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Southeast Asian Journal of Case Report and Review

Journal homepage: https://www.sajcrr.com/

Case Report

Gastric neuroendocrine hyperplasia and dysplasia in a patient with Lynch Syndrome

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ARTICLE INFO

Article history:
Received 20-04-2024
Accepted 03-10-2024
Available online 30-11-2024

Keywords:
Lynch syndrome
Neuroendocrine neoplasm
Low grade
Hyperplasia
Dysplasia

ABSTRACT

Background: Lynch syndrome (LS), previously known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder that predisposes individuals to various malignancies, most commonly adenocarcinomas. While low-grade neuroendocrine tumors (NETs) associated with Lynch syndrome are rarely reported, gastric neuroendocrine tumors (g-NETs) account for less than 1% of all gastric tumors.

Case Report: This case report presents a rare occurrence of gastric neuroendocrine hyperplasia and dysplasia in a 68-year-old female diagnosed with Lynch syndrome. The patient, previously treated for well-differentiated adenocarcinoma of the colon, was found to have a polyp in the gastric fundus during routine surveillance. Histological analysis revealed adenocarcinoma alongside neuroendocrine cell proliferation, confirmed by synaptophysin immunostaining.

Conclusion: This case highlights a novel association between Lynch syndrome and gastric neuroendocrine hyperplasia/dysplasia. This finding raises awareness among clinicians regarding Lynch syndrome in patients with low-grade NETs or neuroendocrine precursors and underscores the need for comprehensive surveillance and further research to understand the underlying mechanisms and clinical implications. It suggests that mutations in mismatch repair (MMR) deficiency may play a role in neuroendocrine cell proliferation, expanding the spectrum of Lynch syndrome-associated tumors, and pointing to new directions for studying the molecular pathways and pathogenesis of NETs.

1. Introduction

Lynch syndrome (LS), previously known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant disorder leading to a high risk of cancers involving various organs, namely gastrointestinal tract, pancreas, uterus and even the brain.[1] The histological types of tumour most commonly seen in Lynch Syndrome are adenocarcinomas.[1] Low-grade neuroendocrine tumors (NETs) and neuroendocrine precursors associated with Lynch syndrome are rarely reported.

Gastric neuroendocrine tumors (NETs) are rare, accounting for less than 1% of gastric tumors.[2] Only a few cases of gastric neuroendocrine neoplasms associated with Lynch syndrome have been reported, and nearly all were high-grade neuroendocrine carcinomas.[3–5]The incidence of Lynch syndrome-associated low-grade NETs and neuroendocrine precursors is unknown because it is not reported before. Here, we firstly reported a case of gastric neuroendocrine hyperplasia/dysplasia in a patient diagnosed with Lynch syndrome.

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https://doi.org/10.18231/j.sajcrr.2024.027

2. Case Report

The patient is a 68-year-old female with a history of well-differentiated adenocarcinoma arising from a tubular adenoma in the colon. She underwent a right hemicolectomy at 61 years old. The adenocarcinoma exhibited loss of mismatched repair proteins MLH1 and PMS2, leading to a diagnosis of Lynch syndrome confirmed by genetic testing.

During follow-up, oesophagogastroscopy and colonoscopy revealed large polyps in both the transverse colon and the gastric fundus. Biopsies of these polyps were performed. Gross examination revealed a 3.5 cm polyp in the transverse colon and a 2.4 cm polyp in the gastric fundus. Microscopically, the transverse colon polyp showed invasive adenocarcinoma with typical features of Lynch syndrome-associated adenocarcinoma (Figures 1 and 2). The gastric fundus polyp revealed adenocarcinoma with tubular formations (Figure 3) and poorly differentiated areas (Figure 4). Notably, adjacent to the gastric adenocarcinoma, there were multiple aggregates and nests of uniform ovoid cells with a salt-and-pepper chromatin pattern (Figures 5 and 6), distinct from adenocarcinoma. These cells tested positive for Synaptophysin by immunohistochemistry staining (Figure 7), confirming neuroendocrine differentiation. Small nests infiltrating beyond the muscularis mucosae were observed without significant cytological pleomorphism or atypia. These were not forming a mass, with the largest focus measuring 0.3 mm, classified as neuroendocrine hyperplasia with focal dysplasia.

