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Case Report

Deficient Mismatch Repair Proteins in Gastric Mixed Neuroendocrine Non-Neuroendocrine Neoplasm: A Rare Case Report

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Keywords
Gastric mixed neuroendocrine non-neuroendocrine neoplasm · Microsatellite instability · Mismatch repair protein · Gastric cancer · Adjuvant chemotherapy

Abstract
Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) is a rare type of gastric carcinoma with controversial diagnosis and treatment. Recent data implies that deficiency mismatch repair proteins inducing microsatellite instability are considered one of the potential drivers of this disease. Hence, we report a stomach MiNEN with MMR protein loss. An admitted 60-year-old woman complained of epigastric pain. The pathological analysis of the gastroendoscopic biopsy specimen revealed gastric adenocarcinoma. The radiological staging was cT3N1M0; therefore, she received D2 distal gastrectomy. Suspecting neuroendocrine component admix with adenocarcinoma part on the resected specimen microscopy, applying biomarkers including AE 1/3, synaptophysin, and chromogranin A to confirm the diagnosis of MiNEN. The neuroendocrine part was classified as neuroendocrine tumor grade 2 with Ki 67 at 16.5%. To further understand the molecular characterization of this disease, we evaluated mismatch protein expression by staining MLH1, MSH2, MSH6, and PMS2 antibodies. Interestingly, both components lost MLH1 and PMS2 proteins. Her radical surgery followed oxaliplatin/capecitabine adjuvant chemotherapy. The patient is still well after eight cycles of

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chemotherapy. dMMR gastric MiNENs and dMMR gastric cancer share many clinical and genetic characteristics. Further studies are necessary to survey the role of dMMR in the prognosis and treatment of this entity.

Introduction

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) have been delineated in many gastrointestinal tract organs. The development of immunohistochemistry has contributed significantly to recognizing this tumor in clinical practice [1]. However, these neoplasms are very scarce, particularly in the stomach. The number of stomach MiNEN cases documented as of 2015 was less than 40. Since 2015, the number of reports has increased, and case series studies have also appeared in the English literature, but most of these are retrospective with small sizes [2–4]. Moreover, because the range of MiNENs is a mixture of two constituents having multiple ways of combining; as a result, the sample population is often heterogeneous, so the conclusions are inconsistent [5]. Most cases have been presented in Eastern countries, probably due to the high overall incidence of stomach cancer in these countries [6].

Mixed adenoneuroendocrine carcinomas (MANECs) are mingled epithelial tumors composing glandular and neuroendocrine parts, a histological subtype of gastric cancer. According to the WHO 2010 classification, gastroenteropancreatic tract MANECs are tumors containing both endocrine and exocrine malignancies, in which the minimum proportion of each must exceed 30%. The rationale for the threshold value of 30% is that if a component is present below that percentage, it is unlikely to affect the biological behavior of the entire neoplasm. In the WHO 2019 revised classification, MANECs were turned into MiNENs, with two changes. The first was the replacement of the term carcinoma by neoplasm to acknowledge that one or both parts can be a low-grade malignancy. The second was the term exocrine conversed to the general term "non-endocrine" to add other histological components of non-neuroendocrine such as squamous or sarcomatous phenotypes [7]. Currently, WHO has extended the use of the name MiNENs to all tumors that meet the diagnostic criteria derived from any location of the GEP tract; compared to MANECs, MiNENs is believed to be better suited to refer to the heterogeneous range of possible combinations between neuroendocrine and non-neuroendocrine constituents and their morphological variability.

Once on hematoxylin and eosin-stained slides, detecting two morphological components, neuroendocrine and non-neuroendocrine, led to the presumptive diagnosis of MiNEN. A proper immunohistochemistry panel is then required to confirm the diagnosis [1]. Chromogranin A, synaptophysin, and CD56 are typical for determining neuroendocrine in combination with markers such as CDX2, CEA, and AE 1/3 for non-neuroendocrine [2–5, 8–11]. Microscopically, the endocrine component can be exhibited by either well-differentiated neuroendocrine tumors (NETs) or, more commonly, poorly differentiated neuroendocrine (NECs). NETs are specialized by relatively homogeneous cells with fine chromatin and indistinct nucleoli organized into regular lobular or trabecular structures. Focal necrosis was sometimes seen. NECs contain cells arranged in big trabecular architectures, diffuse sheets, or solid nests that often reveal plenty of necrotic foci accompanied by rich mitotic activity [1, 12]. Regarding differentiating, NETs are well-differentiated parts divided into three grades, including G1, G2, and G3, with mitotic rates of <2, 2–20, >20 mitoses/2 mm^2, respectively, and

