CASE REPORT

NEUROENDOCRINE TUMOUR OF UNKNOWN PRIMARY ORIGIN: UNUSUAL CASE OF METASTATIC HEPATIC FOCI IN A FEMALE PATIENT

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Under the banner of cancers of unknown primary origin (CUPs), neuroendocrine tumours account for less than five percent of the neoplasms. The clinical manifestations and management depend upon the tumour's grade and differentiation and its site of growth. At times, despite of aggressive search for primary origin, cancer remains hidden. Herein, we present a case of a middle-aged woman who presented to our tertiary set-up with complaints of abdominal pain and distension. After a series of radiologic and interventional investigations including positron emission tomography with liver biopsy and immunohistochemical analysis, a diagnosis of the well-differentiated neuroendocrine tumour was made, located in the right lobe of the liver. However, the primary origin could not be identified. The patient was managed with trans-arterial chemoembolization (TACE) followed by hepatic resection and was followed biennially afterwards. In our case, hepatic metastasis was treated with chemoembolization and staged-resection and provided a good prognosis to the patient. Our case is unique as only a few case reports have been published with following presentation and documentation of efficacious treatment is needed to contribute to the literature. Proper trials with exteriorization of bowel and radiological imaging is necessary to stage the primary tumour, even if end result is in vain. This will help to further improve the prognosis.

Keywords: Neuroendocrine tumour; Cancer of unknown aetiology; Metastasis; TACE

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INTRODUCTION

Neuroendocrine tumours are one of the rarest neoplasms that comprise of less than five percent cases of unknown primary cancers with an annual incidence rate of one to two per 100,000 cases. Mostly, it originates from neuroendocrine cells derived from embryologic neural crest cells which are found in various regions of the gastrointestinal tract and respiratory system.[1,2] In 13% of the cases, the primary site of origin of neuroendocrine tumours remains undetectable. Gastric and ileal neuroendocrine tumours commonly metastasize to the liver.[2] However, a diagnostic and therapeutic challenge arises when the primary site remains unidentifiable even after all the necessary investigations are executed. Here, we present a case of a middle-aged female who was diagnosed with a neuroendocrine tumour located in the liver with an unknown primary site. She subsequently underwent TACE and hepatic resection under a multi-disciplinary approach.

CASE PRESENTATION

A 48-year-old female with no known co-morbid, presented to our tertiary set-up with a four-month history of progressive pain and distension of abdomen. Initially, she had mild abdominal discomfort which increased in intensity over a couple of weeks. The pain was non-radiating, constant, dull in nature, localized in the right upper quadrant of the abdomen and had no associated aggravating or relieving factors. She reported several episodes of watery, non-bloody diarrhoea which she attributed to changes in dietary habits. diarrhoea was self-limiting and usually lasted for two to three days; it wasn't relieved with fasting. Her appetite remained unchanged and she did not experience excessive fatigue in the past few months. In fact, all the mentioned symptoms did not hamper activities of her daily living (ADL) and her quality of life remained unaffected. No history of fever, night sweats, weight loss, constipation, melena, nausea or vomiting were reported. Past surgical history comprised of lower segment caesarean section (LSCS) fifteen years back and open cholecystectomy five years ago. Past medical history and family history were non-contributory of any malignancy or familial syndromes.

On admission, the patient appeared to be healthy weighing 152 pounds (lbs). She was alert, oriented to time, place and person. The patient was afebrile and vitally stable. On examination, the abdomen was asymmetric with visible distension of the right quadrant. A non-tender, hard mass was palpated at the lower border of the liver. Percussion note was found to be dull in the distended area while bowel sounds were

normoactive in all four quadrants. No bruit was auscultated in the epigastric region. The patient did not have any clinical signs of ascites. Lymphadenopathy, cyanosis, clubbing or rash could not be appreciated. Respiratory, cardiovascular, nervous and musculoskeletal systems were also normal on physical examination.

Laboratory workup including complete blood count, coagulation profile, electrolytes, glycosylated haemoglobin (HbA1c), serum lipase, serum amylase, liver function tests (LFTs), lipid panel and thyroid function tests were within normal ranges. Serum alpha-fetoprotein (AFP) levels turned out to be 0.58 ng/ml (normal: 0.5–11 ng/mg).

