MULTIDISCIPLINARY MANAGEMENT OF METASTATIC NEUROENDOCRINE TUMOURS

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Abstract
A 65-year-old man presented to his GP with right upper quadrant abdominal pain and weight loss. Abdominal ultrasound showed multiple gallstones and some ill-defined liver lesions. CT scan diagnosed a terminal ileal lesion causing cicatrisation of the terminal small bowel but do liver abnormality. Patient was worked up with serum gut hormone profile and MRI of the liver which demonstrated multiple liver lesions and biochemical suspicion of Neuro-endocrine tumour (NET). The patient underwent a right hemicolectomy and excision/ablation of 44 liver metastases. He made a good post-operative recovery and remains disease free after 18 months. We also present a brief literature review regarding advances in the management of metastatic neuroendocrine tumours.

Keywords: Neuroendocrine tumours, Hepatic metastases, Radiofrequency ablation, CT, MRI

Introduction:
Neuroendocrine tumours (NET) represent a diverse group of neoplasms containing membrane-bound neurosecretory granules [1]. Clinical presentations depend on the staging of this disease and its functionality, i.e. autonomous hormone secretion, which may lead to carcinoid syndrome characterized by nausea, vomiting, diarrhoea and abdominal cramps [2]. There has been a recent increase in the incidence of all gastrointestinal NETs, especially small bowel NETs (SB-NET) [3] which may be due to an increased awareness and advances in diagnoses rather than a true rise in disease incidence. Modlin et al. reported SB-NET to be the most common small bowel neoplasm with a threefold increase in incidence over the last three decades [4].

The Surveillance, Epidemiology and End Results Programme showed that carcinoid syndrome typically present in the 6th-7th decade of life [5], with an estimated prevalence of about 35/100,000 population [2]. The commonest primary tumour sites are the small bowel and pancreas [6] while the commonest site of metastasis is the liver [7].
partially calcified lymphadenopathy in the mid small bowel mesentery measuring 1.8 cm with spiculations and a similarly calcified poorly visualised mass in the adjacent small bowel measuring 1.8 cm which was consistent with mid-gut NET. CT scan did not identify any metastatic liver (figure 1), lung or bony lesions. However, MRI of the liver (figure 2) demonstrated more than 25 T2 hyperintense lesions in both lobes of the liver. On dynamic contrast-enhanced sequences, these lesions showed intense enhancement on arterial phase, complete rim enhancement on portal venous phase and complete washout on delayed phase, features consistent with hypervascular liver metastases. The patient also had radionuclide Octreotide SPECT scan which showed a primary lesion in the small bowel, mesenteric nodal deposits and multiple liver metastases showing abnormal uptake. There was no evidence of overexpression of somatostatin receptors elsewhere. His chromgranin A and B were raised at 214 pmol/L (<61) and 164 pmol/L (<151) respectively. Rest of the gut hormone profile was normal.

The patient was seen by a NET specialist and was started on somatostatin analogues. His case was also discussed at the combined hepatobiliary and NET multidisciplinary meetings and it was decided to offer him surgery to remove the primary tumour and debulk the liver disease as much as possible.

An upper midline laparotomy with extension to right sub-costal region was performed. On the pre-operative ultrasound, it was felt that even MRI had underestimated the size and number of liver lesions. The patient underwent right hemicolectomy and regional lymphadenectomy, cholecystectomy and excision of 34 liver lesions from both lobes of the liver. Further 5 superficial lesions were diathermy ablated and 5 deep seated lesions were radiofrequency ablated. A total of 44 liver lesions were treated and no disease was left at the post-operative ultrasound scan.

The patient made a remarkable recovery and was able to return home 5 days after the surgery with long-term octreotide treatment. Follow-up scans were scheduled bi-annually in the first 24 months post-operation and every 9-12 months thereafter. The histopathology showed a well differentiated grade 1 (Ki-67 immunostaining showed less than 1% staining) neuroendocrine tumour of the terminal ileum with multiple mesenteric and liver metastases (T3N1M1).

In the post-operative period, there was a significant reduction in the neuroendocrine tumour markers and improvement in the patient’s symptoms. The patient reported disappearance of episodic facial flushing but did complain of minor diarrhoea with fatty stools. Faecal elastase levels were found to be low (163 µg E1/g stool) indicating mild to moderate exocrine pancreatic insufficiency secondary to long-term octreotide use. This was addressed by an increase in the patient’s pancreatin (Creon) dose.

The patient was advised to remain on long term octreotide in case there were smaller undetected metastases that could not be resected and to relieve any residual functional symptoms of carcinoid syndrome. At 6, 12 and 18 month follow-up, the patient is asymptomatic. Chest, abdomen and pelvic scans remain negative for recurrence and chromogranin A and B levels remain normal at 35 and 72 pmol/L respectively.

DISCUSSION
Surgical resection of SB-NET remains the treatment of choice when possible [8]. The survival rates improve further when the metastatic disease is also removed [9]. The treatment strategy has been outlined by the European Neuroendocrine Tumour Society (ENETS) and is recommended in patients with low morbidity and mortality, including the absence of extra-abdominal metastases, diffuse peritoneal carcinomatosis and right heart insufficiency [10].

In this case, cytoreductive surgery (de-bulking) enabled resection of the primary tumour, liver metastases and lymph nodes. One study showed that aggressive intra-abdominal debulking of such tumours resulted in a median survival of 139 months, compared to 69 months for those who did not undergo debulking [11]. Of those with liver
involvement, liver-directed intervention prolonged survival by 216 months compared to 48 months [11].

Cytoreductive surgery is not without its potential complications; these commonly include post-operative infections, abscess formation, bile leak and hepatic failure. Parenchymal sparing techniques such as ablation, enucleation and wedge resections however offer greater safety and efficacy than other surgical techniques [12].

It is interesting to see that multiple liver lesions were not seen at the CT scan, and even the MRI of the liver underestimated the bulk of liver disease. To our knowledge there is no study directly comparing the utility of CT and MRI in localizing primary NET lesions and distant metastases, but it is appreciated by experts that MRI of the liver gives better information than a CT scan. Multiple studies have compared the usefulness of a variety of imaging modalities (CT, MRI, SRS and PET) all of which showed reasonable sensitivity and specificity in localizing primary lesions and distant metastases [14-20].

In summary, this case has demonstrated the superiority of MRI in detecting liver metastases with the benefit of zero radiation to the patient, and in our opinion is the investigation of choice. It is also important to recognise that NETs are slow growing tumours and do not behave like adenocarcinomas. It is therefore entirely reasonable to be aggressive in the surgical resection for these patients as cytoreductive therapy significantly improves their prognosis

Learning Points
- Neuroendocrine tumours are rare and may present with trivial symptoms
- MRI is superior to CT imaging in detecting NET liver metastases.
- Cytoreductive surgery is effective in managing metastatic disease.

Fig 1: Preoperative CT scan (late arterial phase). No liver lesions seen

Fig 2: Preoperative MRI (STIR sequence): Multiple hyperintense metastases in both lobes of the liver

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