corresponding Ki 67 index is <3, 3–20, >20%. It is no longer necessary to evaluate the differentiated degrees of NEC since they have been uniformly defined as poorly differentiated and classified as large and small cells [7].

As MiNENs are rare, the pathogenesis of these diseases is still debated. Because of the broad spectrum of MiNEN in different organs, it is impossible to explain the mechanism of this entity with only one hypothesis [1]. Based on the biomolecular analyzes of case reports as well as case series studies, three hypotheses are suggested in summary. The first hypothesis proposed was that the neuroendocrine and non-neuroendocrine constituents arise separately, either synchronously or metachronously, from different precursor cells and merge into two constituents developing adjacent to each other concurrently. This pathway is related to collision tumors [1, 3, 8, 13]. The second postulates that the two parts come from a common pluripotent stem cell, which experienced biphenotypic differentiation during the cancer's growth [1, 8]. The two unique histologic parts of mixed neoplasms have a close genetic correlation, advocating this hypothesis [14]. The third explanation also assumes that both elements have a common monoclonal origin but hypothesizes that rather than the other way around, the neuroendocrine differentiation arises from a cell phenotype that was initially non-neuroendocrine. Moreover, the molecular analysis of neoplasms in which a high-grade neuroendocrine carcinoma represented the neuroendocrine part demonstrates a multistep progression from a common precursor lesion, showing a higher frequency of chromosomal and gene abnormalities in the neuroendocrine component than in the non-neuroendocrine one [1, 8, 15–17].

Microsatellite instability (MSI) and TP53, KRAS, BRAF, APC, PI3KCA are well-characterized as significant genetic mutations of GEP MiNENs [15]. Mismatch repair protein deficiency causes repeated length changes leading to MSI [18]. No longer available MMR protein function results in a highly mutant phenotype with many frameshift mutations in oncogenes and suppressor genes. Recent evidence has demonstrated that MSI cancer has a 100–1,000 fold increase in mutations compared to MSS neoplasm [19]. MSI/dMMR status is pivotal in treatment strategy options, irrespective of primary neoplasm location [20]. Considering the mixed neoplasms, few studies also recommended that dMMR GEP MiNENs had a favorable prognosis. The evaluation of MMR status is necessary for the treatment strategy of these neoplasms [12].

Case Report

A 60-year-old female patient was referred to the hospital for intermittent epigastric discomfort. Her medical history, as well as her family's medical history, was unremarkable. The physical examination did not reveal any other noticeable symptoms. The laboratory analyses demonstrated mild anemia, while all other parameters were within acceptable ranges. Gastroendoscopy found a lesion which an irregular protruding border combined with a central ulcerated lesion 2.5 cm in size located in the minor curvature of the stomach (Fig. 1a). The pathology of the biopsy tissue was invasive adenocarcinoma (Fig. 1b). Abdominal CT scan illustrated a gastric wall lesion, sized 12 × 30 mm, with loss of layer structure without serosa invasion (Fig. 1c) combined with a few lymph nodes suspected of metastasis, with the biggest measuring 11 × 18 mm (Fig. 1d). Other radiological imaging did not reveal any evidence of distant metastases. The cT3N1M0 gastric cancer was confirmed, and then she underwent distal gastrectomy and D2 lymphadenectomy. Microscopy of the resected tissue visualized epithelial cells with deformed nuclei and alkaline rough chromatin organized in glandular shapes (Fig. 2b). This component coexisted with solid nests comprising relatively uniform aberrant cells with fine chromatin and conscious nucleoli (Fig. 2c), displaying eight mitoses per 10 high-power fields. The malignant non-neuroendocrine component disrupted

