https://doi.org/10.22516/25007440.1394

Case report

Hepatoid Gastric Adenocarcinoma with Adenosquamous Overlap, a Diagnostic Challenge in a Poor-Prognosis Tumor: Case Report

Mónica Arcos-Ramírez,[1] Sara Catalina Aguirre,[2] Miguel Ángel Apraes-Delgadillo,[3] María Alejandra Benavides,[4] Camilo Mena-Caicedo,[5] José Darío Portillo-Miño.[6]*

OPEN ACCESS

Citation:
Arcos-Ramírez M, Aguirre SC, Apraes-Delgadillo MA, Benavides MA, Mena-Caicedo C, Portillo-Miño JD. Hepatoid Gastric Adenocarcinoma with Adenosquamous Overlap, a Diagnostic Challenge in a Poor-Prognosis Tumor: Case Report. Revista. colomb. Gastroenterol. 2026;41(1):113-118. https://doi.org/10.22516/25007440.1394

[1] Specialist Physician in Anatomic Pathology, Department of Pathology, Fundación Hospital San Pedro. Pasto, Colombia.
[2] Physician and Surgeon, Resident in Anatomic and Clinical Pathology, Universidad del Valle. Cali, Colombia.
[3] General Practitioner, Emergency Department, Fundación Hospital San Pedro. Pasto, Colombia.
[4] General Practitioner, Faculty of Medicine, Universidad Cooperativa de Colombia. Pasto, Colombia.
[5] General Practitioner, Faculty of Health Sciences, Fundación Universitaria San Martín. Pasto, Colombia.
[6] Physician Researcher, Research Group on Infectious Diseases and Cancer (GINFYCA), Clinical Research Center, Fundación Hospital San Pedro. Research Group in Science and Health (GICIENSA), Faculty of Health Sciences, Medical Program, Universidad de Nariño. Pasto, Colombia.

***Correspondence:** José Darío Portillo Miño.
dario.portillomd@gmail.com

Received: 11/06/2025
Accepted: 20/10/2025

Abstract

Introduction: Gastric cancer (GC) remains one of the most lethal malignancies worldwide and represents a major global public health concern. The most common histological subtypes are classically classified as intestinal and diffuse. According to the World Health Organization (WHO) classification, gastric adenocarcinomas are further categorized as papillary, mucinous, poorly cohesive, mixed, and tubular types. Hepatoid gastric adenocarcinoma is considered an exceptionally rare tumor, with an incidence ranging from 0.3% to 1.0% of all gastric cancers. **Clinical Case:** A 68-year-old male patient was diagnosed with hepatoid adenocarcinoma with adenosquamous overlap. He presented with epigastric pain and three episodes of coffee-ground emesis. Upper gastrointestinal endoscopy was performed, and biopsy samples were obtained. Based on histopathological and immunohistochemical analysis, the tumor was classified as a hepatoid subtype with adenosquamous overlap. **Discussion and Conclusion:** This case represents a true clinical and histopathological diagnostic challenge, as definitive characterization was achieved only through immunohistochemistry. Fundamental aspects of these histopathological subtypes are described, highlighting their low incidence and potential tumor histogenesis, with particular emphasis on their aggressive biological behavior and poor prognosis.

Keywords

Gastric cancer, epidemiology, prognosis, health classifications.

INTRODUCTION

Gastric cancer (GC) is among the most lethal malignancies worldwide and represents a major global public health concern. According to recent data from the Global Cancer Observatory (GLOBOCAN), GC remained the fifth leading cause of cancer-related mortality in 2022[(1)]. Projections for 2040 estimate more than 1,300,000 deaths and 1,800,000 new cases[(2)]. Chronic infection with *Helicobacter pylor*i is responsible for at least 80% of gastric cancers worldwide[(3)], including approximately 90% of non-cardia (distal) tumors and 50% of cardia (proximal) tumors[(4,5)]. GC can be classified as cardia or non-cardia, each exhibiting distinct epidemiological and clinical characteristics. Cardia GC is associated with genetic factors, the diffuse histotype, and reduced survival, reflecting more

aggressive biological behavior and diagnosis at advanced stages. In contrast, non-cardia GC predominantly exhibits the intestinal histotype. It typically arises in the antropyloric region, is strongly associated with environmental factors, demonstrates improved prognosis when detected early, and shows higher prevalence of chronic *H. pylori* infection[6–9]. According to the Lauren and Jarvi classification, GC is categorized as intestinal or diffuse based on clinical and epidemiological features.

