Concomitant intraductal papillary mucinous neoplasm with invasive adenocarcinoma and neuroendocrine tumor grade 3 of the pancreas: a case report

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Case Report

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Abstract

Background: Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) usually consist of a ductal adenocarcinoma and a neuroendocrine neoplasm. However, other components mixed in MiNEN also need to be focused on in our clinical pathologic diagnosis.

Case presentation: Herein, we shared a 65-year-old male sought medical advice to our hospital with diarrhea and epigastric pain. Enhanced MRI displayed a patchy abnormal signal shadow of 2.8cm in the pancreatic head and malignancy was assessed. Pancreatoduodenectomy (PD) was carried out and thorough histopathology diagnosis including immunohistochemistry were revealed a mixed NET-IPMN with invasive adenocarcinoma. The neuroendocrine components finally determined as NET G3 grade. In some areas, the two components of IPMN and NET relatively existed separately, whereas in other areas they were intermingled: The papillae were composed of epithelial cells of IPMN, and neuroendocrine cells formed glandular or solid structures in the same duct.

Conclusions: We report a rare case of mixed neuroendocrine-exocrine neoplasms (NET G3 and IPMN with invasive adenocarcinoma) to provide basis for the diagnosis and classification of histopathology.

Background

According to the latest version of 2019 WHO classification of digestive system tumors, each of neuroendocrine and non-neuroendocrine components in pancreatic blended neuroendocrine non-neuroendocrine neoplasms (MiNEN) should constitute 30% of the tumor volume [1]. Most MiNENs consist of a ductal adenocarcinoma usually companied with a NEC, while other components or subtypes are seldom reported.

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas is a grossly visible intraductal epithelial neoplasm of mucin-producing cells, originating from the main pancreatic duct or branches of pancreas. IPMNs are more commonly seen in elderly people [2, 3]. Histologically, the characteristics of IPMNs are the intraductal different-degree dysplasia of mucous-secreting cells, which can be flat or form papillary. IPMN also can encounter invasive carcinoma [1]. However, it is very rare for the co-exist of pancreatic IPMN and neuroendocrine tumor (NET) and only a few literatures have been reported. Here, we described a unique case report of a concomitant mixed type of IPMN with associated invasive carcinoma and well-differentiated high-grade NET (G3) of the pancreas.

Case Presentation

A 65-year-old male with diarrhea for 3 months and epigastric pain for 20 days was referred to our hospital. He had no symptoms of stained yellow skin and mucos, nausea or vomiting. He had past histories of type 2 diabetes mellitus and pancreatitis. He had taken some drugs (the names and types of the drug were dimness) but it didn't work. Abdominal enhanced MRI presented a patchy abnormal signal

shadow with slightly unclear boundary in the pancreatic head. The maximum cross section of the shadow was 2.8cm×1.4cm and it was considered as a malignancy (Fig. 1A-C).

Then, the patient underwent pancreatoduodenectomy and the macroscopic appearance of the tumor is a solid tumors measuring 2.3cm×1.5×1.1cm in the pancreatic head. Histopathology showed mixed complex components in this tumor (Fig. 2A). One component was intraductal villous papillae consisted of tall columnar cells with pseudostratified nuclei, apical mucin and high-grade dysplasia and invasive carcinoma (Fig. 2B-2C). Another component was well-differentiated organoid growth and glandular patterns with round and fair uniform cells (Fig. 2D-2E).