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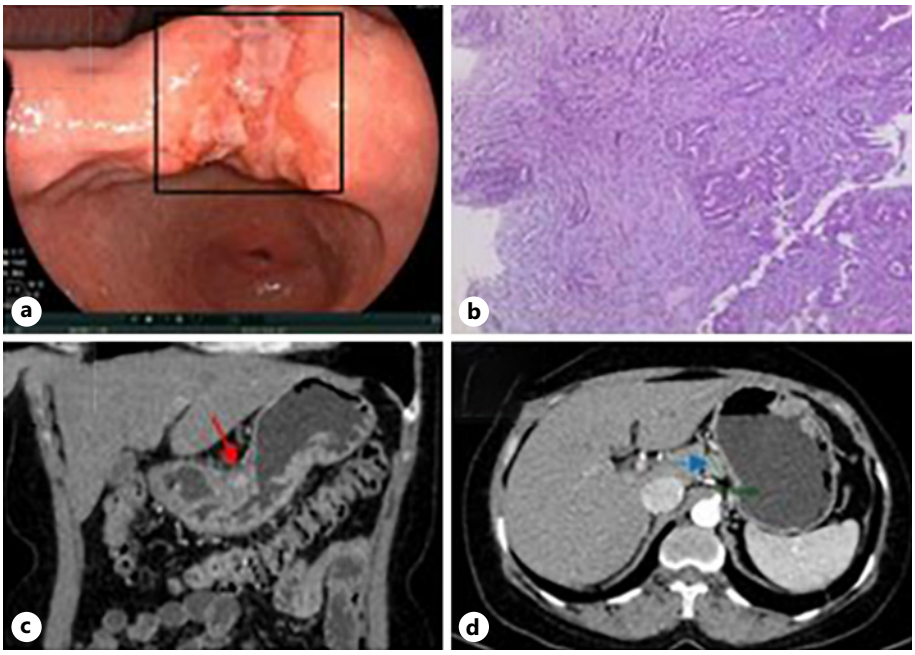

Fig. 1. Preoperative tests. **a** Gastroendoscopy shows a central ulcerated area surrounded by rough, protruding border. **b** Hematoxylin-eosin (H&E) stain (original magnification, ×10) of endoscopic biopsy specimen illustrates malignant cells arranged in irregular glandular structures. **c**, **d** Abdominal CT scan shows lesser curvature lesion of the stomach (red arrow) and enlarged regional lymph node (blue arrow).

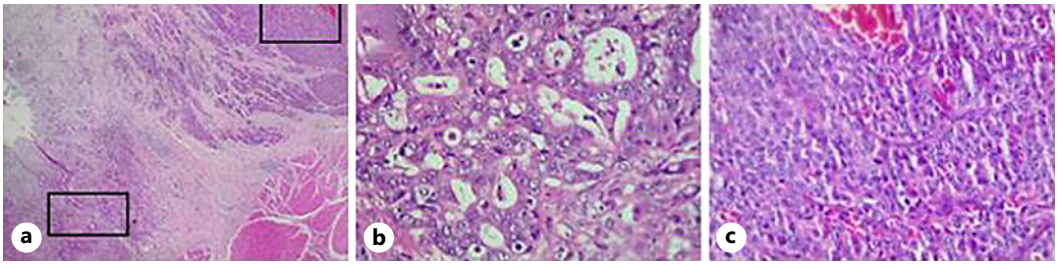

Fig. 2. H&E stains of resected specimen. **a** Two components without clear boundary (original magnification, ×4). **b** Moderately differentiated adenocarcinoma component (original magnification, ×40). **c** NET component (original magnification, ×40).

the muscle layer, infiltrating gastric subserosa and causing metastasis to two regional lymph nodes. These traits led to a doubtful diagnosis of MiNEN. Immunohistochemistry markers, including chromogranin A, synaptophysin, AE 1/3, and Ki 67, were indicated. Both constituents had AE 1/3 stains (Fig. 3a, e). Chromogranin A and synaptophysin were positive in the solid nest portion (35%) but negative in the adenocarcinoma (65%) (Fig. 3b, f, c, g). Ki 67 was 16.5% and 51% in the neuroendocrine sections and the adenocarcinoma structure, respectively (Fig. 3d, h). Consequently, we identified her diagnosis of gastric MiNEN with moderately differentiated adenocarcinoma and grade 2 neuroendocrine. Realizing the rarity of this case, we investigated the expression of MMR proteins by immunohistochemistry staining four antibodies, including MLH1, MSH2, MSH6, and PMS2, to understand this entity's

