Case study

A RARE CASE OF MIXED ADENONEUROENDOCRINE (MiNEN) CARCINOMA OF THE GALL BLADDER

Abstract

Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) of the gall bladder is an extremely rare neoplasm of the gall bladder. We present a case of a 71-year-old female who came to our clinic with an incidental gall bladder mass and subsequently underwent laparoscopic radical cholecystectomy with liver cuff resection. Histology findings showed moderately differentiated carcinomatous component mixed with poorly differentiated large cell neuroendocrine carcinoma invading into muscular layer with clear resection margin (pT1bN0). Post operatively, she refused to undergo adjuvant therapy and unfortunately at 4 months after surgery she developed metastasis at the segment 5 of her liver. In conclusion, GB-MiNEN is an extremely rare and aggressive tumour of the gall bladder and surgery with adjuvant chemotherapy combined with somatostatin analogue may offer a better survivcal outcome.

Keywords: Mixed non-neuroendocrine neuroendocrine neoplasm. Gallbladder cancer. Liver metastasis.

Introduction

Neoplasm of the gall bladder is rare and accounts for 1.2% of all global cancer diagnoses with papillary adenocarcinoma being the commonest type (98%) while neuroendocrine tumours only account for 0.5%. Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) is extremely rare and defined as association of at least 2 morphologically different neoplastic components with at least 30% each including the neuroendocrine component. (1,7,10). We hereby report a case of MiNEN of the gall bladder who presented with an incidental gall bladder mass.

Case summary

A 71-year-old female initially presented to our surgical clinic for an incidental finding of a gall bladder mass on abdominal ultrasound. Clinically, she was well with no jaundice while abdominal examination was unremarkable with no mass palpable. Her serum Ca 19.9 level was elevated at 48mg/L and a contrast-enhanced CT scan of her abdomen done showed a heterogeneously enhancing irregular intraluminal mass (3 x 3.2 x 4.4cm) at the fundus of the gall bladder (see figures 1 and 2). Endoscopic ultrasound (EUS) assessment showed gall bladder mass which was confined within with no extraluminal extension. Subsequent PET-CT scan showed a hypermetabolic enhancing mass in the gall bladder with no evidence of regional or distant metastasis (see figure 3).

The patient underwent laparoscopic cholecystectomy with liver cuff resection and porta hepatis lymph nodes clearance. Intraoperatively, there was a 3 cm x 3 cm mass at the fundus of her gall bladder with intraoperative ultrasound confirmation of an intact gall bladder wall (see figure 4 for the ultrasound scan finding and figures 5 and 6 for which has illustrated the tumour specimen). There was no liver or peritoneal nodule seen. The patient recovered well post-surgery and she was discharged well at day 5 post surgery.

The final histopathological report showed mixed adenoneuroendocrine carcinoma of the gall bladder with a moderately differentiated adenocarcinoma mixed with poorly differentiated large cell neuroendocrine carcinoma with clear margins (see figures 7, 8, and 9 which illustrate the histopathology and immunohistochemistry study findings and the Ki67 findings of the tumour). In addition, the 6 porta hepatis lymph nodes were all negative with a staging of pT1bN0.

The patient refused to undergo adjuvant chemotherapy and she was on our clinic follow up for surveillance. Her serum Ca 19.9 remained elevated at 45 at 4 months post surgery and a repeated CT TAP showed possible segment 5 liver metastasis. She was started on chemotherapy and she was scheduled to undergo reassessment PET scan in 6 months' time.

Discussion

Gall bladder cancer is considered an uncommon cancer and ranked the 22nd most incident cancer with a disproportionately high cancer related death due to its difficulty in screening and early diagnosis. (10, 11) Patients were often diagnosed in advanced stage or with metastatic disease with as high as 40% of them being diagnosed late resulting in an average of only 18% of 5 year survival rate. (12, 13) The commonest type is papillary adenocarcinoma which accounts for 98% of all gall bladder cancer. Neuroendocrine carcinoma (NEC) is a rare tumour which accounts for less than 1% of all malignant tumours with majority the tumours still found in the gastrointestinal tracts especially in the rectum, jejuno-ileum and pancreas. (15). NEC of the gall bladder is extremely rare (0.2% of all gastrointestinal NEC) due to absence of neuroendocrine cells in the gall bladder. However, this type of malignancy is usually highly aggressive with a high risk for the development of metastasis and commonly presenting at late stages.