After laboratory workup, ultrasound (US) abdomen was performed which revealed an enlarged liver with multiple cystic areas in the right lobe of the liver with no changes in echogenicity of pancreatic parenchyma. Triphasic Computed tomography (CT-scan) of abdomen and pelvis demonstrated enlarged liver with evidence of large, ill-defined heterogeneous mass, about 22.4×15 cm in measurement, with pan-segmental involvement of right lobe of the liver. Multiple areas of low densities and septations likely representing internal necrosis were also observed within the mass (Figure-1).

A provisional diagnosis of multi-cystic fibrolamellar hepatocellular carcinoma (HCC) was made. However, the indicative picture of neoplastic lesion necessitated ultrasound-guided hepatic biopsy. Microscopic study exhibited linear cores of neoplastic lesions arranged in nests and pseudo glandular structures lined by columnar to cuboidal cells. These cells showed a moderate amount of eosinophilic cytoplasm. Nuclei were mildly pleomorphic and hyperchromatic with finely dispersed (salt and pepper) chromatin on a background of the fibrotic stroma. Immunohistochemical (IHC) analysis showed positive staining for Chromogranin A, Synaptophysin, Cytokeratin AE1/AE3, Cytokeratin 7, alpha-methyl acyl-CoA racemase (AMACR) and Caudal type homeobox-2 (CDX2). IHC was negative for Glypican-3, hepatocyte paraffin-1 (Hep Par-1), Thyroid transcription factor-1 (TTF-1) and Prostatic serum antigen (PSA). The proliferative index (Ki 67) was also noted to be less than 2% denoting low grade of neoplasm. Urinary 5-hydroxy indole acetic acid (5-HIAA) was 12.2 mg/24 hour (Normal: 2–7 mg/24 hours). Henceforth, a final diagnosis of metastatic well-differentiated, low grade neuroendocrine tumour was concluded upon.

Before devising a treatment plan, several investigations were pursued to detect the primary origin of the tumour. Large bowel was investigated by means of colonoscopy which yielded insignificant results. Subsequently, the patient underwent combined positron emission tomography-computed tomography (PET/CT) scan. Contrast images were obtained from skull to mid-thigh after 70 minutes of intravenous administration of 4.06 mCi Gallium-68-DOTATATE (Figure-2 and 3). The bulky right-lobed liver mass showed heterogeneous enhancement with patchy areas of radiotracer activity and photopenia. No radiotracer-avid lymph nodes were visualized in neck, chest, abdomen or pelvis. No radiotracer-avid focal lesions were detected in the spleen or lungs. Hence, the primary origin of the corresponding hepatic metastatic lesion remained a mystery.

A multidisciplinary team of surgeons, radiologists, gastroenterologists, and medical oncologists met to review the case and the first step of diagnostic laparoscopic exploration of abdomen and pelvis was undertaken. The bowel was carefully visualized for any serosal dimpling and later, palpated and exteriorized cautiously to rule out any possibility of multiple foci. However, none of these measures resulted in any significant finding. Therefore, given the uni-lobar extensive involvement of the liver, it was decided to perform trans arterial chemoembolization (TACE) of the right hepatic artery.

After a 6-week interval, CT scan of the abdomen was repeated which showed a significant reduction in tumour size and adequate hypertrophy of left hepatic lobe. Repeated LFTs were also within normal ranges, ruling out the possibility of postembolization syndrome. Ultimately, a right hepatic lobe resection was performed. The patient was observed meticulously for two weeks in the intensive care unit and was discharged shortly thereafter. She had a follow-up after six months in which she did not report any active complaints and a CT scan performed was also unremarkable.

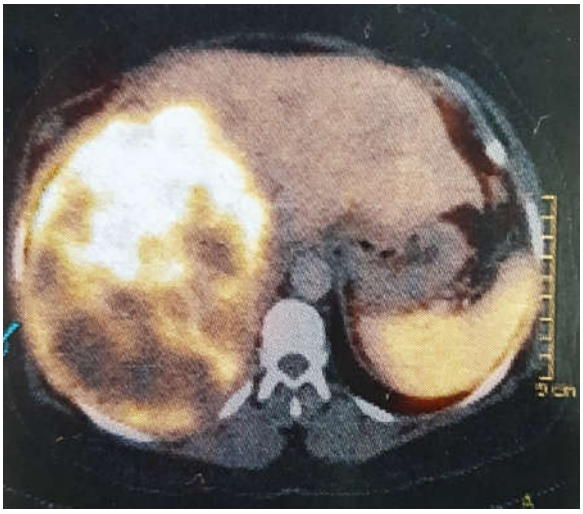

Figure-1: Whole body low-dose computed tomography (CT) showing 22.4 cm × 15cm mass with multiple septations and areas of low densities