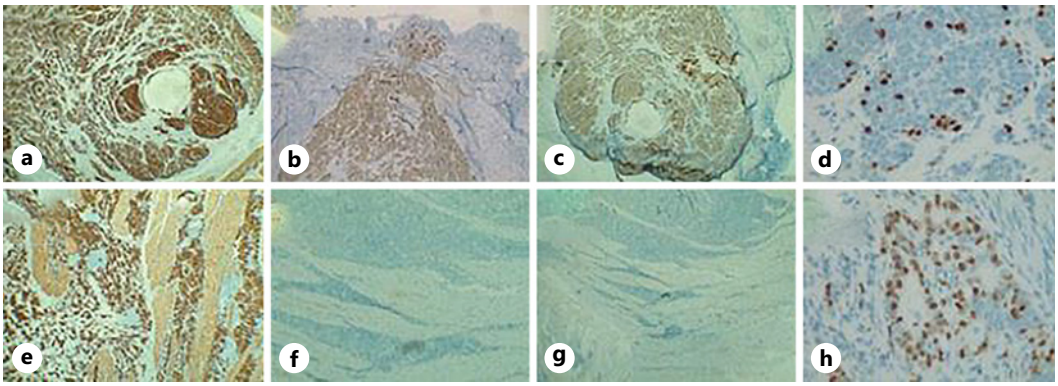

Fig. 3. Immunohistochemistry stainings for resected specimen. Neuroendocrine constituent: positive with AE 1/3 (**a**), positive with synaptophysin (**b**), positive with chromogranin A (**c**), Ki 67 16.5% (**d**). Muscle invasive adenocarcinoma part: positive with AE 1/3 (**e**), negative with SP 11 (**f**), negative with chromogranin A (**g**), Ki 67 51% (**h**).

biomolecular makeup better. The result was intriguing. Loss of display proteins MLH1 and PMS2 and proficient staining proteins MSH2 and MSH6 were both parts of the neoplasia (Fig. 4). The local invasive structure and metastasis regional lymph nodes were stained with AE 1/3 but not with chromogranin A or synaptophysin (Fig. 3e, f, g, and Fig. 5). The post-operative diagnosis was pT3N1M0 dMMR gastric MiNEN with adenocarcinoma as a more aggressive component. Based on the current recommendations, we decided to treat in the direction of adenocarcinoma. There is considerable debate over the role of dMMR in managing gastric adenocarcinoma. The patient was assigned adjuvant chemotherapy with capecitabine/oxaliplatin regimen. Until now, she has completed eight cycles of chemotherapy without significant toxicity, and there have been no signs of the disease returning. Table 1 shows the timeline summarizing the main events of this case report.

Discussion and Conclusion

MiNENs comprise between 0.8 and 2.5% of gastric cancer diagnoses and exhibit clinicopathological features and outcomes comparable to gastric adenocarcinoma [21, 22]. Most reported MiNENs are MANECs, which have two malignant constituents. The grade 2 NET MiNENs are only made up of approximately about 12.4% of this neoplasm [23]. MiNENs are more common in males than females, with males accounting for over 80% of cases [24]. In keeping with Choi et al. [25] result, women are more frequently in grade 2 NET group; our case is female. The incidence of MiNENs rises after age 60 (ranging from 44 to 83 years) [4, 5, 8]. The woman was diagnosed at 60, within the range noted in earlier investigations.

As with traditional gastric adenocarcinoma, gastric MiNENs frequently manifest without particular symptoms such as epigastric pain, bloating, dyspepsia, or dysphagia. Occult gastrointestinal bleeding can happen in some instances [5]. As a result, most cases are detected at an advanced stage [2, 3, 6, 9]. We discovered no significant symptoms in the reported case besides intermittent epigastric pain. Therefore, we believe epigastric pain is a warning sign of gastric cancer in people over 40; a suitable diagnostic strategy should exist for these subjects.