Immunohistochemical (IHC) results displayed that both components were positive for CK19 (Fig. 3A). While the component in intraduct was identified as intestinal-type IPMN with associated invasive carcinoma, which was positive for CEA, MUC2 (Fig. 3B), MUC5AC and CDX2 (Fig. 3C), and negative for MUC6 and EMA. The other component was positive for CD56, CgA (Fig. 4A), Syn (Fig. 4B), SSTR2 (2++, Fig. 4C), Rb (Fig. 4D), ISM1, p53 (30% weak expression) and negative for MUC2, CEA, CDX2 and EMA. This component preliminary considered as NET, not NEC. Histological grading in NET is very important for clinical therapy and prognosis judgment. This NET was with a 21 mitoses/ mm2 (Fig. 4E) and Ki-67 proliferative index up to 50–60% (Fig. 4F). Synthesized Histological morphology and IHC staining, it finally assessed as NET G3. Based on the all data above, we finally made the diagnosis as concomitant IPMN with associated invasive carcinoma and NET G3 of the pancreas with nerve and vessel invasion but no lymphatic metastasis. The pathological T stage of the tumor was pT2. On the 10th day after the operation, the patient was conscious and in good mental state, and asked to be discharged from the hospital and the doctor ordered regular reexamination. Unfortunately, six months after operation, liver metastases occurred and one year later, the patients were died with multiple metastases and coma.

Discussion And Conclusions

As the description of 2019 WHO Classification of Tumors of digestive tumors, the term “MiNEN” was defined as neoplasms composed of morphologically recognizable neuroendocrine and non-neuroendocrine components, each constituting at least 30% of the tumor volume [1]. Well-differentiated grade 3 neuroendocrine tumors (NET G3) have been distinguished from poorly differentiated neuroendocrine carcinomas (NEC) in this WHO classifications. Most of them are usually mixed ductal adenocarcinoma with neuroendocrine carcinoma (NEC), but the combination of NET G3 and IPMN are rarest. In our report, we describe a case of concomitant IPMN with associated invasive carcinoma and NET (MiNENs) of the pancreas.

The most common tumors of the neoplasms in pancreas are IPMN and more and more attentions are attracted to its unique features and malignant. It can be subclassified into three subtypes including gastric, intestinal, and pancreatobiliary by their predominant cell differentiation pattern. In clinical, about 70% IPMNs are gastric-type which usually occurs in branch ducts and most of them are low-grade lesions. The second most common type of IPMN is intestinal-type, which accounts about 20% of cases

and usually involves in the main duct. They often present high-grade lesions and even an associated invasive carcinoma. Pancreatobiliary-type of IPMN typically occurs in the main pancreatic duct and often are high-grade lesions [4]. According to the histology and the results of immunohistochemistry, the intraductal lesions in our case were identified as intestinal-type IPMN with associated invasive carcinoma which was positive for the markers of intestinal differentiation such as CDX2, MUC2 and MUC5AC, and negative for MUC6 and EMA (pancreatobiliary-type IPMN).

Due to the high index of Ki-67 and mitoses in this case, another key point of identification was that the neuroendocrine component in the tumor was NET G3 or NEC. Comparing with NEC, NET is with higher rates of avidity on somatostatin receptor scintigraphy (SRS), lower Ki67, poorer responses to platinum base chemotherapy, and longer survival. Histologically, NET G3 is a high grade and well-differentiated NEN with moderate atypia, often presenting organoid patterns and less necrosis. However, NECs usually shows flaky or trabecular pattern with high heterogeneity. Necrosis is easy to be discovered. But in many cases, it is difficult to distinguish them only from morphology. Fortunately, some markers may help us make a right judgment. Primary NET G3 almost always have no damage in TP53 and RB1, and reveals loss expression of DAXX and ATRX. However, NECs have a mutation of TP53 and RB1, showing p53 nuclear accumulation and lack expression of RB1 expression and SMAD4. The Ki-67 proliferation index of NECs is commonly > 60–80%. Anymore, the expression of SSTR2A in NET is always higher than that in NEC. In our cases, the tumor presented a well-differentiated organoid growth in histopathology. In immunohistochemistry, p53 showed as a wild type and RB1 is intact. SSTR2A was strongly expressed (2++) in a membranous pattern. The Ki-67 proliferation index was about 50%. Based on the data above, we made a final diagnosis of MiNENs (NET G3 and IPMN with associated invasive carcinoma).

