Metastatic Insulinoma: A Case of Conversion from a Non-Functional Neuroendocrine Tumor

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Introduction

Pancreatic neuroendocrine tumors are a subset of Neuroendocrine tumors (NET) that mainly originate from the neuroendocrine system. They account for less than 10% of total NETs and have a general incidence of 0.5 per 100,000 persons per year [1]. Only 10 to 30% of these tumors are hormone-secreting, with the majority being insulinomas. The tumors are often found incidentally in the pancreas or GI system on imaging. Pathological specimens are generally positive for Chromogranin A and Synaptophysin but can additionally be positive for other serum markers such as Insulin, Gastrin, and VIP, depending on the subtype of NET [2]. General management includes surgery for localized disease and surgery/chemotherapy in combination for extensive disease. Prognosis is poor for those with liver metastases, with an overall mortality rate greater than $> 80\%$. Functional tumors are generally localized and rarely present as metastatic disease [3].

Among functional NETs, Insulinomas are the most common. Incidence is around 1 to 3 cases per million and is usually present in the pancreas over 99% of the time [4]. Diagnosis is established with symptomatic hypoglycemia in the setting of elevated insulin and c-peptide levels after a 72-hour fasting test. Blood glucose levels usually improve with Glucagon or Dextrose administration. These lesions are amenable to treatments such as alcohol ablation, radiofrequency ablation, embolization, or surgical resection. Surgical resection is the preferred option for isolated lesions as it is often curative [5]. Symptomatic management of hypoglycemia involves dextrose administration and Diazoxide. Diazoxide inhibits the release of insulin from insulinoma cells and is often the only effective measure prior to surgery [6]. Somatostatin analogs such as octreotide are also used in combination with diazoxide in more severe cases but can lead to episodes of hypoglycemia [7]. Cases involving surgical management have a good prognosis [6,7].

Malignant insulinomas only account for about 5% of all insulinomas at presentation [8,9]. In patients with distant metastases, surgical resection with lymph node dissection improves prognosis. However, the overall difference is minimal, and the data is limited in these cases [10]. Overall, these patients do quite poorly due to limited treatment options. There are very few case reports that discuss the conversion of non-functional metastatic NET into a malignant insulinoma. This case report presents such a conversion in an elderly female patient.

Case Presentation

Our case involves a 73-year-old woman with a prior medical history of Diabetes Mellitus type 2 and a recent diagnosis of non-hormone-secreting high-grade pancreatic neuroendocrine tumor with metastases to the liver, who presented for admission for bilateral pulmonary embolism. Pancreatic neuroendocrine tumor had been diagnosed from liver biopsy specimens showing positivity for Synaptophysin and Chromogranin. The pathology images are shown in Figure 1A and 1B.

<Insert Figures 1A and 1B>

The patient's only complaints were generalized weakness, and she denied any respiratory complaints upon presentation. The patient was previously diabetic as well and was on a home regimen of Tresiba insulin 20 units daily and Metformin 1000mg twice daily. She had taken both medications the day before the presentation, and neither was restarted on admission as the patient's blood glucose was near normal. Physical examination findings were unremarkable, including a normal oxygen saturation on room air. Laboratory findings revealed significant hypoglycemia with a blood glucose of 48. The patient was started on IV Dextrose 5% with normal saline at 125ml/hr and IV heparin infusion at 18 units/kg/hr and was subsequently admitted for further management. Of note, the patient's pancreatic tumor prior to presentation was 2.7cm in size and was a Grade 3 tumor with a Ki-67 proliferative index of 40%. Figures 2 and 3 demonstrate the initial pancreatic mass with liver metastases on imaging. She was stage IV at this point in time based on the scoring of T2, N1, M1a using the WHO guidelines.