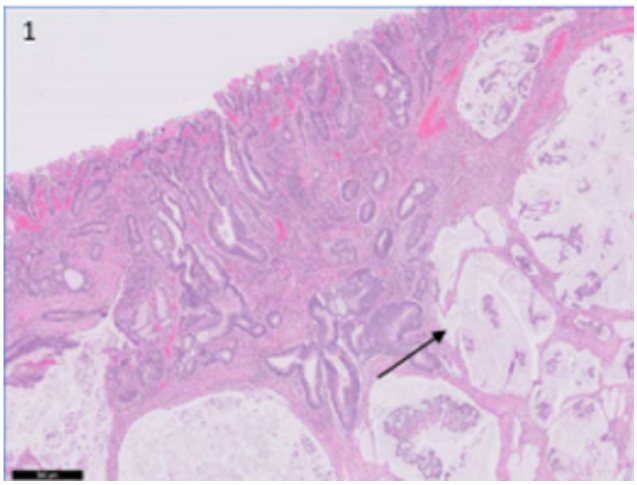

Figure 1: Moderately differentiated adenocarcinoma with mucinous features (arrowed).

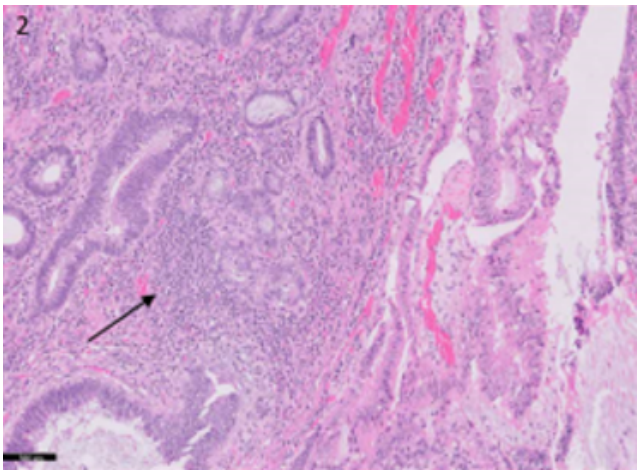

Figure 2: Marked peritumoral lymphocytic infiltration (arrowed), indicating Lynch syndrome.

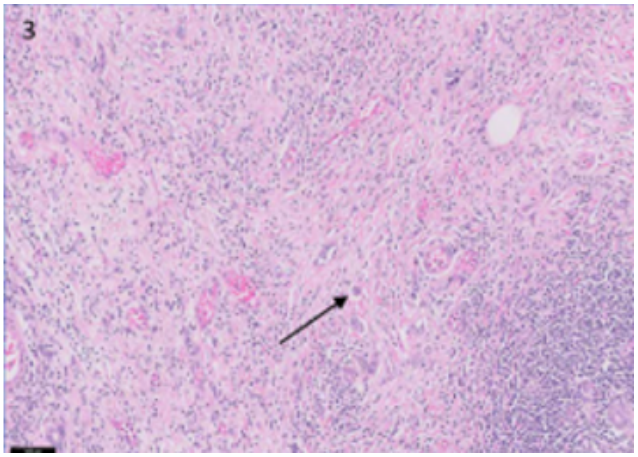

Figure 3: Gastric polyp: adenocarcinoma Poorly differentiated area with discohesive cell infiltrate (arrowed).

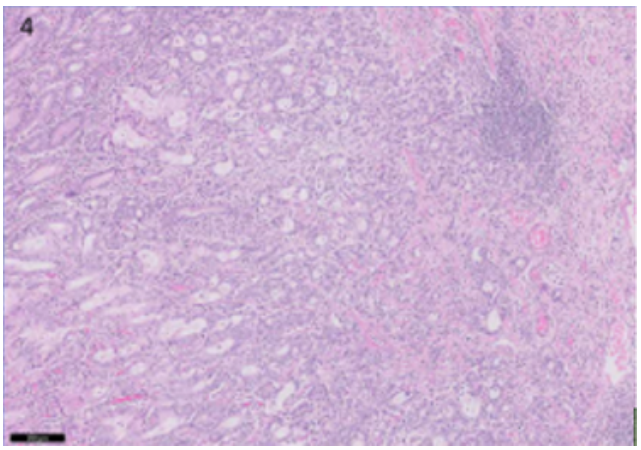

Figure 4: Tumor with tubular formation consistent with intestinal-type adenocarcinoma.

