



# Mixed Neuroendocrine-Non Neuroendocrine Neoplasm of the Pancreas with a Pulmonary Metastasizing Pattern: A Case Report

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## Abstract

**Background:** Malignant pancreatic tumors usually present exocrine or endocrine differentiation, with pancreatic ductal adenocarcinoma making up for 90% of pancreatic malignancies. In contrast, both acinar cell carcinomas and neuroendocrine tumors only make up for about 2% to 5% in pancreatic neoplasms. Mixed Acinar Neuroendocrine Carcinoma (MANEC) of the pancreas is extremely rare and only a few cases have been reported so far. The diagnosis is correlated with a poor prognosis and short overall-survival rate. We herein describe a case of such a carcinoma with multiple pulmonary metastases.

**Case Presentation:** In 2011, a 28-year-old male patient presented with abdominal pain and ikterus in a local hospital. Physical examination and imaging revealed a pancreatic mass and multiple suspiciously enlarged locoregional lymph nodes. Biopsy confirmed a mixed acinar-neuroendocrine carcinoma of the pancreas, previously termed as MANEC and now, recently established by the World Health Organization (WHO), as Neuroendocrine-Non Neuroendocrine Neoplasm (MiNEN). He underwent neoadjuvant chemotherapy (1<sup>st</sup> line: Oxaliplatin/Streptozocin/5-Fluorouracil; 2<sup>nd</sup> line: Cisplatin/Etoposid) before an extended total pancreatectomy and lymph node resection was performed, followed by adjuvant chemotherapy (Cisplatin/Gemcitabine). The patient was declared tumor-free in consecutive follow-ups until 2014. After subsequent discovery of multiple and bilateral pulmonary nodules, sequential metastasectomies were performed in 2014 and 2017 with all tissue containing metastases of the mixed acinar-endocrine pancreatic carcinoma. Since then the patient has been recurrence-free.

**Conclusion:** To our knowledge this the first report of a metastatic MiNEN tumor of the pancreas in a very young patient with long-term survival. The tumor was treated with a multidisciplinary approach, combining surgery and neoadjuvant as well as adjuvant chemotherapy. So far no consensus exists regarding treatment of MiNENs and how outcome can be influenced most favorably. Survival for more than 7 years after initial diagnosis seems exceptional, still the pathological and immunological dynamics are not fully understood and response to treatment as well as prognosis appear to remain unpredictable.

## Background

Mixed Acinar-Neuroendocrine Carcinoma (MANEC) is classified by the World Health Organization (WHO) as a tumor consisting of adenocarcinoma as well as at least 30% neuroendocrine carcinoma components [1]. Recently, in 2017 the term was substituted by a new terminology, namely Mixed Neuroendocrine-Non Neuroendocrine Neoplasm (MiNEN) [2]. These tumors are also called composite or collision tumors due to consisting of two different histopathologic components while located in the same organ or anatomic structure [3,4]. They can occur in various organs of the digestive system and are rather uncommon [5]. Cases have been reported for manifestations in the gallbladder, bile duct, stomach, colon and caecum [6-12]. However, MiNEN of the pancreas are extremely rare and as of today only about 20 cases have been reported [3,13]. Due to the low case number, no therapy guidelines have been established concerning the treatment of this entity. Pancreatic malignancies are known to be aggressive in growth and metastasizing patterns, usually

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**Received Date:** 06 Mar 2019

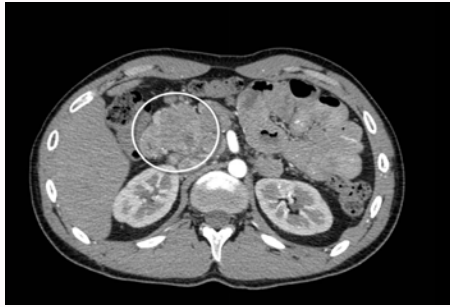
**Accepted Date:** 25 Mar 2019

**Published Date:** 27 Mar 2019

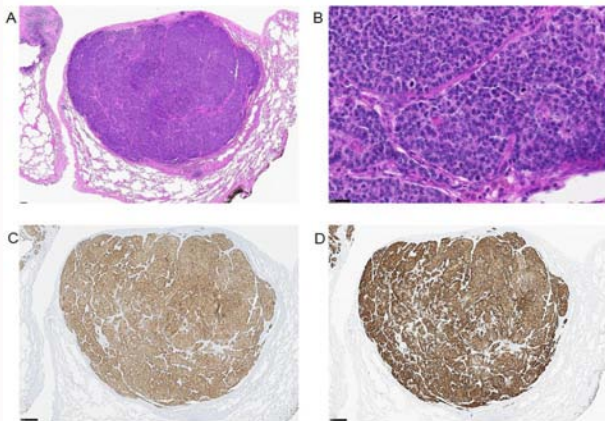
### Citation:

Lettau F, Siebenhüner A, Vrugt B, Weder W. Mixed Neuroendocrine-Non Neuroendocrine Neoplasm of the Pancreas with a Pulmonary Metastasizing Pattern: A Case Report. *Ann Surg Case Rep.* 2019; 2(1): 1011.