Macroscopically, on endoscopic imaging, the tumor is described as polypoid masses or ulcerating stenotic lesions likely found anywhere in the stomach. According to Ito Y. et al., the endocrine component lies in the deepest part of the mixed tumor. As the tumor became more and more extensive, the adenocarcinoma component sloughed off; as a result, the tumor

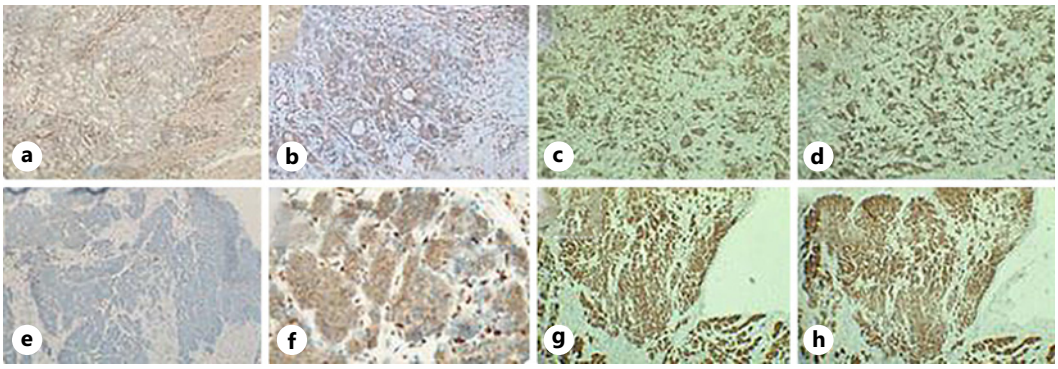

Fig. 4. Immunohistochemistry stainings for MMR protein expression of resected tissue. Adenocarcinoma part: deficient expression of MLH1 (**a**), deficient expression of PMS2 (**b**), intact expression of MSH2 (**c**), intact expression of MSH6 (**d**). Neuroendocrine component: deficient expression of MLH1 (**e**), deficient expression of PMS2 (**f**), intact expression of MSH2 (**g**), intact expression of MSH6 (**h**). **b**, **f** Both imaging reveal background staining in the acceptable positive internal control.

Fig. 5. Immunostainings (original magnification, ×10) for metastasis in regional lymph node. **a** Positive with AE 1/3. **b** Negative with chromogranin A. **c** Negative with synaptophysin.

center became concave and gradually ulcerated [22]. The endoscopic feature of the case presented here is consistent with Ito Y. judge, with a lesion demonstrating a core ulcer surrounded by an uneven protrusion border of approximately 2.7 cm in lesser curvature. The previous literature reported that MiNENs had an average size of about 5 cm, ranging from 0.5 to 14 cm [3]. NET grade 2 gastric MiNENs were generally smaller than NEC. In a few recent reports on early gastric MiNENs, the Japanese authors emphasized that the possible existence of a neuroendocrine constituent should be taken into account if there is a loss of surface structure in concavity surrounded by a poorly differentiated adenocarcinoma component [24, 26].

Notably, the inability of biopsy tissue samples to represent the heterogeneous components of the tumor accurately lowers the probability of preoperative identification of mixed neoplasm [1–3, 6, 9]. The deepest part of the lesion is usually where the endocrine component exists, making it simple to miss when the biopsy sample is insufficient [24]. As a result, postoperative diagnosis occurs in two-thirds of cases [15]. We made the same in our instance. Only postoperative gastric tissue samples showed relatively homogeneous abnormal cells with fine chromatin and distinct nucleoli arranged in solid foci assumed to be likely poorly differentiated adenocarcinoma. Due to the heterogeneous nature of these neoplasms, we supposed that adequate qualitative and quantitative biopsies should be required. Some authors recommend considering the presence of a neuroendocrine structure in these cases [27]. An appropriate immunohistochemistry panel is then required to confirm the diagnosis [1].