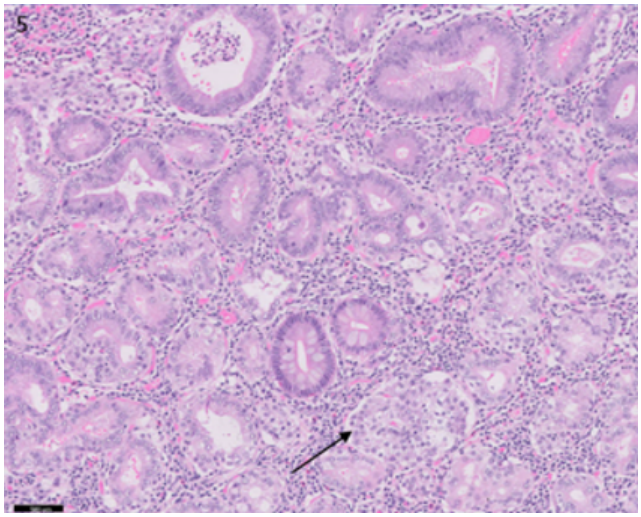

Figure 5: Small aggregates and nests of neuroendocrine cells within the mucosa (arrowed).

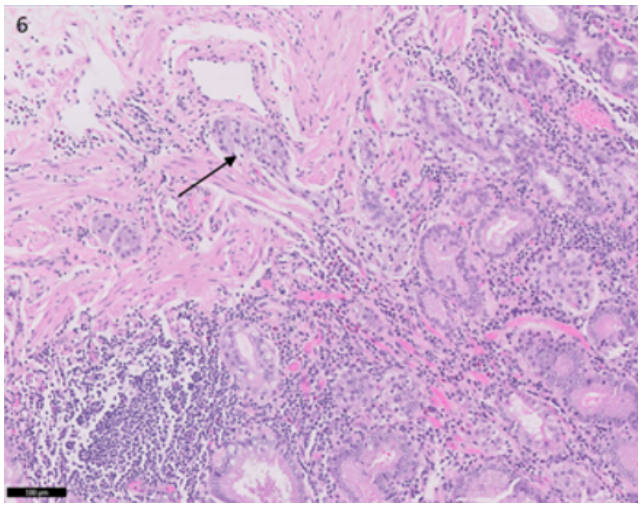

Figure 6: Submucosal neuroendocrine cell aggregates (arrowed).

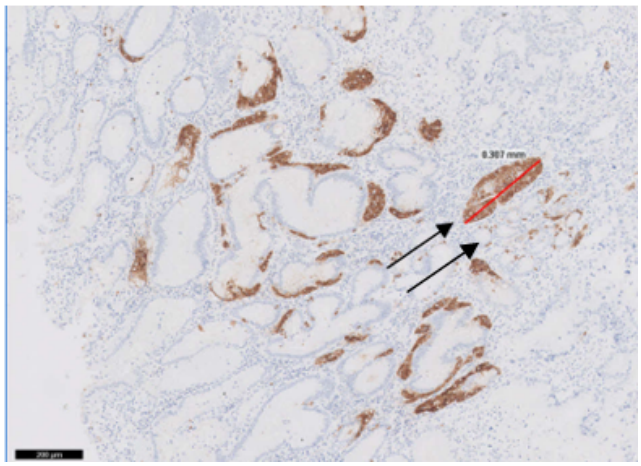

Figure 7: Immunostain of Synaptophysin highlighting neuroendocrine cell proliferation (arrowed).