<Insert Figures 2 and 3>

The patient continued to have persistent hypoglycemia over the next few days and was subsequently started on dextrose 10% with free water at 80 ml/hr. The patient's appetite was also poor, contributing to her hypoglycemia episodes. On hospital day 4, the patient had a syncopal episode due to a blood glucose level of 30. This improved with the administration of two dextrose 50 ampoules. Endocrinology workup was initiated, and the patient was started on a 72-hour fasting test. Plasma glucose was 130mg/dL at the start of the test (normal is >70mg/dL). The patient made it to only 2 hours of fasting before becoming symptomatic. Blood glucose reached 53 mg/dL at that time, and the decision was made to discontinue the test. Blood work done at that time revealed elevated c-peptide levels of 7.0 ng/ml (normal range is 1.1 to 4.4 ng/ml) and an insulin level of 136 μU/ml (normal range is 2 to 25 μU/ml). The patient was confirmed to have had a conversion of her high-grade neuroendocrine tumor from non-hormone-secreting to an insulinoma. On hospital day 5, the patient was started on an octreotide injection of 100 mg thrice daily by the consulting endocrinologist. She was also started on Dexamethasone 2mg twice daily. Despite these interventions, the patient continued to have frequent episodes of hypoglycemia. Her oral caloric intake had improved during this time and did not significantly contribute to hypoglycemia. At this point, the first line treatment for insulin-related hypoglycemia, Diazoxide, was considered by the treatment team. On hospital day 7, the patient was started on diazoxide 50mg every 8 hours. Her blood sugar continued to fluctuate after this treatment, and she remained on a Dextrose 10% infusion. Her Dexamethasone was switched to oral prednisone 40 mg daily. On this regimen, the patient's blood glucose levels did improve. She was weaned from Dextrose 10% infusion with further episodes of significant hypoglycemia. She was discharged home on hospital day 10 with a regimen of prednisone 40 mg daily and diazoxide 75 mg at night. The patient was also started on FOLFOX chemotherapy prior to discharge. The entire timeline of our case is shown in Figure 4.

<Insert Figure 4>

The patient did establish outpatient follow-up with oncology and endocrinology. The patient was hospitalized multiple times for recurrent hypoglycemia. After these episodes, she was also maintained on Octreotide as an outpatient. Alternative treatment options such as Everolimus and Sunitinib were discussed with the patient and family, including their risks and benefits. The patient and family declined these interventions. On repeat staging imaging, the patient was noted to have a spinal lesion at T12. This was biopsied and positive for synaptophysin and chromogranin, confirming the further spread of the neuroendocrine tumor. Ki-67 proliferative index was greater than 50%, indicating a grade 3 tumor as well.

The patient continued to do poorly overall. She declined palliative chemotherapy and was eventually placed

in hospice care. The patient was discharged home and passed away a few weeks later.

Discussion

A literature review reveals a limited number of case reports that describe the conversion of a non-functional NET into a functional one. Multiple case series estimate the rate of conversion to be between 3.4% and 6.8%, but this date is mostly observational [11,12]. The mechanism behind this conversion remains unclear, although some studies have shown secondary conversion post-therapy with sunitinib or traditional chemotherapy [13,14]. These studies suggest epigenetic conversion of the primary NET, which may occur because of treatment, but the mechanism is not well described. Among the few treatment options for malignant insulinoma are Everolimus and Sunitinib. Everolimus inhibits the MTOR pathway that is a part of insulin-related gluconeogenesis and is effective as an adjunctive therapy in patients who are not a candidate for surgical treatment [15]. Sunitinib is a tyrosine kinase inhibitor that directly inhibits tumor growth, thereby reducing insulin production, but it can sometimes cause paradoxical hypoglycemia on its own [13,16].

Our patient was already diagnosed with metastatic pancreatic NET in the outpatient setting prior to presentation. She had known metastases to the liver and lungs when she was admitted for management of acute pulmonary embolism. This tumor had tested positive for NET tumor markers of synaptophysin and chromogranin on initial evaluation. It is not common for functional testing to occur for tumors unless the patient demonstrates any clinical signs of a functional tumor, which is what this case report describes. While hospitalized, the patient developed symptomatic hypoglycemia with decreased blood glucose levels that improved with glucose administration. These three clinical findings, also known as Whipple's triad [4], strongly raised the suspicion for conversion of the primary pancreatic NET into an insulinoma. Subsequent measurements of fasting insulin and c-peptide levels confirmed this diagnosis. Interestingly, our patient did not receive any treatment prior to conversion and had a much shorter time of conversion than is described in the literature, 3 months vs. a median of 15 months in other reports [11]. Due to her metastatic disease prior to conversion, treatment options remained limited, and our patient's prognosis was poor. She was hospitalized numerous times for insulin-related complications and was not a candidate for any aggressive therapy.

