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A rare case of poorly differentiated mixed neuroendocrine-non-neuroendocrine tumor of the caecum with long term survival: A case report

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A 59-year-old woman presented with flushing attacks accompanied by tachycardia and hypotension, which lasted approximately 30 to 60 minutes, underwent 18 years ago a gastrointestinal tumor resection. The histologic examination revealed a poorly differentiated mixed neuroendocrine/adenocarcinoma located in the caecum with regional metastases. Postoperatively, the patient received combined chemotherapy of 5-fluorouracil with interferon for six months and since has remained asymptomatic. Her examination revealed positivity for chromogranin A (CgA) and a-Fetoprotein (aFP) (580 ng/24 h, normal range 27–94, and 10 IU/mL, normal range 0–6, respectively). Urinary 5-hydroxy indole acetic acid excretion was remarkably high (41.8 mg/24 h, normal range 2–10 mg/24 h). An abdominal Magnetic Resonance Imaging scan revealed multiple focal loci in the liver whose histological examination revealed a carcinoid tumor confirmed by an Octreoscan. Additional uptake was noted on the right shoulder and the right sternum-clavicle joint confirmed by Tc-99m MDP scan. The patient received somatostatin analogue therapy followed by long-acting release octreotide analogue therapy (30 mg/month) showing a partial improvement of relevant biomarkers. Two years later, carcinoid syndrome symptoms reappeared and due to the tumors expression of somatostatin receptors the patient received peptide receptor radionuclide therapy with 177Lu-DOTATATE that resulted in both clinical and biochemical improvements.

Key words: MiNEN caecum carcinoid syndrome

Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNENs) is a rare type of tumor exhibiting both neuroendocrine and other components usually epithelial that are histologically characterized as either adenocarcinomas or signet ring cell carcinomas or even squamous cell carcinomas with malignant cells in variable concentration. Clinical manifestations vary and could be attributed to either mass effects or to the secretory behavior of the tumor, carcinoid syndrome being one of them. The prognosis is usually poor, depending on the aggressive nature of its characteristics, while long-term survival is short.

Neuroendocrine tumors (NETs), also known as carcinoid tumors, originate in neuroendocrine cells that are widely distributed throughout the body. NETs of the gastrointestinal tract, bronchopulmonary system, and genitourinary tract have traditionally been classified based on their origin from the embryonic divisions of the alimentary tract (foregut, midgut, or hindgut) (Williams and Sandler 1963). Most of them reside in the gastrointestinal tract (approximately 55%) and lung (30%) (Maggard et al.

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2004). Within the gastrointestinal tract, most NETs develop in the small intestine (45%), followed by the rectum (20%), appendix (16%), colon (11%), and stomach (7%). Colonic carcinoids exhibit the worst prognosis in all gastrointestinal carcinoid tumors, probably because of the large tumor size at the time of diagnosis and the high percentage of metastases (Waisberg et al. 2009). In the last two decades, the introduction of routine colonoscopy, as a screening test after the age of 50, has led to the detection of patients with rectal NETs of greater proportion than those diagnosed with small intestine NETs (Taghavi et al. 2013; Montminy et al. 2021). NETs located in the pancreas, previously known as islet cell tumors, are not referred as carcinoids, but as pancreatic NETs, even though histologically are more similar to those located in the tubular gastrointestinal tract.

In some cases, gastroenteropancreatic aggressive neuroendocrine carcinomas contain non-neuroendocrine components (of at least 30% representation each), usually epithelial that are histologically characterized to be either adenocarcinomas or signet ring cell carcinomas or ever squamous cell carcinomas (Kitajima et al. 2013). These extremely rare neoplasms have previously been known as mixed adenoneuroendocrine carcinomas (MANECs) and were categorized according to the new 2019 WHO classification, as mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) (La Rosa et al. 2016). Currently, due to their aggressive nature and poor prognosis, it is unclear whether those tumors should be treated as non-endocrine cancers (according to earlier recommendations by WHO) or pure neuroendocrine carcinomas, which are also aggressive, especially in the case of low-grade neoplasms (Smith et al. 2014; Brathwaite et al. 2016; de Mestier et al. 2017). In the existing literature, there are only occasional reports of MiNENs originating in different organs, however, the MiNENs of the digestive system have been better characterized (La Rosa et al. 2012; de Mestier et al. 2017).