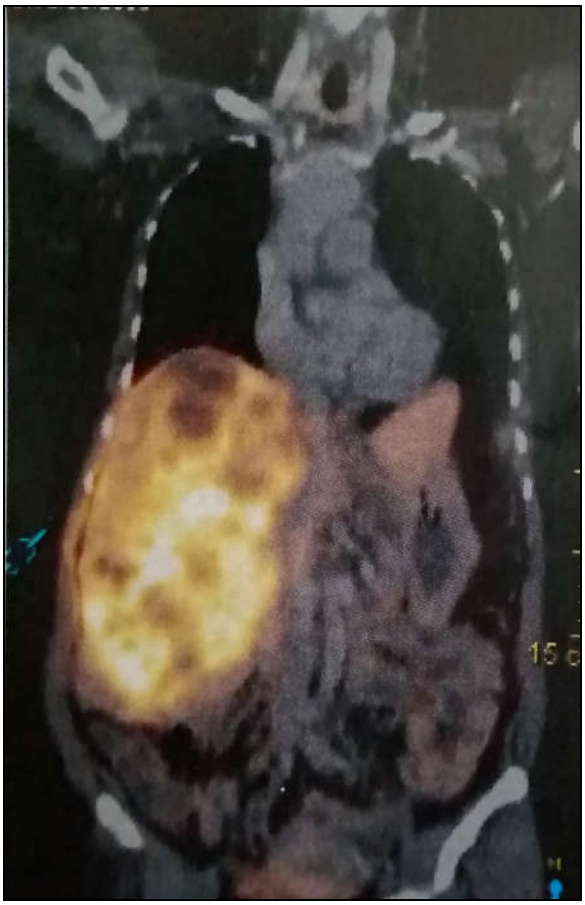

Figure-2: Coronal view of positron emission tomography (PET) showing heterogeneous enhancement of right bulky lobe of liver with patchy areas of radio-tracer activity and photopenia

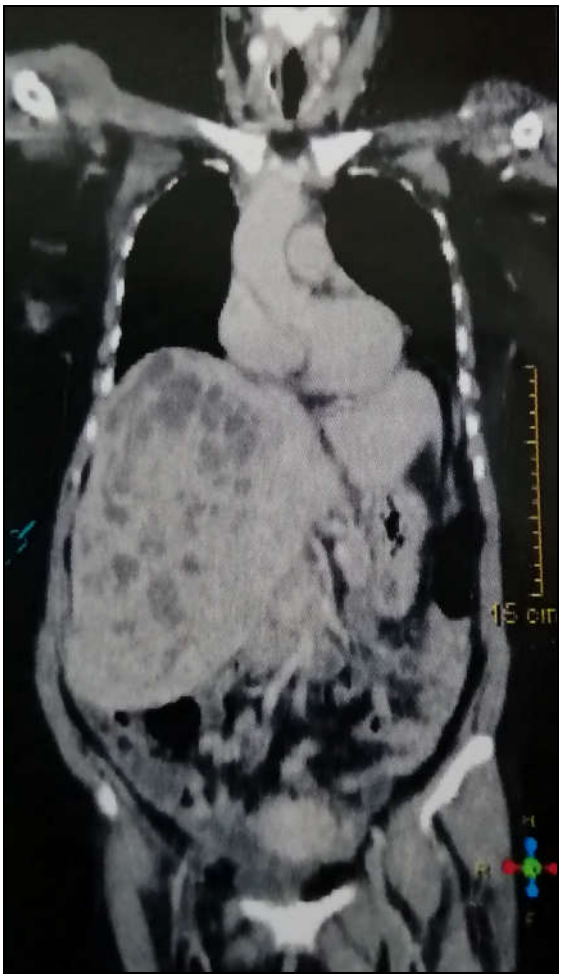

Figure-3: Axial view of computed tomography (CT) of abdomen showing enlarged right lobar mass with variable radio-tracer uptake in liver