The intestinal type is more frequent in men and older populations, predominantly involves the antropyloric region, and is strongly associated with environmental risk factors, including suboptimal public health conditions, water sanitation deficiencies, chronic *H. pylor*i infection, and premalignant conditions described in Correa's cascade[10,11]. The diffuse histotype is more common in women and in younger individuals and is associated with mutations in the *CDH1* gene, which encodes E-cadherin. These molecular alterations contribute to carcinogenesis in this tumor subtype. Diffuse-type GC shows limited association with environmental factors and *H. pylori* infection[10,11]. According to the most recent World Health Organization (WHO) classification, the most common histological subtypes include tubular, papillary, poorly cohesive, mucinous, and mixed adenocarcinoma. Within this classification framework, hepatoid gastric adenocarcinoma (HGA) is described as a rare subtype included in the category of hepatoid adenocarcinoma and related entities[12–14]. HGA is an uncommon entity, accounting for approximately 0.3%–1.0% of all gastric cancers, and exhibits morphological features highly similar to hepatocellular carcinoma (HCC). This subtype is characterized by high short-term mortality, as it is frequently diagnosed at advanced stages[15].

This report presents the clinical case of a 68-year-old male patient diagnosed with hepatoid adenocarcinoma with adenosquamous overlap. The diagnosis represented a significant challenge and was ultimately clarified through immunohistochemistry. In addition to describing the fundamental features of this histopathological subtype, the present report highlights its low incidence and possible tumor histogenesis.

CASE DESCRIPTION

A 68-year-old male patient presented to the emergency department with progressive dysphagia initially affecting solid foods and later liquids, with long-standing progression. The patient also reported anorexia and severe weight loss of 20 kg over a three-month period. At the time of consultation, he presented with intermittent burning epigastric pain without radiation and three episodes of coffee-ground emesis occurring eight hours prior to admission. No relevant personal or family medical history was reported. Physical examination revealed a hemodynamically stable patient with marked wasting of adipose and muscle tissue, mucocutaneous flaccidity, anorexia, and kwashiorkor-type malnutrition. No additional abnormalities were identified on physical examination. Upper gastrointestinal endoscopy revealed a protruding and ulcerated lesion (Bormann type IV), from which biopsy samples were obtained.

Histopathological evaluation described a strongly eosinophilic tumor arranged in a rosette-like pattern, mimicking hepatoid, squamous, and neuroendocrine differentiation (**Figure 1**). Immunohistochemical analysis demonstrated strong positivity for HepPar-1 and moderate positivity for alpha-fetoprotein (AFP), CK7, and Ki-67, with negative expression for SALL-4 (sal-like protein 4), findings that confirmed hepatoid differentiation (**Figure 2**). Computed tomography (CT) scans of the abdomen and chest were performed as part of staging studies, revealing hepatic and retroperitoneal metastases as well as peritoneal carcinomatosis. Given the patient's clinical condition, the multidisciplinary tumor board referred the patient for comprehensive management by Clinical Oncology, Nutrition, Psychology, and Palliative Care. After six months of multidisciplinary management, the patient died due to cardiorespiratory arrest.

DISCUSSION

This case is noteworthy because this rare histological subtype may be confused with other uncommon tumor types within the WHO classification and may also overlap with metastatic hepatocellular carcinoma (HCC) due to its similar histopathological architecture. As in the present case, overlap with adenosquamous carcinoma may occur, representing a significant diagnostic challenge. Immunohistochemistry plays a crucial role in clarifying cellular lineage and establishing an accurate diagnosis, as conventional histopathological evaluation using hematoxylin and eosin staining may be insufficient to definitively determine tumor origin and biological nature. Diagnostic uncertainty may negatively affect diagnostic timing and prognosis due to the aggressive biological behavior of this tumor subtype.