Our case describes one of the few instances of conversion from a non-functional NET into an insulinoma without any prior treatment and over a much shorter time frame. It also describes an aggressive clinical course in these patients due to uncontrolled symptoms related to hypoglycemia and a paucity of treatment options therein. Traditional insulinoma treatments, including surgical resection, could have been utilized, but metastatic disease made this impossible. Newer drugs such as Everolimus and Sunitinib could have been an option for our patient but were not an option as the patient declined these treatments. There may have been some hesitation due to the novelty of these treatments and a lack of strong evidence in their favor.

Conclusion

Our case report involves the conversion of a metastatic non-functional NET into a functional malignant insulinoma. The key clinical points from this case report are as follows: 1) When a non-functional neuroendocrine tumor converts into a functional one, the prognosis worsens significantly. 2) Alternative treatments beyond conventional chemotherapy are required for patients with aggressive insulinomas. 3) More research is required to evaluate treatments such as Everolimus and Sunitinib for their use in cases of malignant insulinomas.

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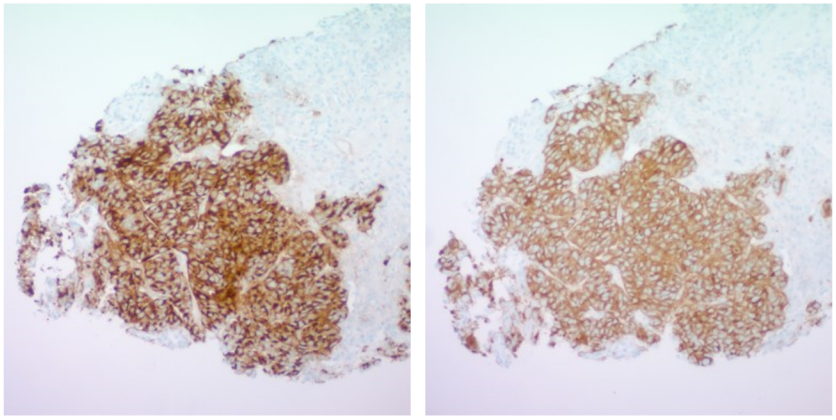

Figure 1A and 1B: Liver tissue specimen showing positive staining for Chromogranin and Synaptophysin

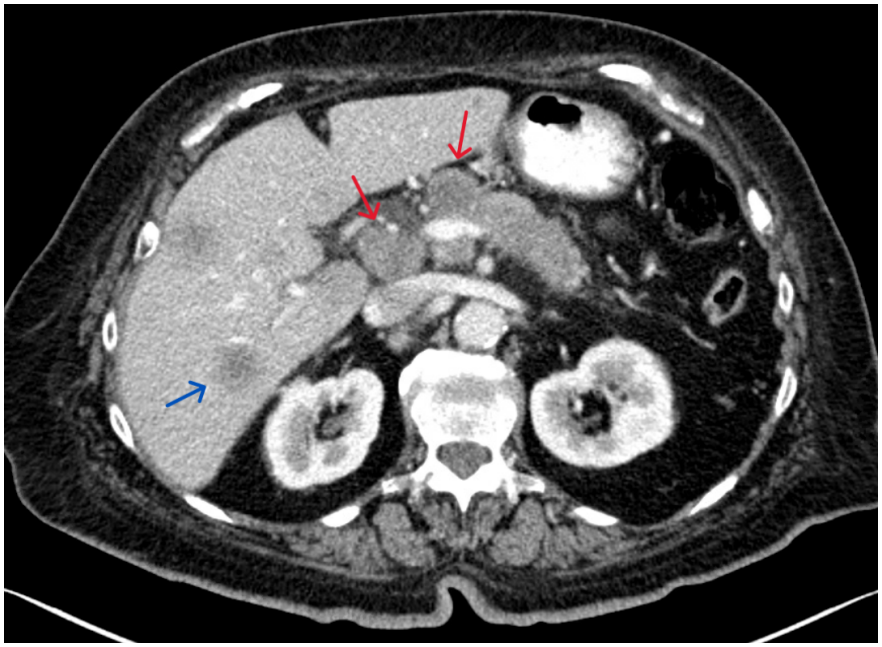

Figure 2: Axial post contrast CT image demonstrates the heterogeneously enhancing mass in the pancreatic head and proximal body (red arrows), compatible with the known primary neuroendocrine tumor. Incidentally, hepatic metastases are also partially seen (blue arrow).