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**Figure 1:** Large, heterogenous mass in the head of the pancreas, first discovered in a CT scan in 2011.

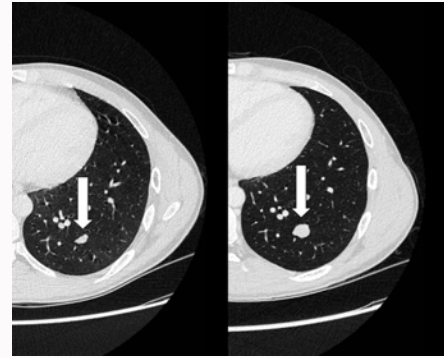


**Figure 2:** Histopathological features of a mixed neuroendocrine-non neuroendocrine neoplasm. A: Haematoxylin and eosin image, 15x; B: Haematoxylin and eosin image, 400x; C: Immunostaining for synaptophysin, 20x; D: Immunostaining for chromogranin-A, 20x.

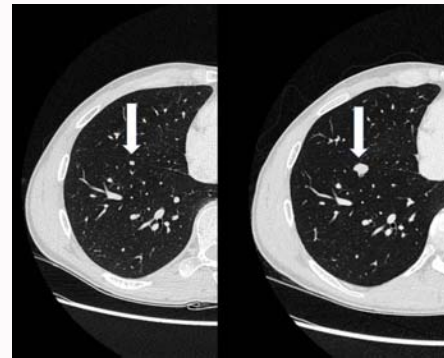
linked with a poor prognosis and short-term survival after diagnosis. MiNEN of the pancreas has so far proven to be no exception, however behaviour of the tumor, treatment strategies and prognosis for patients are unclear [14]. In this report we describe the case of a young, otherwise healthy male with a large MiNEN of the pancreas with metastases to the lymph nodes and the lung who has survived for more than seven years to date.

### Case Presentation

The 28-year-old white male initially presented with symptoms of persistent upper abdominal pain and icterus in January 2011. A CT scan confirmed a large mass located in the head of the pancreas (Figure 1) as well as pathologically enlarged mesenterial and retrocaval lymph nodes. Furthermore, lymph nodes close to the porta hepatis and the hilus of the left kidney were suspiciously enlarged and pulmonary nodes could be discovered, however all of these were found to be metabolically inactive in a PET-CT scan. A biopsy confirmed a malignant tumor with neuroendocrine and acinary marker expression. Immunohistochemistry revealed NSE and Chromogranin A levels were elevated and the diagnosis of a mixed acinar-endocrine carcinoma of the pancreas was subsequently confirmed. The patient was then referred to neoadjuvant chemotherapy with Oxaliplatin/Streptozocin/5-Fluoruracil for two weeks with signs of partial regression. Three weeks later, a second-line-chemotherapy was initiated with Cisplatin/Etoposid for the course of two months which decreased the size of the tumor and its suspected extra-abdominal manifestations. In June 2011 total pancreatectomy,



**Figure 3:** Progression of an exemplary nodule in the lower left lobe (left: CT scan 2015; right: CT scan 2017).

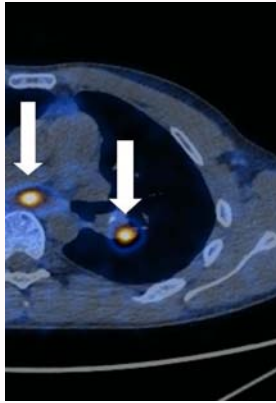


**Figure 4:** Progression of an exemplary nodule in the lower right lobe at the fissura (left: CT scan 2015; right: CT scan 2017).