The incidence of HGA ranges between 0.3% and 1.0% of all gastric tumors. Hepatic metastases and increased peritoneal dissemination occur in 46.3%–75.6% of patients with HGA[15-17]. A recent systematic review by Ling et al.[18] reported low three-year overall survival (hazard ratio [HR]: 3.21; 95% confidence interval [CI]: 1.54–6.67; p = 0.002). The most common clinical manifestations include abdominal pain, epigastric discomfort, hematemesis, and melena[19]. HGA demonstrates low incidence but high diagnostic complexity and aggressive biological behavior,

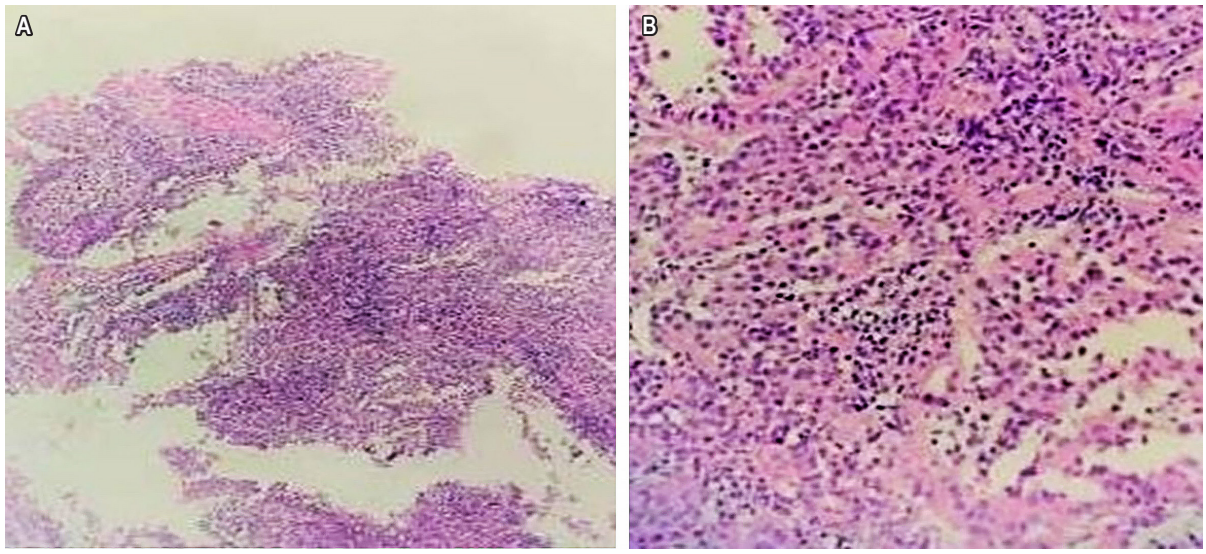

Figure 1. Histopathological description of the tumor. **A and B.** The images show a strongly eosinophilic tumor arranged in a rosette-like pattern with cells resembling hepatocytes. Images obtained from the archives of the Department of Pathology, Fundación Hospital San Pedro.

