MINI REVIEW

Merkel Cell Carcinoma with Solitary Pancreatic Metastases Resembling Primary Neuroendocrine Tumor of the Pancreas

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ABSTRACT

Merkel Cell Carcinoma (MCC) is a rare but highly malignant skin tumor of neuroendocrine origin. MCC is a highly metastatic cancer with a very fast rate of progression. Its metastatic sites usually include the regional para-aortic lymph nodes, the liver, the bones, and the lungs. Metastases to the pancreas are exceptionally rare more so with solitary metastasis. This causes diagnostic dilemmas; with frequent misinterpretation as primary Pancreatic Neuroendocrine Tumors (pNETs), especially Poorly Differentiated Neuroendocrine Carcinomas (PNECs). It is most important to accurately distinguish MCC metastases from pNETs because of differences in treatment and outcome. Of the two, the morphology is fairly similar in imaging and initially in the histopathological examinations where they both appear to be pancreatic neuroendocrine tumors.

Keywords: Soft tissue masses; Cutaneous masses; Cutaneous tumors; Cutaneous metastases; Neuroendocrine tumor; Pancreatic neuroendocrine tumor; Merkel cell carcinoma

INTRODUCTION

An extensive literature review using PubMed and Google Scholar databases was done. In total, evidence involving 45 cases of pancreatic metastases from MCC was reviewed. Among them, 22 cases of isolated pancreatic metastases were analyzed [1-3]. This mini review aims to discuss the difficulties in diagnosis and treatment plans for MCC that has solitary metastasis to the pancreas compared to pNETs through a narration of the literature review. Solitary pancreatic metastases of MCC seemed more frequent in the older population (60-80 years), predominantly males (68.19%). Most of them with history of MCC of skin. The median time from initial MCC diagnosis to pancreatic metastasis was about two years in 62% of patients.

Symptoms included abdominal pain (26.08%), jaundice (17.39%), nausea/vomiting (4.34%), and dyspepsia (4.34%). However, most were asymptomatic (47.82%) [3]. Symptoms are generally vague, secondary to surrounding area invasion, and indistinguishable from symptoms of pNETs. The most common imaging modality used to identify pancreatic metastases was Computed Tomography (CT) scan (72.72%) followed by Positron Emission Tomography (PET)-CT (18.18%), Magnetic Resonance Imaging (MRI) (4.54%), and ultrasound (4.54%) [3]. However, these do not help distinguish pancreatic metastases of MCC from primary pNETs regarding their origin. Fine Needle Aspiration Cytology (FNAC) may raise a suspicion of a neuroendocrine tumor but the definitive diagnosis is hence done through Immunohistochemistry (IHC) [4].

The staining pattern plays a major role in correctly distinguishing MCC from primary pNETs and ensuring correct clinical management. MCC is unique in the sense it exhibits characteristics of both neuroendocrine and epithelial features. Positive epithelial markers include AE1/AE3, epithelial membrane antigens, Ber-EP4, pancytokeratin, Cytokeratin (CK) 20, oncoprotein Huntingtin-Interacting Protein 1 (HIP1), tumor Protein 63 (p63), and CAM 5.2. Occasionally CK8, CK18, and CK19 may be positive [5-8]. Neuroendocrine markers demonstrated by MCC include neuron-specific enolase, Neurofilaments (NF), synaptophysin, CD56, chromogranin, bombesin, somatostatin, Vasoactive Intestinal Peptide (VIP), proconvertases PC1/ PC3, PC2.7 and BCL-2 oncoprotein while being negative for CD45, mammalian Achaete-Scute Homolog 1 (ASH1), vimentin and S100 [9-14]. Sometimes, CD117, CD99, and Terminal Deoxynucleotidyl Transferase (TdT) can also be positive [4-7]. PNECs are positive for chromogranin, synaptophysin, keratin, and CD171 and negative for BCL2 and CK20 [15]. The most sensitive (89%-100%) and specific marker for distinguishing MCC and pNET is Cytokeratin (CK) 20, which is characterized by a paranuclear dot-like positivity [16,17]. Special AT-rich Sequence Binding Protein-2 (SATB2) which

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helps to distinguish the original site of a metastatic neuroendocrine tumor, is positive in MCC, but negative in pNETs [18,19].