Table-1: Utilizing immunohistochemistry (IHC) to target underlying primary source of neuroendocrine tumour

Key Markers	Primary origin sites (In descending order of frequency)
Caudal type Homeobox 2 (CDX2)	Colon, Rectum, Appendix, Duodenal, Gastric, Ovary
Thyroid Transcription Factor-1 (TTF-1)	Lung, Thyroid
Paired Box Gene 8 (PAX8)	Pancreas, Duodenum, Rectum
Insulin Gene Enhancer Binding Protein Isl-1 (Islet 1)	Pancreas, Extra-pancreatic poorly differentiated neuroendocrine carcinoma
Cytokeratin 20 (CK 20)	Intestine, Pancreas (poorly differentiated)
Cytokeratin 7 (CK 7)	Lung, Ileum, Pancreas (well differentiated)
Neuroendocrine Secretory Protein 55 (NESP55)	Pancreas, Adrenal Gland, Ileum
Pancreatic and Duodenal Homeobox 1 (PDX1)	Pancreas, Duodenum (conflicted primaries)
Progesterone Receptor (PR)	Pancreas
Prostatic Acid Phosphatase (PrAP)	Rectum, Jejunum, Ileum (well differentiated)
S-100 Protein	Appendix (well differentiated)
Vesicular Monoamine Transporter 2 (VMAT2)	Stomach

DISCUSSION

Cancer of unknown primary origin (CUPs) is a term that creates a nuisance when brought up in surgical or medical grounds. It accounts for five percent of invasive carcinomas, and neuroendocrine tumours specifically account for less than five percent of all CUPs.[1] Neuroendocrine tumours (NETs) have always been an uncommon entity amongst cancers and they mostly originate from the gastrointestinal system, lungs, and pancreas. The rarity of Neuroendocrine tumour (NET) can be assumed by its annual incidence of around one in 2,100,000. 70% of the total primary sites of NET

involve the gastrointestinal system. In approximately 13% percent of the diagnosed NETs, the primary source cannot be identified.[2,3]

NETs are classified broadly into two categories based on tumour grade and differentiation, which itself is based on mitotic index and Ki-67 protein expression (indices of proliferation). Ki-67 is a nuclear-associated antigen which reflects cellular proliferation. NETs can either be well-differentiated NETs (WDNETs) or poorly differentiated carcinomas (PDNECs). The World Health Organization (WHO) 2010 classification system divides NETs into a low grade (Ki67 of below three percent) and intermediate grade (Ki67 of around three to twenty percent), and poorly differentiated neuroendocrine carcinomas (Ki-67 of above twenty percent). Poorly differentiated carcinomas (PDNECs) have a histologic appearance resembling that of small cell lung cancer. Although, usually, morphologic features of neuroendocrine tumours cannot be appreciated.[4,5]

Classification of neuroendocrine tumours and localization of primary origin is extremely important due to the disparity in prognosis and treatment of both the variants. Poorly differentiated carcinoma (PDNEC) are usually biologically inert, while well-differentiated tumours (WDNETs) can present with clinically significant symptoms due to the associated release of bioactive amines.[4,5] Most of the NETs with unknown primary origin are well-differentiated histologically. Such NETs present initially as liver metastasis.[6]

An important caveat in localizing primary sites is the utilization of immunohistochemistry and molecular cancer classifier assay (MCCA) on the biopsied tissue; though it should be noted that none of the immunohistochemical stains are fully specific for a primary site (Table-1).

However, MCCA with 92 gene panel can help in specifying tumour's origin with utmost accuracy because of overlapping genetic patterns but even with this, a specific diagnosis cannot be coined in most cases.[3,7]