Although the histology origins of IPMN and NET seems different, the associations between them have been described in the several literatures. In most cases, IPMN and NET were apparently self-governed and probably represented two different neoplasms. In molecular, about 40% of NETs occurs somatically inactivation of MENI gene [5]. About 40% of NETs have mutation in DAXX or ATRX [6, 7]. There are also showed NETs also showed HIF1A, VHL, TSC2 and PTEN alterations [8–10]. On the other hand, IPMNs frequently harbour mutations in KRAS, GNAS and RNF43[11, 12]. Missense mutations of TP53 can occurs in high-grade IPMNs or invasive carcinomas associated with IPMN [13]. Anymore, loss of SMAD4 occurs uncommonly in the invasive carcinomas associated with IPMN [14]. While, in some reports both the two components shared KRAS and GNAS mutations, which were common in IPMNs and are often not appeared in pancreatic NET, indicating that the NET might originate from IPMN [11,12]. Moreover, Alterations of the CDKN2A and CCND1genes have also been found in both NETs and IPMNs [15–17]. In our case, in some area the two components were distinct, but in some area, they were intermingled. Unfortunately, the NGS of the two components in our case were not detected. Further analyses the molecular alterations of the IPMN and NET should be done in our next study.

In conclusion, we share a rare case of MiNEN which consists NET G3 and IPMN with associated invasive carcinoma, and expect that this very rare association, still of unknown molecular basis, should be kept in mind.

Abbreviations

MiNEN: mixed neuroendocrine-exocrine neoplasms;

IPMN: intraductal papillary mucinous neoplasm;

NET: neuroendocrine tumor;

IHC: immunohistochemical;

NEC: neuroendocrine carcinoma;

NET G3: grade 3 neuroendocrine tumors;

Declarations

Ethics approval and consent to participate

A case report is intended to develop information to be shared for medical and educational purposes and do not meet the definition of “research”. Ethical approval was not necessary. Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

Not applicable.

Competing interests

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Authors’ contributions

XLR, LZY, YRZ and JW collected the information of the patient and wrote the manuscript. XLR and JMW was also a major contributor in writing the manuscript. All authors have read and approved the final

manuscript.

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Figures

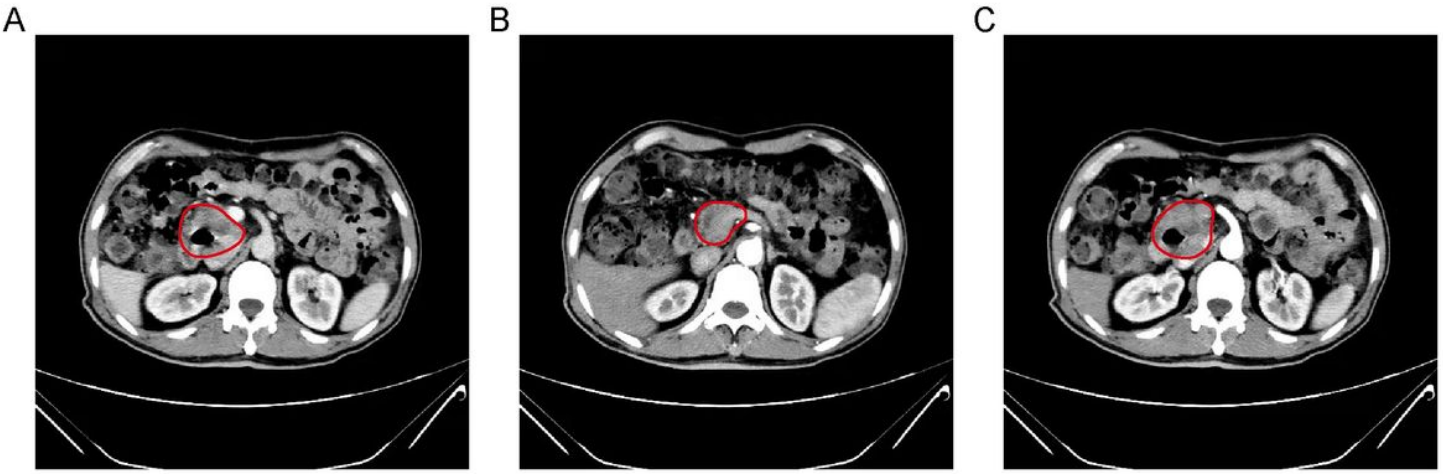

Figure 1

Magnetic resonance imaging (MRI) scan. (A-B) Magnetic resonance imaging (MRI) scan showing the density shadow of soft tissue (red circle) in the area of pancreatic head, and the enhancement degree of enhanced scanning was lower than that of surrounding pancreatic tissue.