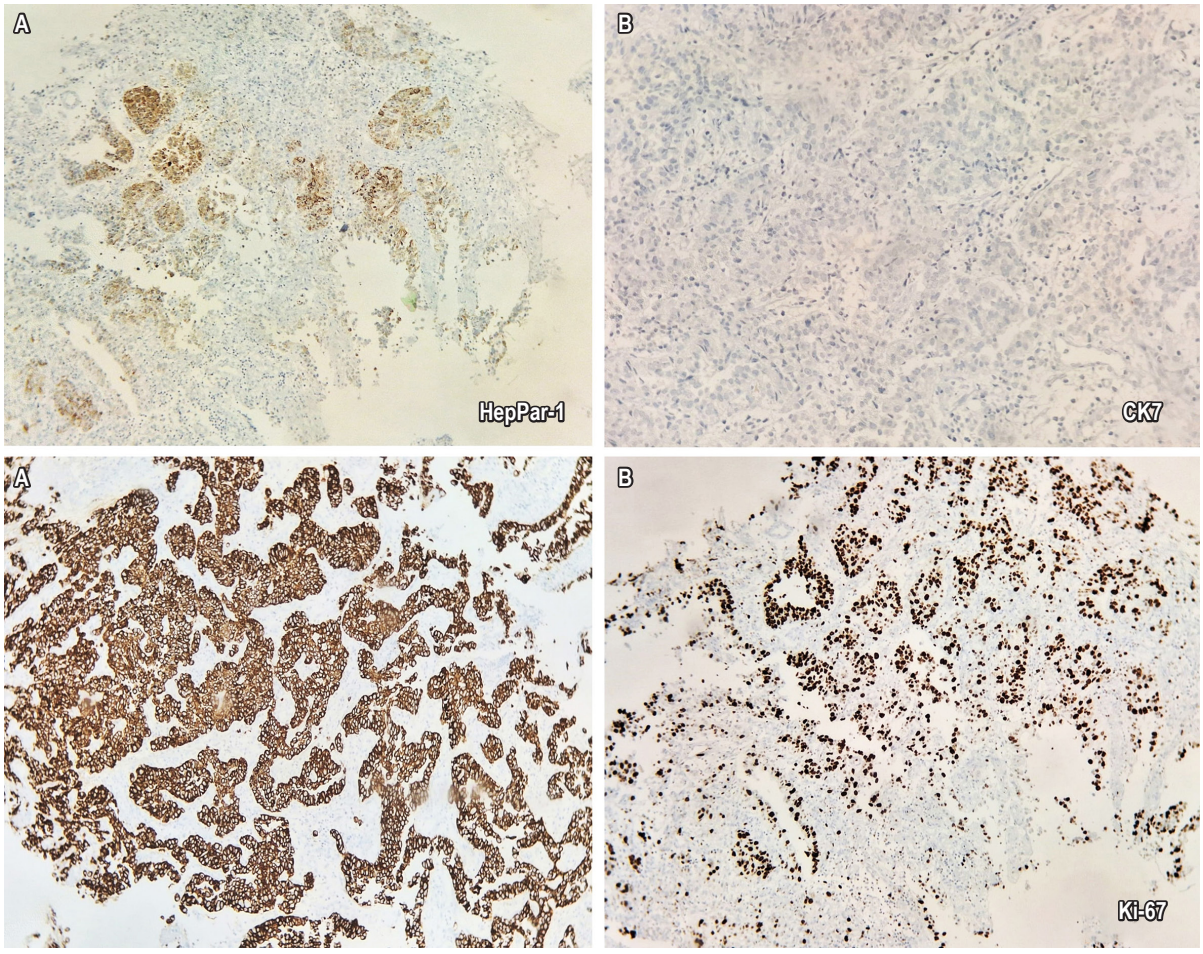

Figure 2. Tumor immunohistochemistry. **A, B, C, and D.** The slides show strong immunoreactivity for HepPar-1 and alpha-fetoprotein (AFP), confirming hepatoid differentiation. Immunohistochemical staining for cytokeratins (CK7) and Ki-67 was also performed. Images obtained from the archives of the Department of Pathology, Fundación Hospital San Pedro.

with marked propensity for vascular invasion and early metastasis, particularly to the liver (97.3%) and peritoneum (35.3%)[20]. Less frequent metastatic sites include the lungs, spleen, and brain[18].

Given the inherent limitations of conventional hematoxylin and eosin histopathology, accurate diagnostic confirmation requires immunohistochemistry. Immunohistochemical characterization is the cornerstone of correct tumor identification, as macroscopically HGA resembles a Bormann type III–IV tumor with poor differentiation. Histopathological evaluation demonstrates morphology similar to hepatocellular carcinoma, characterized by large eosinophilic cells arranged in trabecular architecture or solid nested patterns separated by sinusoidal vascular channels[21,22]. Immunohistochemical markers with the highest specificity include HepPar-1 for determining tumor lineage and cellular differentiation. Increased mismatch repair (mMR) protein proficiency has been reported. Positive expression of alpha-fetoprotein (AFP) and transcription factor SALL-4 (Spalt-like transcription factor 4) has also been described. Overexpression of HER2 and negative expression of EBER (Epstein–Barr virus-encoded small RNA) have been observed. The molecular profile of HGA is characterized by negative EBER expression and mMR status, whereas AFP and SALL-4 expression support definitive diagnosis[23]. In the present case, immunohistochemistry showed positive expression for HepPar-1 and AFP.