Besides immunohistochemical staining of the biopsied metastatic tissue, radiologic studies play a pivotal role in localizing primary sources. Computed tomography (CT) of chest, abdomen, and pelvis with endoscopic ultrasound for pancreatic masses should be done to identify the primary location. CT abdomen may show mesenteric masses with peculiar central/coarse calcifications which usually indicate a small intestinal neuroendocrine tumour. This tumour itself cannot be appreciated due to its small size, submucosal origin, and multifocal nature. Fibrosis along the superior mesenteric artery (SMA) also suggests the involvement of small bowel. Somatostatin receptor imaging can be used to locate around 80% of the well-differentiated NETs of unknown primaries (including pancreatic NETs and gastrointestinal NETs) owing to the high concentration of somatostatin receptors in these tumours. Such tumours can be located by utilization of positron emission tomography (PET) with somatostatin receptor-targeting radiotracer like 68-Ga DOTATATE PET/CT scan (DOTA-0-Tyr3-Octreotate scan).[8,9] DOTATATE scan is preferred over conventional 111-Indium pentetreotide (Octreotide Scan) for the detection of small tumours.[10] Contrarily, Fluorodeoxyglucose (FDG)-PET scanning is a sensitive imaging modality capable of detecting the high metabolic rate of poorly differentiated NECs.[11]

As mentioned earlier, owing to the small size and multifocal nature of NETs, preoperative evaluation often goes in vain. It is, however, crucial to locate the primary source before initiating therapy as most of the treatment protocol depends on the grade and categorical division of tumour. Diagnostic laparoscopy should be done to rule out extensive peritoneal involvement and to localize small-intestinal NETs, which typically can be identified by observing dimpling of serosa. A hand-access port or a wound retractor can then be used to exteriorize the bowel for detection of the underlying tumour. Similarly, jejunum and ileum are carefully palpated to rule-out multifocal primaries. Exteriorization also aids in the dissection of associated enlarged and calcified mesenteric glands which cause loco-regional obstruction of the gut in around one-third of the patients.[6,9]

Well-differentiated NETs with increased uptake on somatostatin receptor imaging can be targeted with long-acting somatostatin analogues such as octreotide or lanreotide. Patients with active biological amines in their system may present with carcinoid syndrome features, and these somatostatin analogues will help in both curbing tumour growth and reducing symptoms. Everolimus has also been studied in RADIANT-4 trial which concluded that it shows improvement in progression-free survival (PFS) of lung and gastrointestinal NETs.[9,12] Another modality named Peptide Receptor Radiation Therapy (PRRT) has also been devised and has shown improved PFS in somatostatin positive low and high-grade WDNETs. It utilizes Lutetium (Lu-177) dotatate analog.[13] On the other hand, poorly differentiated tumours do not need an aggressive search for primaries and are mainly targeted with chemotherapy containing platinum agents: carboplatin or cisplatin with or without etoposide as an adjunct.[9]

As discussed earlier, WDNETs can present with the hepatic predominant disease. In such cases, liver-directed therapies like orthotopic liver transplant, hepatic resection, ablation, and hepatic artery chemo and radio-embolization should be considered. Hepatic artery embolization is usually done for nonresectable, hepatic-predominant disease. This can be achieved by

both radio and chemo-embolization utilizing doxorubicin-loaded poly-vinyl or superabsorbent microspheres.[14]

Based on the tumour's morphology and functional imaging, uni-lobar (limited) hepatic disease may be treated with surgical resection. Radiofrequency ablation (RFA) or trans-arterial chemoembolization (TACE) can also be performed if surgery is contraindicated. Bi-lobar (complex pattern) involvement of the liver can be approached with RFA followed by staged resection, commonly known as debulking surgery. Diffuse pattern of liver involvement is also treated through TACE or by trans-arterial embolization (TAE) with concomitant use of chemoradiation therapy.[15]

CONCLUSION

The presented case is unique as there are only few cases documented in literature indicating unknown primary origin of hepatic metastatic neuroendocrine tumour. Treatment of isolated metastatic disease should be tailored by the multi-disciplinary team according to the individual presentation of the patient with unknown primary disease. A massive metastatic uni-lobar involvement of the liver can be treated with staged embolization and resection to increase progression-free interval. All effort should be utilized in bowel exteriorization and imaging to locate the primary cancer. Even if surgeon is unable to locate tumour, improved progression free interval can be expected with timely management of metastasis and regular follow-up with imaging.

AUTHORS' CONTRIBUTION

AAK: Main participant in patient care, history part with conclusion. SHBW: Main participant in patient care Discussion. OM: Main participant in patient care, Abstract, Picture, graphic design. ME: Drafting and grammar check, introduction, picture graphic design. SJ: Drafting and grammar check, conclusion and references.

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