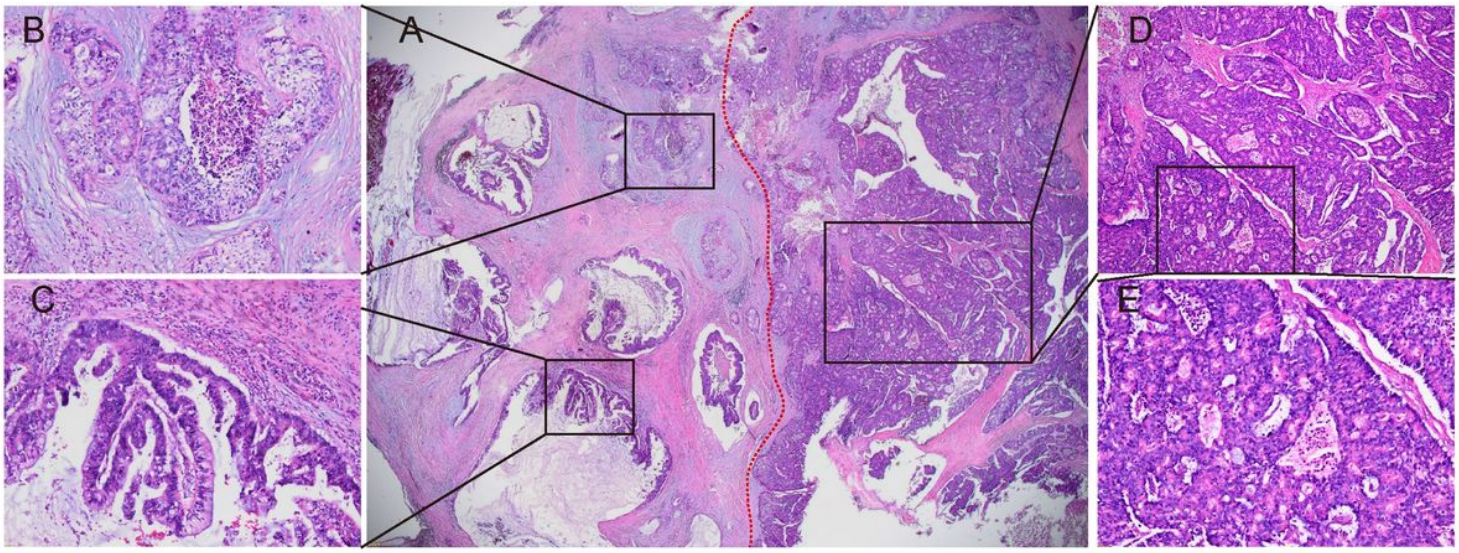

Figure 2

Histopathological findings. (A) low magnification (×20) of resected pancreas tissue showing papillary proliferation (left) and solid growth of the neuroendocrine tumor (right) by hematoxylin and eosin staining (HE). (B) Invasive carcinoma in pancreas tissue HE (×200). (C) Main pancreatic duct with papillary proliferation of mucinous cells with high atypia (HE, ×200). (D and E) high magnification of neuroendocrine tumor area in pancreas tissue (HE, ×100 and ×200, respectively).