3. Discussion

Low-grade NETs or neuroendocrine precursors are frequently encountered by pathologists, typically in association with Zollinger-Ellison syndrome and Multiple endocrine neoplasia (MEN).[6] However, their association with Lynch syndrome has not been previously reported. This case represents the first documented instance of low-grade NETs or neuroendocrine precursors linked to Lynch syndrome, adding new insights and practical value to clinical pracgtice.

First, this case enhances clinicians' awareness of Lynch syndrome in patients diagnosed with low-grade NETs or neuroendocrine precursors. Previously, a diagnosis of low-grade NETs would not have prompted consideration of Lynch syndrome, but this case suggests that such a link should now be contemplated.

Second, this case underscores the importance of comprehensive surveillance. It highlights that Lynch syndrome may present with low grade NETs or neuroendocrine precursors at an early stage. Given the potential for high grade NETs to evolve from low grade NETs even neuroendocrine precursor, and the known accelerated adenoma-to-carcinoma progression in Lynch syndrome-associated colorectal cancers[7], these findings suggest that endoscopic surveillance with frequent intervals may be beneficial. Additionally, this novel case broadens the differential diagnosis that clinicians should consider during surveillance.

The findings from this case and reviewed literatures suggest that Lynch syndrome patients should undergo regular upper GI surveillance to detect early-stage malignancies, including both adenocarcinomas and potential neuroendocrine proliferations. While the role of surveillance in preventing neuroendocrine tumors specifically is less clear, the detection of early-stage gastric cancers can significantly improve patient outcomes.[8]

Third, Lynch syndrome is characterized by mutations in mismatch repair (MMR) genes, including MLH1, MSH2, MSH6, and PMS2.[1] The presence of gastric neuroendocrine hyperplasia in the context of Lynch syndrome raises the question of whether MMR deficiency directly influences neuroendocrine cell proliferation, suggesting new directions for research into the molecular pathways and pathogenesis of NETs.

Recent studies have provided insights into the molecular pathways and tumor heterogeneity in Lynch syndrome. For instance, Pereira D etc, reported a gastrointestinal tract mixed neuroendocrine and non-endocrine neoplasms (MiNENs) associated with loss of MLH1 and PMS2 mismatch repair proteins.[9] A case reported by Sorscher S, described a patient with both adenocarcinoma and NET, indicating distinct molecular pathways for each tumor type based on morphological and immunohistochemical differences.[10] This supports the notion that Lynch

syndrome-associated tumors can exhibit significant heterogeneity.

As the understanding of Lynch syndrome-associated tumorigenesis evolves, it is crucial to consider the diverse pathways leading to different tumor types. This case report emphasizes the need for tailored surveillance and management strategies that address the full spectrum of malignancies associated with Lynch syndrome.

Future studies should aim to elucidate the genetic and molecular pathways linking Lynch syndrome with neuroendocrine proliferations. Collecting and analyzing additional cases with detailed molecular profiling could enhance our understanding of the oncogenesis of neuroendocrine tumors in the context of MMR deficiency. This could potentially lead to targeted therapeutic strategies and improved management protocols for patients with Lynch syndrome.

In conclusion, this case highlights a novel association between Lynch syndrome and gastric neuroendocrine hyperplasia/dysplasia. This finding raises awareness among clinicians regarding Lynch syndrome in patients with low-grade NETs or neuroendocrine precursors and underscores the need for comprehensive surveillance and further research to understand the underlying mechanisms and clinical implications. It suggests that MMR deficiency may play a role in neuroendocrine cell proliferation, expanding the spectrum of Lynch syndrome-associated tumors, and pointing to new directions for studying the molecular pathways and pathogenesis of NETs.

4. Data Availability Statement

For this case report, there were no associated datasets to avail.

5. Author Contribution Statement

Li Yihan was involved in the patient's care and was the only author of the manuscript. All authors read and approved the final manuscript.

6. Declarations

The authors declare that there is no conflict of interest, no affiliation or financial involvement with any commercial organisations, and no financial interest in the subject or materials discussed in the manuscript.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Yihan LI. Gastric neuroendocrine hyperplasia and dysplasia in a patient with Lynch Syndrome. *Southeast Asian J Case Rep Rev* 2024;11(4):113-116.