Genetic mutations reported in this tumor subtype include *DK12, MYC, OCT4-pg1, HUWE1*, and *MYCBP2*[20]. Functional MYC overactivation induces hepatoid differentiation through the influence of pluripotent stem cells, a mechanism that contributes to tumor clonality and poor prognosis[18].

The therapeutic approach to HGA is based primarily on surgical management and comprehensive perioperative treatment; however, prognosis remains poor despite adherence to current therapies. These findings underscore the importance of early and accurate diagnosis to guide appropriate treatment strategies[20,24-26]. Further research is required to characterize the molecular pathology of HGA, identify novel biomarkers for targeted therapy, and improve treatment strategies. Potential therapeutic targets such as *ERBB2, FGFR2, MET*, and *HGF* appear promising[27].

CONCLUSIONS

HGA is a rare and aggressive clinical entity that represents both a diagnostic and therapeutic challenge. Immunohistochemistry is essential for confirming the diagnosis using markers such as AFP (64%), HepPar-1, GPC3, and SALL4. HGA is typically diagnosed at advanced stages and demonstrates aggressive biological behavior, with high incidence of hepatic and peritoneal metastases.

Acknowledgments

None.

Funding sources

None.

Conflicts of interest

None.

REFERENCES

1. International Agency for Research on Cancer. Cancer Today Stomach - The Global Cancer Observatory 2022[Internet]. IARC; 2024 [consultado el 31 de mayo de 2025]. Disponible en: https://gco.iarc.who.int/media/globocan/factsheets/cancers/7-stomach-fact-sheet.pdf
2. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: A population-based modelling study. EClinicalMedicine. 2022;47:101404. https://doi.org/10.1016/j.eclinm.2022.101404
3. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180-90. https://doi.org/10.1016/S2214-109X(19)30488-7
4. Han Z, Liu J, Zhang W, Kong Q, Wan M, Lin M, et al. Cardia and non-cardia gastric cancer risk associated with Helicobacter pylori in East Asia and the West: A systematic review, meta-analysis, and estimation of population attributable fraction. Helicobacter. 2023;28(2):e12950. https://doi.org/10.1111/hel.12950
5. Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health. 2021;6(12):e888-96. https://doi.org/10.1016/S2468-2667(21)00164-X
6. Zhao J, Zhao J, Du F, Zhang Y, Shen G, Zhu H, et al. Cardia and Non-Cardia Gastric Cancer Have Similar Stage-for-Stage Prognoses After R0 Resection: a Large-Scale, Multicenter Study in China. J Gastrointest Surg.