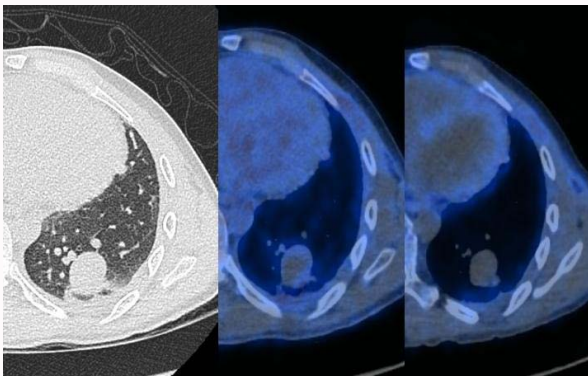
splenectomy, cholecystectomy, resection of the portal vein and extensive lymphadenectomy was successfully performed.

Pathological examination showed a mixed acinar cell neuroendocrine carcinoma with multiple metastases to the locoregional lymph nodes (12/29) and partial infiltration of the portal vein. Immunohistochemistry revealed SSTR2-positivity in 60% of the tumor cells, whereas Ki-67, as indicated via Mib-1-marking, was heterogenous but up to 80% in focal hotspots, thus pointing towards a G3-tumour (Figure 2).

Afterwards the patient received adjuvant radiochemotherapy with 5-Fluoruracil and 25 × 1.8 Gy for four weeks from July to August 2011 and with Gemcitabine and Cisplatin for approximately six weeks from September to November 2011. Follow-up visits confirmed clinical and radiological remission. However, in 2014 progress of the suspected pulmonary metastases was reported. In June 2014 a resection of segment IV, V and VI was performed via thoracotomy on the left lung. All nodules were histopathologically confirmed to be metastases of the mixed acinar-endocrine carcinoma of the pancreas. A CT scan in 08/2015 then revealed a slight progress of two other nodules suspicious for metastases in both lower lobes of the lung as well as a new nodule in the upper left lobe. As none of these showed susceptibility to Dotatate in a PET scan surgery was weighed against active surveillance. By this time, the patient consulted our clinic for the first time. In agreement with the previously treating colleagues we advised an observant approach with regular CT controls. In June 2017, almost two years after initial discovery of slight growth in the previously mentioned pulmonary nodules, a CT scan proved further progression (Figure 3 and 4).

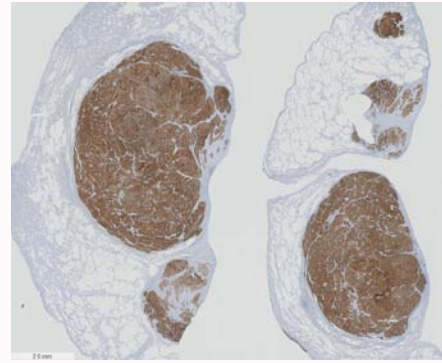


**Figure 5:** Ga-68-Dotatate-PET-CT scan in September 2017 reveals strong activity in mediastinal and focal lymph nodes, highly suspicious for neuroendocrine metastases.



**Figure 6:** Tumorous manifestation in the lower left lobe four weeks postoperatively after resection of pulmonary metastases. Though no signs for FDG-activity were seen the nodule was resected and turned out to be fibrotic without any signs of malignancy.

Additionally, newly Dotatate-susceptible mediastinal lymph nodes were discovered (Figure 5), therefore highly likely to be metastases of neuroendocrine origin. Surgical resection was recommended by an interdisciplinary board and the patient admitted himself to our clinic for further treatment. We decided on sequential surgery, starting on the right side and in August 2017 the patient underwent robotic assisted wedge resection on the lower right lobe and resection of five subcarinal lymph nodes. Both wedges proved to include metastases of the primary MiNEN of the pancreas with partial expression of Somatostatin Receptor 2 (SSTR2) in approximately 60% of the tumor cells. All lymph nodes were tumor free. Prior to surgical intervention on the left side radiation of the central noduli in the left lower lobe was alternatively brought up. Positivity for SSTR2 in the metastases made immunoradiology with Dotatate-radiation a viable option. However, after interdisciplinary treatment planning with oncologists, radiooncologists and endocrinologists surgery on the left lung was advised. In September 2017, we performed resection of the noduli on the left side, two in the left lower lobe, two in the left upper lobe and one interlobar. All were confirmed to be metastases of the pancreas carcinoma while fortunately all four lymph nodes (Level 4, 7 and 8) again showed to be tumor-free. Next Generation Sequencing (NGS) with Oncomine Focus Assay showed no signs of genetic mutation, amplifications or fusions. Four weeks postoperatively FDG- and Dotatate-PET scans showed rapid growth of a nodule in the left lower lobe without any signs of FDG-activity or SSTR2-susceptibility,



**Figure 7:** The resected metastases proved to stain positively for synaptophysin, strongly indicating to stem from the original pancreatic malignancy.

thus previously deemed unsuspecting (Figure 6). Possibility of a haematoma or infection was evaluated. Nevertheless, as another focal metastasis could not be excluded, biopsy was strongly advised and performed in December of that year. Histopathology showed signs of fibrosis and granulomatosis without any malignancy.