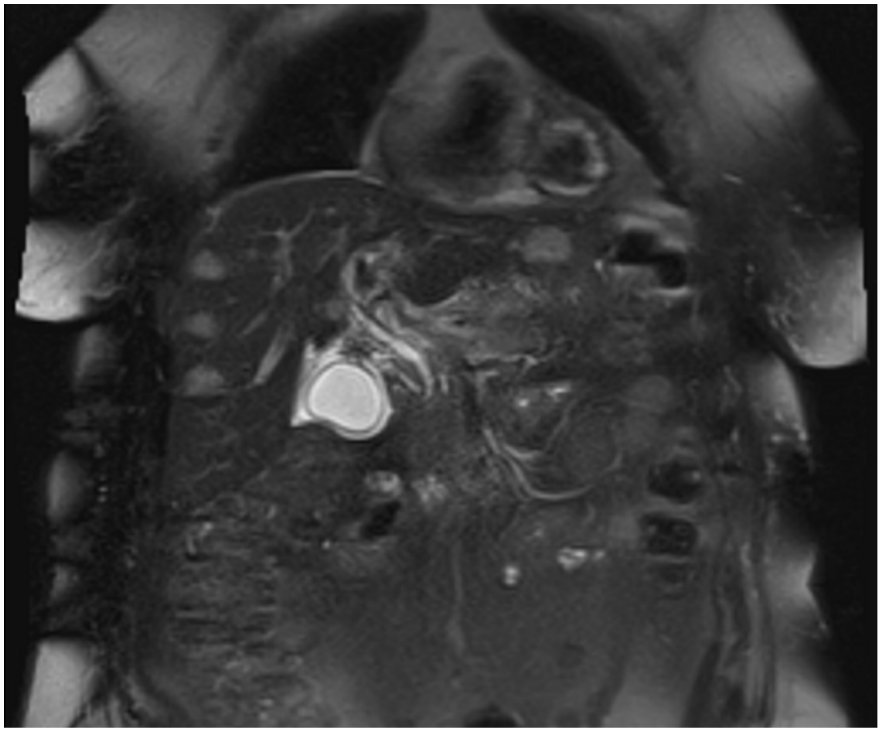

Figure 3: Coronal T2 weighted image of the abdomen demonstrates a cystic lesion in the pancreatic head, corresponding to the patient's known pancreatic neuroendocrine tumor. Also seen are faintly T2WI hyperintense right hepatic lobe lesions, in keeping with the widely metastatic disease

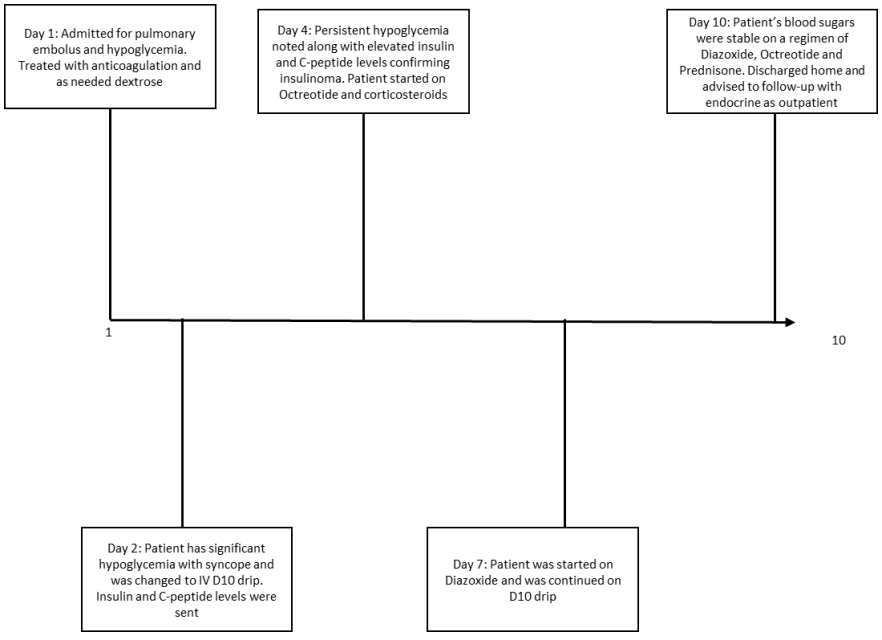

Figure 4: A timeline of our case presentation