In the present case report, we are demonstrating a rare case of a woman with history of MiNEN in caecum treated initially by surgical excision and chemotherapy that remained silent for 18 years and reappeared with the carcinoid syndrome symptoms.

Case Report

A 59-year-old woman, presented to the Dpt. of Endocrinology, Metabolism and Diabetes Mellitus of our Hospital complaining of facial and trunk flushing that started three months ago. The flushing attacks were accompanied by tachycardia and hypotension. At that point she was not receiving any medication.

The previous medical history included a gastrointestinal tumor resection in 1992. The histologic examination revealed a poorly differentiated mixed neuroendocrine/adenocarcinoma located in the caecum. Multiple size infiltrations (1–2 cm in diameter) were found in the colon fat with additional perineural invasion. The tumor had invaded the cecum intestinal wall in total and regional lymph node infiltration was also reported (two positive lymph nodes out of three). Immunohistochemically, the tumor was strongly positive for neuron specific enolase (NSE) and chromogranin A and less positive for CEA (carcino-embryonic antigen). Her TNM staging was IIIB (T3N1M0). Postoperatively, she received combination chemotherapy with 5-fluorouracil and interferon for six months. From that point the patient remained asymptomatic for 18 years.

In June 2010 she begun to experience multiple attacks of facial and trunk flushing accompanied by tachycardia and hypotension, which lasted approximately 30 to 60 minutes. She was therefore admitted to our department for further investigation. The physical examination and the transthoracic echocardiogram were normal. The blood analyses showed no abnormalities except low vitamin 25(OH)D3 levels. The neuroendocrine tumor biomarkers chromogranin A (CgA) and aFP (a-Fetoprotein) were increased (580 ng/24 h, normal range 27–94, and 10 IU/mL, normal range 0–6, respectively). In addition, urinary 5-hydroxy indole acetic acid (5-HIAA) excretion was remarkably high (41.8 mg/24 h, normal range 2–10 mg/24 h, HPLC method) (four times the normal upper limit).

The abdominal Magnetic Resonance Imaging (MRI) scan showed multiple focal loci in the liver. Consequently, a liver biopsy was performed and the histological examination revealed carcinoid tumor, as expected. The hepatic lesions were also confirmed by an Octreoscan (octreotide labeled with 111 In) with additional uptake reported on the right shoulder and the right sternum-clavicle joint. The bone metastases were also noted at the Tc-99m MDP scan.

The treatment included somatostatin analogues administered subcutaneously three times per day, for 15 days followed by long-acting release octreotide analogue therapy (octreotide LAR) 30 mg per month. The patient reported that her symptoms were relieved within a few days after starting the aforementioned treatment. Levels of Chromogranin A and 5-HIAA (23.5 mg/24 h) were reduced but still remained above the upper normal limit.

Two years later, while the patient was still on medication, carcinoid syndrome symptoms reappeared with flushing, tachycardia, and hypotension as previously described. At that point, considering the fact that the tumor expressed somatostatin receptors, the patient received 9 cycles of peptide receptor radionuclide therapy with 177Lu-DOTATATE that resulted in improvement of both clinical and biochemical parameters.

Discussion

Tumors or cancers displaying a combination of neuroendocrine and non-neuroendocrine features have been described in various organs (Volante et al. 2006; La Rosa et al. 2016). Different terms have been employed based on both the extent and the structural patterns of their specific components. The last proposed recommendation by WHO in 2019 classifies them as mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) (Nagtegaal et al. 2020). The coexistence of dual histology in tumors ranges from 1 to 99%; however, the cut-off criterion for characterization of at least 30% implementation of both components, was proposed by Lewin in 1987 and it is still unanimously accepted (Lewin 1987). This 30% proportion is supposed to be important to determine the biological behavior of the neoplasm, however, there is a paucity of data in the literature to support its clinical relevance (Volante et al. 2006). Morphologically, they are classified as collision (when the two malignant cell populations coexist without missing), composite (when they coexist in blended pattern), and amphicrine (when a single cell population displays both phenotypes) MiNEN (de Mestier et al. 2017).

Their origin is thought to be a multi-potent stem cell present in the submucosa that has the ability to acquire biphenotypic differentiation into various cell lines (Ho et al. 1984; Casas et al. 1997). Another theory suggests synchronous or metachronous, yet independent, development of both components that merge later in the course of the disease. A third hypothesis describes an initial non-neuroendocrine tumor, in which further genetic or molecular changes lead to additional clones that bare neuroendocrine differentiation (Bazerbachi et al. 2015).