2016;20(4):700-7.
https://doi.org/10.1007/s11605-016-3089-z
7. Park JC, Lee YC, Kim JH, Kim YJ, Lee SK, Shin SK, et al. Clinicopathological features and prognostic factors of proximal gastric carcinoma in a population with high Helicobacter pylori prevalence: a single-center, large-volume study in Korea. Ann Surg Oncol. 2010;17(3):829-37.
https://doi.org/10.1245/s10434-009-0785-x
8. Piso P, Werner U, Lang H, Mirena P, Klempnauer J. Proximal versus distal gastric carcinoma--what are the differences? Ann Surg Oncol. 2000;7(7):520-5.
https://doi.org/10.1007/s10434-000-0520-0
9. Saito H, Fukumoto Y, Osaki T, Fukuda K, Tatebe S, Tsujitani S, et al. Distinct recurrence pattern and outcome of adenocarcinoma of the gastric cardia in comparison with carcinoma of other regions of the stomach. World J Surg. 2006;30(10):1864-9.
https://doi.org/10.1007/s00268-005-0582-z
10. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol. 2006;12(3):354-62.
https://doi.org/10.3748/wjg.v12.i3.354
11. Correa P, Camargo MC, Piazuelo MB. Overview and pathology of gastric cancer. En: Wang TC, Fox JG, Giraud AS (editores). The biology of gastric cancers. Nueva York, Estados Unidos: Springer; 2009. p. 1-24.
https://doi.org/10.1007/978-0-387-69182-4_1
12. Kushima R. The updated WHO classification of digestive system tumours-gastric adenocarcinoma and dysplasia. Pathologe. 2022;43(1):8-15.
https://doi.org/10.1007/s00292-021-01023-7
13. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182-8.
https://doi.org/10.1111/his.13975
14. WHO Classification Tumours Editorial Board. WHO classification of tumours: digestive system tumours. 5.ª edición. Lyon, Francia: IARC Press; 2019.
15. Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. World J Gastroenterol. 2013;19(3):321-7.
https://doi.org/10.3748/wjg.v19.i3.321
16. Liu X, Sheng W, Wang Y. An analysis of clinicopathological features and prognosis by comparing hepatoid adenocarcinoma of the stomach with AFP-producing gastric cancer. J Surg Oncol. 2012;106(3):299-303.
https://doi.org/10.1002/jso.23073
17. Wang Y, Sun L, Li Z, Gao J, Ge S, Zhang C, et al. Hepatoid adenocarcinoma of the stomach: a unique subgroup with distinct clinicopathological and molecular features. Gastric Cancer. 2019;22(6):1183-92.
https://doi.org/10.1007/s10120-019-00965-5
18. Ling Q, Liu HL, Huang ST, Sun LF, Wu WW, Kudriashov V, et al. Clinicopathological features of hepatoid adenocarcinoma and non-hepatoid adenocarcinoma of the stomach: A systematic review and meta-analysis. Cancer Med. 2024;13(16):e70130.
https://doi.org/10.1002/cam4.70130
19. Zeng XY, Yin YP, Xiao H, Zhang P, He J, Liu WZ, et al. Clinicopathological Characteristics and Prognosis of Hepatoid Adenocarcinoma of the Stomach: Evaluation of a Pooled Case Series. Curr Med Sci. 2018;38(6):1054-61.
https://doi.org/10.1007/s11596-018-1983-1
20. Jiang J, Ding Y, Lu J, Chen Y, Chen Y, Zhao W, et al. Integrative analysis reveals a clinicogenomic landscape associated with liver metastasis and poor prognosis in hepatoid adenocarcinoma of the stomach. Int J Biol Sci. 2022;18(14):5554-74.
https://doi.org/10.7150/ijbs.71449
21. Zhou K, Wang A, Ao S, Chen J, Ji K, He Q, et al. The prognosis of hepatoid adenocarcinoma of the stomach: a propensity score-based analysis. BMC Cancer. 2020;20(1):671.
https://doi.org/10.1186/s12885-020-07031-9
22. Zhang JF, Shi SS, Shao YF, Zhang HZ. Clinicopathological and prognostic features of hepatoid adenocarcinoma of the stomach. Chin Med J (Engl). 2011;124(10):1470-6.
23. Yang X, Wu Y, Wang A, Ma X, Zhou K, Ji K, et al. Immunohistochemical characteristics and potential therapeutic regimens of hepatoid adenocarcinoma of the stomach: a study of 139 cases. J Pathol Clin Res. 2024;10(1):e343.
https://doi.org/10.1002/cjp2.343
24. Huang WP, Li LM, Li J, Yuan JH, Hou P, Liu CC, et al. Computed Tomography Features and Clinical Prognostic Characteristics of Hepatoid Adenocarcinoma of the Stomach. Front Oncol. 2021;11:772636.
https://doi.org/10.3389/fonc.2021.772636
25. Nagai E, Ueyama T, Yao T, Tsuneyoshi M. Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. Cancer. 1993;72(6):1827-35.
https://doi.org/10.1002/1097-0142(19930915)72:6<1827::AID-CNCR2820720606>3.0.CO;2-8
26. Liu X, Cheng Y, Sheng W, Lu H, Xu X, Xu Y, et al. Analysis of clinicopathologic features and prognostic factors in hepatoid adenocarcinoma of the stomach. Am J Surg Pathol. 2010;34(10):1465-71.
https://doi.org/10.1097/PAS.0b013e3181f0a873
27. Wei J, Ji K, Zhang Y, Zhang J, Wu X, Ji X, et al. Exploration of molecular markers related to chemotherapy efficacy of hepatoid adenocarcinoma of the stomach. Cell Oncol (Dordr). 2024;47(2):677-93.
https://doi.org/10.1007/s13402-023-00892-9