Table 1. Timeline summarizing the main events of this case report

Timeline	Event	Result
Week 0	Epigastric pain	
Week 1	Gastroendoscopy and stomach lesion biopsy chest, abdominal, and pelvis CT scan	cT3N1M0 gastric cancer was confirmed
Week 2	Distal gastrectomy and D2 lymphadenectomy	
Week 3	Microscopy of the resected tissue	pT3N1M0 dMMR gastric was diagnosed, and gastric MiNEN was suspected
Week 4	Chromogranin A, synaptophysin, AE 1/3, and Ki 67 stainings	Gastric MiNEN with moderately differentiated adenocarcinoma and grade 2 neuroendocrine was identified
Week 5	MMR protein expression analysis	dMMR gastric MiNEN was clarified
Week 6 to month 8	Adjuvant chemotherapy with capecitabine/oxaliplatin regimen	No adverse effect
Month 9	Follow-up	No evidence of recurrence

Research shows synaptophysin and chromogranin are the most reliable markers for identifying neuroendocrine components [1]. In this clinical case, we used these two markers to determine the neuroendocrine component and AE 1/3 to identify carcinoma. Only the NET part showed an intense and diffuse expressed immunostaining for synaptophysin and chromogranin A, whereas both epithelial and NET elements were positive for AE 1/3. Ki 67 and mitotic rate are cell proliferation indexes useful for classifying neuroendocrine component differentiation in MiNENs. The HE slide of the resected sample revealed eight mitoses per 10 high-power fields and Ki 67 at 16.5%. These findings led us to confirm the grade 2 NET diagnosis of MiNEN.

MiNENs are heterogeneously mixed neoplasms consisting of two components. Consequently, the grade of each component will determine the level of malignancy. Unsurprisingly, some tumors exhibit benign behavior, while others are aggressively spread and metastatic [28]. Clinical behavior can be characterized as NEC, especially when both portions are malignant [3, 11, 13, 29]. The presence of both benign components is rare [28]. In our case, the lower malignancy part was NET grade 2, and both components were cancerous. This existence is compatible with the course of the illness, when adenocarcinoma emerged as a local invasion and regional lymph node metastases.

Understanding the molecular biology of this neoplasm is particularly important in analyzing the pathogenesis, clinical course, prognosis, and treatment prediction. Since dMMR/MSI appeared not only to be one of the driving mutations in the pathogenesis of MiNEN but also to play a crucial role in managing gastric cancer, we investigated the expression of MMR proteins in this instance. Interestingly, both components lost expressions of MLH1 and PMS2, confirming the diagnosis of dMMR/MSI gastric MiNEN. This finding demonstrated how our case relates to the third theory raised above, in which pluripotent stem cells underwent the earliest stages of progression and initially differentiated into non-neuroendocrine cells due to accumulating potential aberrations. One of the driven mutations in the first steps of tumorigenesis seen in this case was MSI resulting from mismatch repair protein deficiency

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being MLH1 and PMS2 [12]. Subsequently, the initially abnormal non-neuroendocrine cells evolved through dual independent and separate directions giving rise to two parts [15]. The first part differentiated in a more malignant pathway and formed a moderately differentiated adenocarcinoma; the other developed into the aberrant neuroendocrine cells and eventually gave rise to a less malignant grade 2 NET. This result may agree with Bazerbachi et al. [28], who supposed that well-differentiated NETs evolved to poorly differentiated phenotypes, which rarely occur [28]. However, this point is contrary to the view of Frizziero et al. [15], suggesting that the neuroendocrine constituent gradually gathers more aberrations and obtains a more deadly phenotype [15].

In the personalized treatment paradigm, the tumor's molecular biology is becoming increasingly important, of which the dMMR/MSI is of interest [20]. There are few studies on dMMR/MSI in patients with gastric MiNENs. La Rosa et al. and Sahnane et al. surveyed dMMR/MSI on gastroenteropancreatic NECs and MiNEN tumors and revealed that MSI/dMMR accounted for roughly 5–12.4% of MiNENs; most of them lost MLH1 expression. The total number of dMMR gastric MiNENs in the two studies was not more than 3 patients; all were MiNENs with NEC components. The authors define MSI MiNENs as a subset of MiNENs with particular biology and better prognosis. Multivariable analysis revealed MSI status as the only independent prognosis factor [12, 16]. These two studies' conclusions suggest that establishing a treatment strategy for NEC or MiNEN in the first phase should consider MSI/dMMR status [1, 12, 20].