Based on the 2019 WHO classification of tumours of digestive system, mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) as the name suggests is a tumour composed of at least 2 morphologically different neoplastic components with at least 30% each, including 1 neuroendocrine component. (5, 7) The postulated pathogenesis is due to biphenotypic differentiation of both components during carcinogenesis secondary to chronic inflammation of gall bladder with gall stone being the commonest risk factor. (6) La Rosa et al has classified MiNEN into low, intermediate and high grade based on the combination of both components in the tumour. High grade MiNEN is a combination of carcinoma or adenoma with poorly differentiated neuroendocrine carcinoma (PDNEC) (G3) of small or large cell type, which was present in our patient. (14) It has a reported median overall survival of 12.2 months which is slightly better than pure PDNEC (9.6 months). (7,8,9,16) Several studies have shown that the behaviour of MiNEN is mainly driven by the neuroendocrine component which is commonly poorly differentiated (90%) and often present

in the distant metastatic sites; therefore, systemic agent of choice is usually targeting against the NEC component. (6) For non-metastatic MiNEN, treatment should include curative surgery, in this case a radical cholecystectomy with liver cuff resection and portal node clearance, followed by adjuvant treatment targeting the more aggressive NEC component. Some case report recommended the use of long-acting somatostatin analogue which was used for high grade NET (2); however, the data on somatostatin receptor 2 (SSTR2) expression is still very limited to support the benefit of this treatment modality. (7) Due to the rarity of gall bladder MiNEN, there is still lack of data on the survival outcomes. Despite our patient being diagnosed and managed early with radical surgery, she developed liver metastasis 4 months after surgery and she was referred to our oncology unit for systemic therapy.

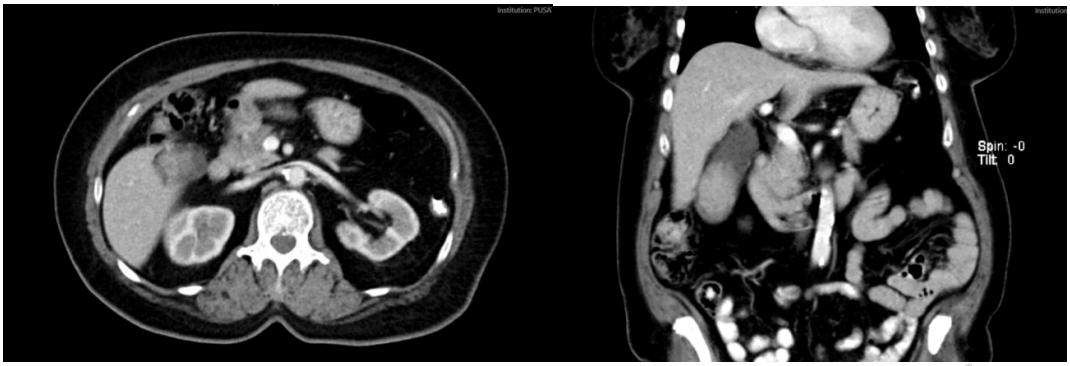


Figure 1 and 2 showed the axial and coronal view of CT images of the gall bladder mass which is heterogenously-enhancing with irregular margin at its fundus