In terms of frequency, MiNENs are extremely rare and, as previously stated, the majority of them appears in the gastrointestinal tract and secondarily in the lung, where neuroendocrine cells normally reside (Maggard et al. 2004). Colorectal MiNENs belong to the most frequent types of which 85% are poorly differentiated neuroendocrine carcinomas containing a non-endocrine component in 25–40% of cases, usually adenocarcinoma (Li et al. 2011; Karkouche et al. 2012; La Rosa et al. 2012; de Mestier et al. 2017). However, the true prevalence of colorectal MiNENs is unknown or underestimated (Komatsubara et al. 2016; Watanabe et al. 2016; Kanthan et al. 2020). The median age at diagnosis is 64–72 years (La Rosa et al. 2012; Komatsubara et al. 2016; Watanabe et al. 2016). Reported symptoms in the majority of cases (69%) include abdominal pain and obstructive signs such as nausea, vomiting, abdominal dilatation, malaise, and weight loss (Kanthan et al. 2020). Although the patient's symptomatology depends on the primary tumor's size and its ability to secrete neuroamines and peptides, the diagnosis is often delayed because most of these tumors (90%) do not secrete biologically active hormones. When they release kinins, prostaglandins, and bioactive hormones carcinoid symptoms may occur including flushing, diarrhea, and abdominal cramping and occasionally wheezing, heart valve dysfunction, and pellagra. The serotonin secreted by the tumor is metabolized into 5-HIAA by the liver and a positive for 5-HIAA urine test confirms the diagnosis. Occasionally, urine 5-HIAA is normal, but high levels of CgA and serotonin lead to the detection of the tumor. High CgA is considered a particularly important factor in establishing the diagnosis of NETs (Nikou et al. 2005; Modlin et al. 2010).

Since the neuroendocrine component of the tumor is characterized by a rapid progression, the diagnosis is set in advanced stages of the disease leading to poorer survival outcomes. In many cases, synchronous metastases could have already occurred during the time of diagnosis. Cell type, vascular invasion, peritumoral lymphoid infiltration, and CD117 immunoreactivity seem to be prognostic parameters correlating with shorter patient survival (La Rosa et al. 2012).

In the contrary to NETs, MiNENs require more elaborate and individualized management that includes complete surgical resection for both primary tumor and metastases and chemotherapy according to the histology of the tumor or the inability to fully resect the tumor (Tanaka et al. 2017; Paspala et al. 2018). The neuroendocrine component of the tumor that is high-grade and poorly differentiated usually guides the therapeutic decision. Depending on the case, radiotherapy, somatostatin analogs, embolization of hepatic lesions, and peptide receptor radionuclide the therapy could additionally be used.

To the best of our knowledge, our patient is the second published case of the gastrointestinal carcinoid tumor with such a long-term survival after initial diagnosis (Kaluzny et al. 2009). The patient's tumor was a poorly differentiated mixed neuroendocrine/adenocarcinoma located in the caecum. Biopsy also showed multiple (1–2 cm in size) infiltrations into the colon fat and additional perineural invasion. It invaded the caecum intestinal wall in total and regional lymph nodes were also positive. The patient presented with face and trunk flushing accompanied with hypotension and tachycardia, suggesting a carcinoid syndrome. After tumor resecting, she remained symptom-free for 18 years. When symptoms reappeared, she received a long-acting release octreotide analogue therapy and two years later peptide receptor radionuclide therapy with 177Lu-DOTATATE. According to literature the five-year survival rate of such patients exhibiting regional metastasis is only 54–73% (Konishi et al. 2007). Our patient, whose tumor remained silent for 18 years, is validated as an extremely rare case.

Conclusion

There are a lot of gaps in the knowledge about MiNENs, including data about its prevalence, incidence, survival factors, and optimal therapy. Nevertheless, MINENs are usually characterized by poor survival. In rare cases (such as in our patient whose histology showed a poorly differentiated tumor), they may remain silent for decades and reappear later in the life.

Statement of ethics: *The patient has given a written authorization to publish her case.*

Conflicts of interest: *The authors reported no conflicts of interest.*

Authors contributions: *A.P. was the supervising physician involved in planning and supervising the work. C.K. and K.M. processed the data and drafted the manuscript. P.K. was attending physicians and aided in the results interpretation. All authors discussed and commented the manuscript results.*

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