Differentiating between MCC with isolated pancreatic metastasis and pNETs is important because the treatment is different. In general, chemotherapy has a high response rate but is not durable in the treatment of advanced MCC cases, while immunotherapy has a durable and meaningful response and survival [20-23]. As seen in the JAVELIN Merkel 200 clinical trial avelumab showed a clinically significant and sustained objective response rate of 33% in patients with previously treated metastatic MCC [20]. Median overall survival was 12.6 months, with 3-year, 4-year, and 5-year survival rates of 32%, 30%, and 26%, respectively. Similar reports showed positive results with pembrolizumab and nivolumab [4, 20-24]. Recently it was published that tumor cell-intrinsic Programmed Cell Death (PD)-1 promotes MCC growth by activating downstream mTOR-mitochondrial Reactive Oxygen Species (ROS) signaling [25]. This brings out opportunities to combine mTOR inhibitors with PD-1 inhibitors. Pazopanib, cabozantinib (inhibitors of multiple receptor tyrosine kinases VEGFR-1, 2 and 3 and C-kit), imatinib, somatostatin analogs, ALT803 (a super antagonist of IL-15) and bevacizumab have also been tried [26-30]. Antibody Drug Conjugate (ADC) Admitter targeting CD56 and Rovalpituzumab targeting notch ligand DLL3 may also have potential therapeutic benefits [31,32]. BI 746532, a DLL3 targeting T cell engager, was also found to have promising results in neuroendocrine carcinoma [33].

B7H3-ADC was proven to be effective in Neuroendocrine (NE) prostate cancer models, especially with Retinoblastoma 1 (RB1) deficiency and/or high replication stress. This supports the proposition that B7H3-ADC has the potential for the treatment of other NE tumors including MCC that are resistant to conventional therapies [34]. DLK1, another notch ligand expressed in various Neuroendocrine Tumors (NETs), treated with ADC, specifically ADCT-701, exposed remarkable *in-vivo* anti-tumor activity in Adrenocortical Carcinoma (ACC) models that displayed tumor regression and prolonged survival. It is also worth mentioning the currently planned phase I clinical trial of ADCT-701 for the treatment of NETs (NCT06041516) [35]. LBL-024, a bispecific antibody against PD-L1 and 4-1BB has shown promising efficacy for extrapulmonary neuroendocrine carcinoma [36]. These ongoing researches can be a milestone in MCC treatment as well.

In pNETs, surgical resection followed by long-acting somatostatin analog therapies is used as first-line treatment. Peptide Receptor Radionuclide Therapy (PRRT) with radiolabeled somatostatin analogs is used as second/third-line treatment for somatostatin receptor-positive well-differentiated neuroendocrine neoplasms [37]. Chemotherapy is recommended for poorly differentiated carcinomas. Patients with pNEC ki67>55% had a response rate of 42%-67% on cisplatin/etoposide while patients with ki67<55% were less responsive to platinum-based chemotherapy. Rather, other agents like temozolomide were found to be more effective [38-40].

The mean time between diagnosis of pancreatic metastases and death was 6.3 months, ranging from<1 to 24 months. According to the Surveillance, Epidemiology and End Results (SEER) database (2012 to 2018), the relative 5-year survival rate for metastatic MCC was found to be 24% [41]. Patients with advanced PNEC have a life expectancy of less than one year [42]. According to the study, 76.74% died from the disease and the average survival was 11 months (range 0-104). 2-5 years' survival rates were 22.5% and 16.1% [15]. Early identification at a preliminary stage is of utmost importance to enhance the chances of improved treatment.

CONCLUSION

Solitary pancreatic metastases from Merkel Cell Carcinoma (MCC) pose significant challenges in diagnosis and treatment, as they are rare occurrences that can result in high levels of clinical morbidity and mortality. This is due to their similarity to Pancreatic Neuroendocrine Tumors (pNETs). It is important for clinicians to differentiate between MCC with a solitary pancreatic metastasis and primary pNET, as the primary treatment for MCC is immunotherapy. Clinicians should always consider the possibility of MCC in patients presenting with a pancreatic mass, especially those with a history of cutaneous neuroendocrine tumors like MCC. Molecular typing through immunohistochemistry, particularly CK20, is vital in distinguishing between these two closely related entities. Antibody Drug Conjugate (ADC) Admitter targeting CD56 and Rovalpituzumab targeting notch ligand DLL3 and bispecific antibody against PD-L1 and 4-1BB have shown potential efficacy for neuroendocrine carcinoma.

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