Until now, studies on prognosis and treatment for gastric MiNENs are limited and inconsistent. There is, therefore, no consensus guideline on the optimal treatment strategy for this mixed neoplasm [3, 11, 30]. Most previous studies indicate that the treatment strategy should rely on the more malignant histological portion [31]; in contrast, the NCCN recommendations encouraged the non-neuroendocrine component [32]. Tomita et al. suggested that vascular invasion frequently happened early in MiNENs. Surgical resection may be optimal in gastric MiNEN, irrespective of the local extension and lymphatic vascular invasion [24]. A first large-scale study on gastric MANECs illustrated that 5FU-based adjuvant chemotherapy was only beneficial for patients with the dominant adenocarcinoma group, supporting the foundation stone for individualized gastric MANEC treatment [33]. With the more aggressive component being the adenocarcinoma component, we staged and treated this cancer according to the stomach cancer guidelines, the recommendations mentioned above. Adjuvant fluorouracil-based chemotherapy followed by radical D2 gastrectomy has emerged as a gold standard for managing locally advanced gastric cancer therapy in the early 21st century.

Based on the theory that adjuvant chemotherapy is detrimental to dMMR colorectal cancers, we query if this is observed in gastric cancer. Moreover, immunotherapy alone or combined with chemotherapy or novel Her2 inhibitors brings notable results and increases the chance of completed response in metastasis dMMR gastric cancer [34–36]. Does this happen with locally advanced gastric cancer patients or not? From the reviewed English literature, many retrospective, institute-level series, and even meta-analyses have attempted to demonstrate whether the MSI status is a valuable biomarker for patient stratification and predicting the benefits of adjuvant chemotherapy for stage II–III stomach cancer. Adjuvant chemotherapy negatively affected dMMR/MSI gastric cancer, according to two post hoc analyses from the CLASSIC and MAGIC trials. However, the findings were conflicting, primarily because the number of cases analyzed was small, and did not approach statistical significance [23, 37]. Interestingly, a phase II clinical trial evaluating perioperative immunotherapy in this patient group has promising preliminary results [38]. Hence, this patient was addressed adjuvant chemotherapy with a capecitabine/oxaliplatin regimen. The patient is still stable with no progression or recurrence symptoms after eight chemotherapy cycles relying on

NCCN guidelines. Once the conclusion from the different clinical trials is inconsistent, management of patients based on proven conventional recommendations to get the best results for patients is a reasonable option.

In conclusion, the natural behavior of gastric MiNEN with a grade 2 NET component is relatively similar to that of gastric adenocarcinoma, making it a rare and likely overlooked condition. dMMR has been proven to be one of the genetic mutations giving rise to these neoplasms. Preliminary data describes that dMMR gastric MiNEN has a favorable prognosis. More research studies are necessary to ascertain the involvement of dMMR status in the pathogenesis, clinical behavior, prognosis, and treatment prediction of this neoplasm. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533707).

Acknowledgment

We appreciate the patient for allowing the presentation of this case. The consent according to patient's perspective:

I feel pleased that my case is a reference document for doctors worldwide. I do not mind when pictures related to my illness are shared.

I want to thank the team of doctors who treated me. I will follow the doctor's treatment regimen to achieve the best results.

Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The informed consent form can be made available upon reasonable request. This case belonged to the study conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee in biomedical research of the University of Medicine and Pharmacy, Hue University (Ethics Approval Number: H2021/441).

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Thi Hong Chuyen Nguyen treated this patient, carried out and analyzed the immunoassays, and conceived and wrote the manuscript. Bao Song Nguyen Tran, Nguyen Cuong Pham, and Thuan Dang Cong conducted pathological diagnosis, provided histological information, and carried out and analyzed the immunoassays. Thu Giang Thi Nguyen reviewed

and edited the manuscript format. Thanh Phuc Nguyen and Huu Hoang supplied the surgical information and designed the figures. Cong Thuan Dang and Thi Minh Thi Ha participated in the sequence alignment and reviewed and edited the manuscript content. All authors contributed to discussions and agreed on the final version of the submitted manuscript.

Data Availability Statement

All data including patient's clinical details and images are included in this article. Further inquiries can be directed to the corresponding author.

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