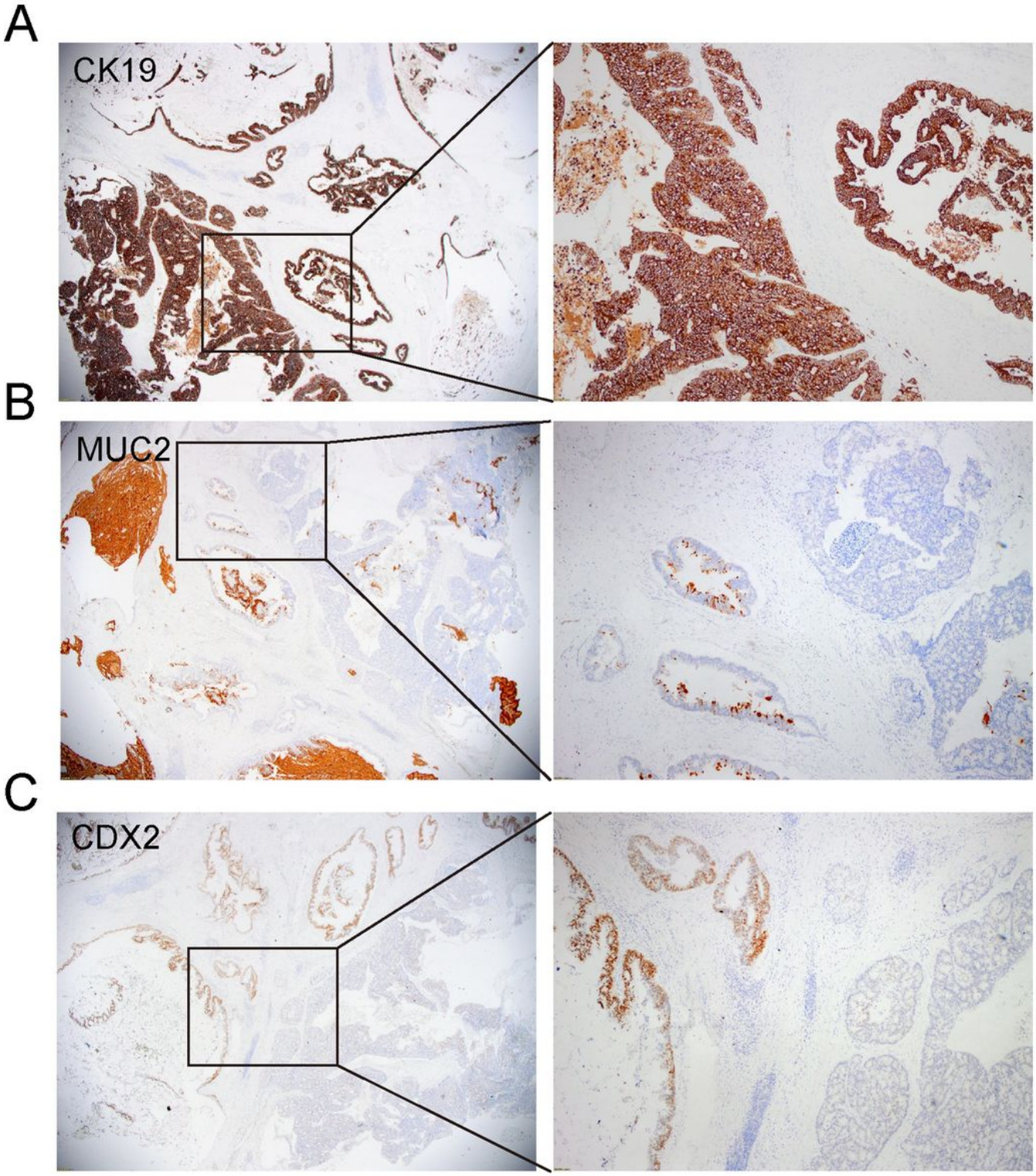

Figure 3

Immunohistochemical findings of IPMN with high atypia and associated invasive carcinoma.
(A) cytokeratin 19 (CK19) was diffusely positive (×20 and ×100, respectively). (B-C) MUC2 and CDX2 was positive for papillary proliferation of mucinous cells and invasive carcinoma and negative for the neuroendocrine component (×20 and ×100, respectively).