As of today the patient has survived seven years after initial diagnosis and without any systemic therapy since November 2011.

**Discussion**

The term MiNEN as an anagram for mixed neuroendocrine-non neuroendocrine neoplasm was recently established by the WHO in 2017 as an update to the classification of neuroendocrine neoplasms in the digestive system [2]. Based on criteria such as mitotic count per high power fields and Ki67-index these tumours are graded as G1 to G3. To classify as MiNEN, the tumour has to contain two different malignant components with neuroendocrine carcinoma cells making up for at least 30% of the tumor. The pancreas itself is composed of exocrine and endocrine cells, therefore possibly more susceptible than other organs for different types of differentiation even in one single neoplasm [15,16]. The most common pancreatic neoplasms are adenocarcinomas, with Acinar Cell Carcinomas (ACC) accounting for only 1% and neuroendocrine carcinoma for about 7% of all pancreatic cancers [13]. It is well-known that ACCs can contain a limited amount of neuroendocrine cells in approximately one third of the cases, thus expressing neuroendocrine markers [15]. However, as both histopathological subtypes are rather uncommon, combined acinar-neuroendocrine malignancies are extremely rare with only around 20 cases reported thus far [3,13]. Therefore, etiology of this kind of malignant tumor as well as pathogenetic behaviour, prognosis and best course of treatment remain unclear. Explanations of origin of MiNENs include embryological pathogenesis as well as the presence of amphicrine cells [16-19].

Pancreatic MiNENs are usually clinically silent for a long time. At the time patients express physical signs, such as abdominal pain, jaundice or paraneoplastic symptoms, tumours are mostly already quite large. They are often located in the head of the pancreas and, as far as previous cases have shown, with a possible predilection for middle-aged women [20]. In our case the patient was a young man, at the time when the tumour was first discovered only 21 years of age. Concerning tumours of the pancreas and especially when a malignancy is confirmed by biopsy, primary surgery is the treatment of choice. Instead, our patient underwent neoadjuvant chemotherapy

as at the time of diagnosis metastatic spread to the lymph nodes and the lungs was suspected due to imaging reports. Definite diagnosis of a MiNEN can only be confirmed by pathologists after morphologic and immunohistochemical examination of the tissue [10,20]. Acinar tumour cells stain positively for trypsin, among others, and neuroendocrine cells express chromogranin A and synaptophysin [21,22]. In our case, the tumour as well as all subsequently resected metastases stained positively for synaptophysin and trypsin (Figure 7), thus proving to stem from the initial malignancy. The number of mitoses per HPF were at 70/10 and Ki67-index was up to 80%, thus indicating a G3-Grading.

In regards to the very young age of our patient, adjuvant chemotherapy was additionally included in postoperative management. When pulmonary nodules, strongly suspicious for pulmonary metastases, showed growth, surgical resection was the approach of choice. Despite the fact that acinar cell carcinomas in general react insufficiently to radiation immunoradiology with DOTATATE-radiation was included as a future therapeutic option as in our case SSTR2-positivity had been confirmed [23]. The prognosis for MiNEN is poor. According to the literature, mean survival in MiNEN patients even after surgical resection is at only 10.5 months [23]. It is highly unusual that our patient has survived for several years, even when lymph nodes were initially affected and, in the course of events, the tumour metastasized to both lungs. Whether our patient is endowed with specific genetic and immunologic preconditions that enable him to fight tumour cells more effectively than other MiNEN patients has yet to be unveiled. In literature, only one case is known when a patient lived for 24 more years [24].

## Conclusion

In conclusion, we herein report the rather exceptional case of a very young patient with MiNEN of the pancreas and metastasizing pattern to the lung. MiNENs of the pancreas are very rare and in consequence, due to the few data accessible, origin of this type of neoplasm as well as optimal treatment plans are still unclear. Presence of a high percentage of neuroendocrine cells may favor a better outcome but the low number of cases makes every outcome susceptible to coincidence. Therefore, reporting of further cases in the future is strongly advised to gain better understanding of this type of carcinoma.

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