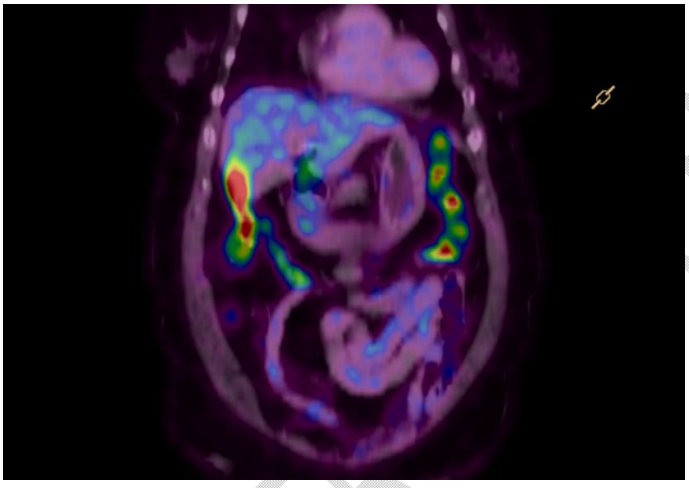


Figure 3 shows PET CT image of gall bladder mass

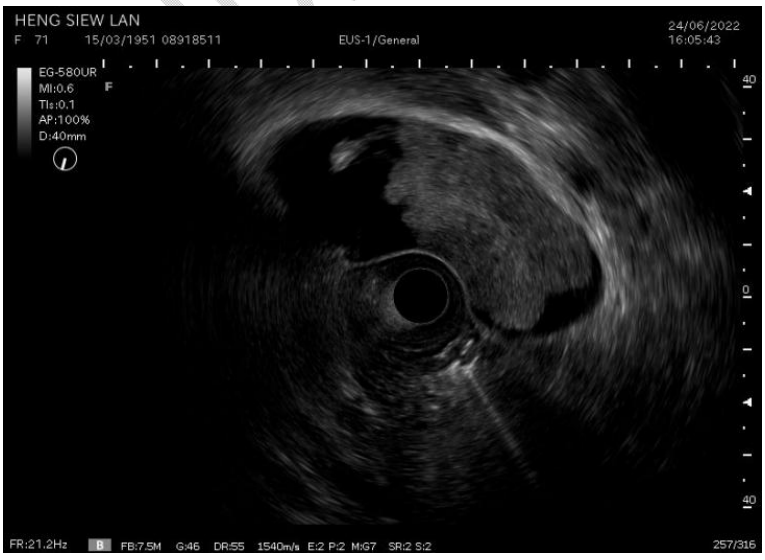
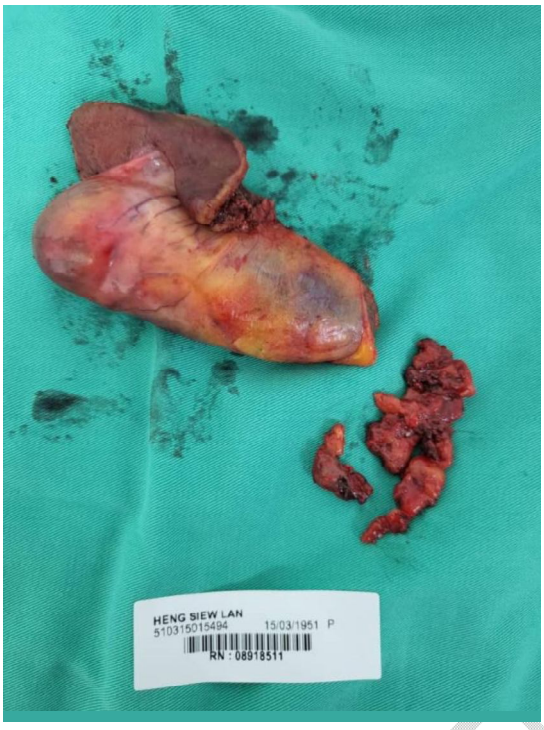


Figure 4 showed endoscopic ultrasound image of the gall bladder mass confined within the gall bladder



