a recently studied entity in which loss of INI1 expression can be easily detected by

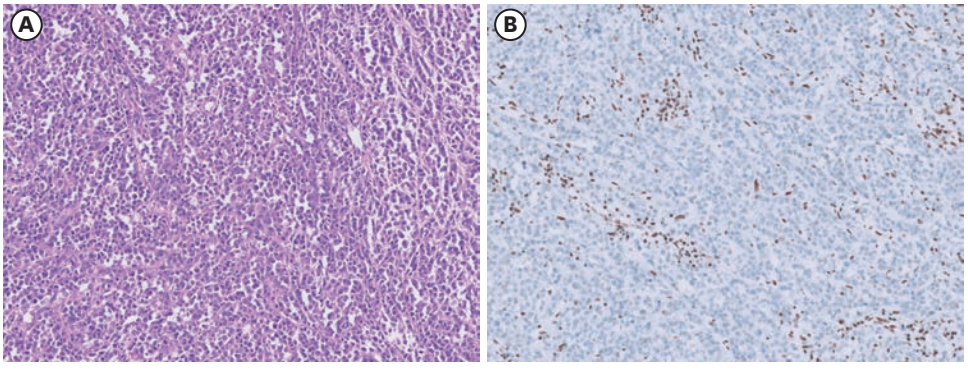

Fig. 10. (A) Undifferentiated carcinoma. The tumor lacks specific cytological or architectural differentiation (hematoxylin and eosin, original magnification, ×100). (B) SMARCA4 mutant carcinoma. BRG1 immunohistochemistry is negative in the tumor cells (BRG1, original magnification, ×100).

https://doi.org/10.5230/jgc.2024.24.e7

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immunohistochemical staining [123]. This group of tumors has a rhabdoid phenotype and an extremely poor prognosis. SMARCA4-deficient neoplasia may present with rhabdoid features in minor cases, and the loss of BRG1 expression can be detected by immunohistochemical staining (**Fig. 10B**) [125].

Given the rarity of undifferentiated carcinoma and its highly aggressive nature, its specific prognostic features remain elusive. The disease stage at the time of diagnosis is believed to be prognostically relevant, with most patients presenting with advanced disease. Undifferentiated carcinomas are known for their rapid progression and many patients develop extensive regional metastases shortly after diagnosis and surgery. The prognosis for patients with undifferentiated stomach carcinoma is generally poor, with a high mortality rate within a year of diagnosis.

EXTREMELY WELL-DIFFERENTIATED ADENOCARCINOMA (EWDA)

EWDA is characterized by nonaggressive nuclear atypia and subtle architectural abnormalities, including tortuous, branching, anastomosing, distended glands, and lateral spreading characteristics of the neoplasm [126-129]. EWDA can be categorized into 2 types: intestinal and gastric. The intestinal type is composed of glands resembling intestinal metaplasia, containing goblet and Paneth cells [126,129]. In contrast, the gastric type features mucin-rich cells with basally located nuclei that appear benign, resembling either hyperplastic foveolar epithelium or expanded pyloric glands [130].

EWDA's innocuous appearance of EWDA often leads to its misinterpretation as regenerating atypia or inflammatory changes, particularly in endoscopic biopsy samples. Different studies have emphasized that the hallmark of EWDA is structural abnormalities rather than cytological atypia. Anastomosing glands, spiky glands, distended glands, discohesive cells, and disproportionately larger glands than the surrounding non-neoplastic glands [129,131].

Endoscopically, they often appear as ill-defined, slightly depressed, or flat lesions without significant mucosal color changes. While generally considered to have a favorable prognosis, there have been reports of certain cases evolving into a more aggressive diffuse type [128].

CONCLUSION

Gastric cancer presents a complex landscape with various histological subtypes, including papillary, squamous, AFP-producing, eosinophilic, and rhabdoid. This review highlights the distinct characteristics, clinical presentations, and challenges associated with the diagnosis and management of various unusual and uncommon gastric cancer forms. These include papillary adenocarcinoma, micropapillary carcinoma, adenosquamous carcinoma, SCC, hepatoid adenocarcinoma, gastric choriocarcinoma, GCLS, carcinosarcoma, gastroblastoma, parietal cell carcinoma, oncocytic adenocarcinoma, Paneth cell carcinoma, GA-FG, undifferentiated carcinoma, and EWDA.

Each subtype presents unique diagnostic challenges and pathological features requiring careful evaluation. Understanding these rare variants is crucial for an accurate diagnosis,

https://doi.org/10.5230/jgc.2024.24.e7

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establishing treatment strategies, and improving patient outcomes. Future research and case studies will play an important role in deepening our understanding of these rare cancers, leading to more effective treatments and improved prognostic assessments. This review underscores the importance of recognizing the diversity of the histological characteristics of gastric cancer, emphasizing that these types of cancers may present unique features that impact their care and prognosis.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Jihun Kim (Asan Medical Center), Dr. Soomin Ahn (Samsung Medical Center), and Dr. Su-Jin Shin (Gangnam Severance Hospital) for kindly providing the cases and photomicrographs.

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