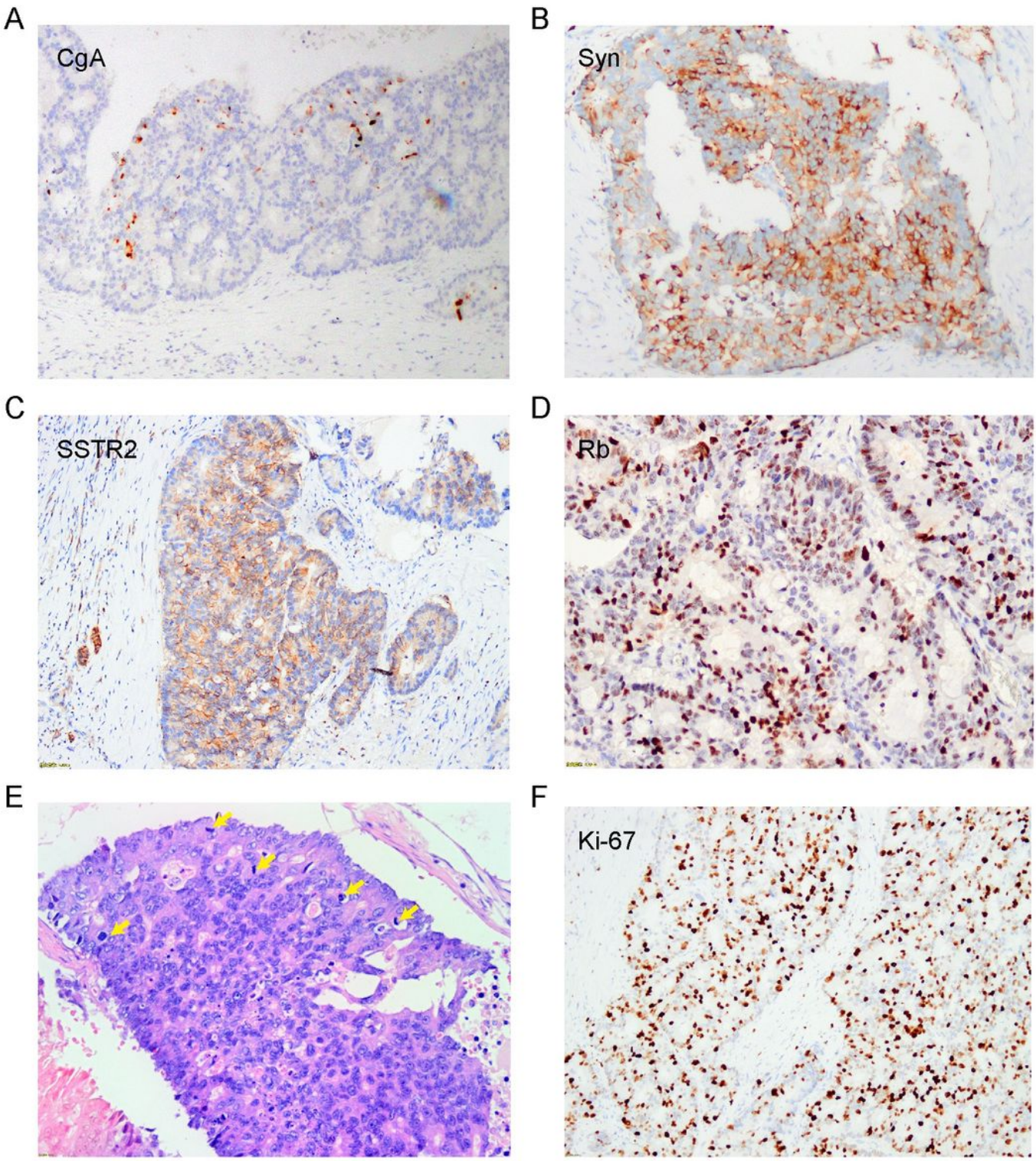

Figure 4

Immunohistochemical findings of the neuroendocrine tumor. (A) About 30% of neuroendocrine component was positive for chromogranin A (CgA) (×200). (B) Synaptophysin is diffusely positive (×200). (C) Approximately 70% of the NET were cell membrane positive for SSTR2 (×200). (D) About 80% of the NET were nucleus positive for RB (×200). (E) Image of mitoses of NET Tumor by HE staining. (F) 50% of NET was positive for Ki-67. (×200).

Supplementary Files

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- CAREchecklist.pdf