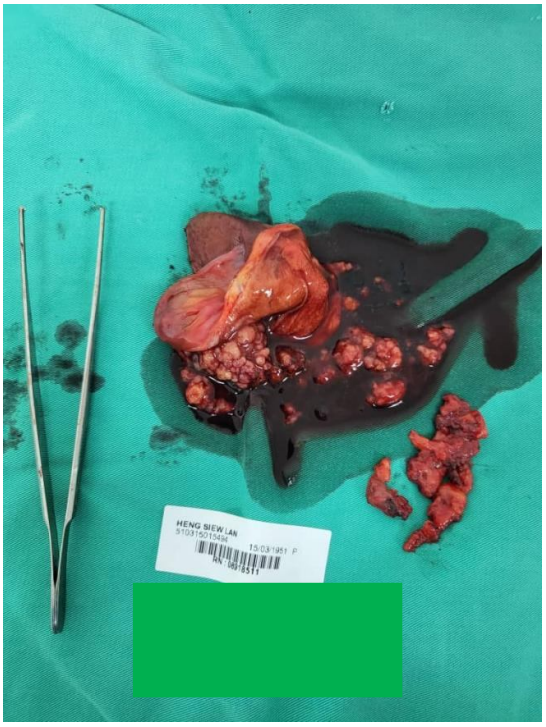


Figure 5 and 6 showing images of the specimen of gall bladder resected

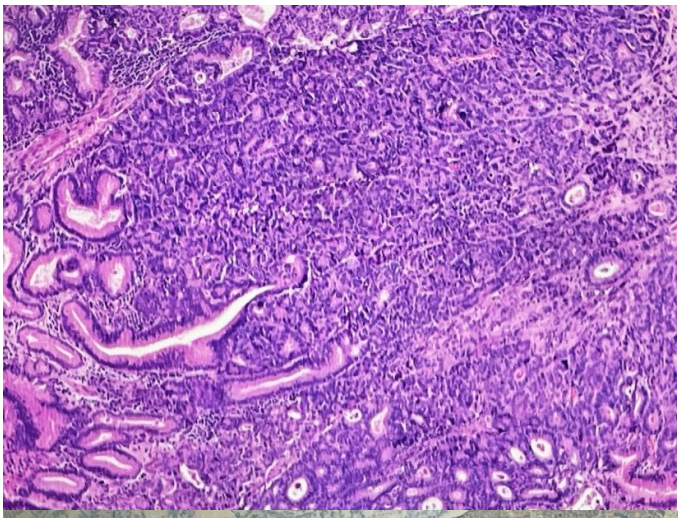


Figure 7 show admixtures of carcinomatous components (on the left) and large cell neuroendocrine component (on the right)

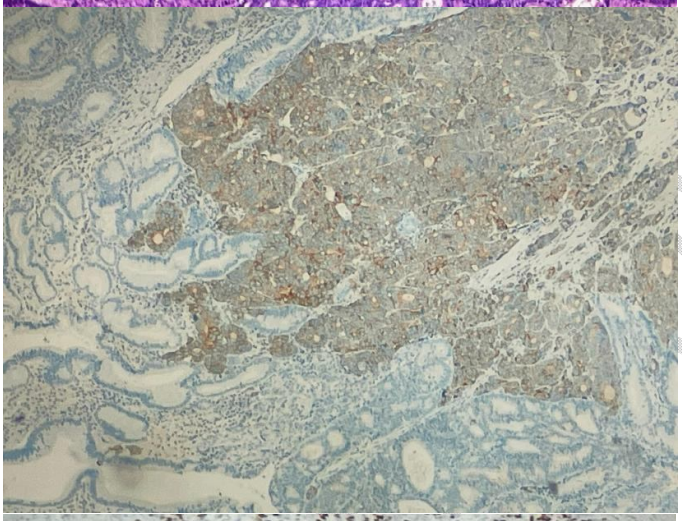


Figure 8 shows neoplastic cells in neuroendocrine component are positive for synaptophysin (brown stained) and the carcinomatous component are immune-negative

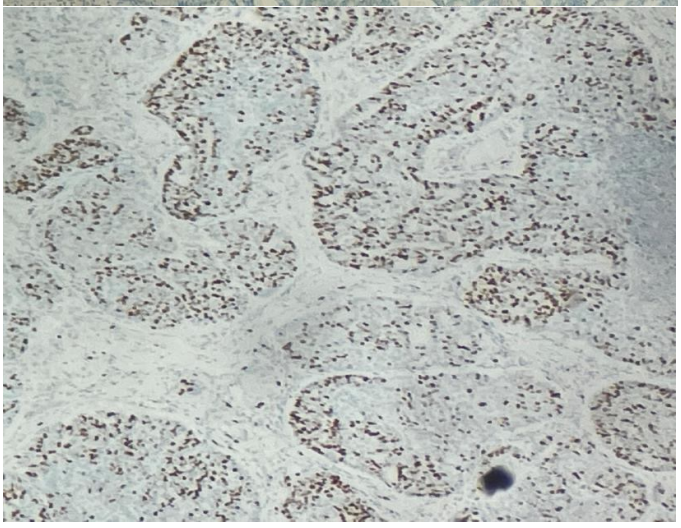


Figure 9 show proliferative index, Ki-67 is about 50-60% in neuroendocrine component

Conclusion

In conclusion, gall bladder cancers are still commonly being diagnosed late due to its nature of asymptomatic disease and often found in late stage of disease. MiNEN of gall bladder is a rare but highly aggressive cancer of the gall bladder with poor survival outcome. Due to its rarity, there is still lacking of evidence in the treatment guideline of managing this subtype of malignancy. Therefore, more cases and studies are required with longer follow up in order to establish standardized treatment guidelines.

Consent – Did you obtain permission from the patient to report the case? Declare your statement of consent from the patient to allow you to publish the case

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