A Rare Type of Colorectal Cancer: Mixed Adeno-Neuroendocrine Carcinoma (MANEC)

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Rezumat

Un tip rar de cancer colorectal: adenocarcinom neuroendocrin mixt (MANEC)

Scopul acestei lucrări este de a raporta datele clinico-patologice aferente unui caz de adenocarcinom neuroendocrin mixt metastatic (MANEC) cecal: mai puţin de zece astfel de cazuri au fost descrise în literatura de specialitate britanică. Un pacient în vârstă de 57 de ani s-a prezentat cu un adenocarcinom neuroendocrin mixt metastatic (MANEC) cecal cu determinări secundare hepatice şi carcinomatoză peritoneală. S-au efectuat hemicolecotomie dreaptă şi omentectomie de urgenţă, urmate de mai multe cicluri de chimioterapie paliativă cu rezultate slabe. Progresia metastatică a continuat, iar pacientul a decedat la 10 luni de la prezentarea la Camera de Gardă. MANEC sunt definite ca formaţiuni alcătuite din minimum 30% componentă neuroendocrină şi minimum 30% din cea adenocarcinomatoasă. Localizarea tumorii, precum şi proporţiile şi comportamentul celor două componente ale sale influenţează tratamentul. Totuşi, ghidurile de chimioterapie rămân slab definite, iar prognosticul rămâne unul sumbru, cu supravieţuirea medie sub un an de zile.

Cuvinte cheie: carcinom adenoneuroendocrin mixt, MANEC, adenocarcinom colorectal, chimioterapie, chirurgie
Abstract
The aim of this paper is to report the clinicopathological data of one case of mixed metastatic adenoneuroendocrine carcinoma (MANEC) in the caecum: less than ten cases of which have been described in the English literature. A 57-year-old male patient presented with a mixed adenoneuroendocrine carcinoma (MANEC) of the caecum with liver metastasis and peritoneal carcinomatosis. An emergency right hemicolecction and omentectomy were performed, followed by several cycles of unsuccessful palliative chemotherapy. The metastasis developed further, and the patient died 10 months after presenting to the emergency room. MANECs are defined as containing at least 30% of both a neuroendocrine and an adenocarcinomatous component. The location of the tumour and the proportions and behaviour of its two components influence the treatment. However, chemotherapy guidelines remain poorly defined, and prognosis remains sombre, with median survival of less than one year.

Key words: mixed adenoneuroendocrine carcinoma, MANEC, colorectal adenocarcinoma, chemotherapy, surgery

Introduction
When investigating and operating on colonic tumours, both adenocarcinomas and neuroendocrine tumours can frequently be encountered. MANECs are rare tumours of the gastrointestinal tract that consist of a dual adenocarcinomatous and neuroendocrine differentiation. They are usually discovered late, after they have already metastasized and prognosis is poor. As imaging features are non-specific, histopathology is necessary to confirm the diagnosis. Cases of MANEC occurring in the caecum are particularly rare, less than ten cases having been described in the English literature.

The characteristics of the case described here, in correlation with data from the literature, prove that MANECs are highly malignant tumours, their aggressiveness being related to the endocrine component, regardless of its proportion. Diagnosis is based on the tumour architecture and morphology, and immunophenotype with specific neuroendocrine markers expression such as chromogranin-A, synaptophysin and CD56, combined with the markers of intestinal differentiation such as cytokeratin 20 and CDX2. Although the incidence of MANECs is no known, Ito et al. reports that in Japan MANECs constitute 0.2% of all colorectal cancers (5).

Case report
A 57-year-old male was brought to our emergency department by ambulance, complaining of intense abdominal pain. The patient reported that the pain had started several months previously - during which time he lost
35 kilograms – and had only intensified over the past few days. On clinical examination the abdomen was very distended with diffuse pain and guarding. A tender mass was palpable in right lower quadrant. Heart rate, blood pressure and temperature were unremarkable. The patient was a smoker with a history of alcoholism, hypertension and type II diabetes.

Laboratory results were as follows: haemoglobin 69 g/l (normal value 140-180 g/l), leukocytes 15 giga/l (normal value 4-10 giga/l) and CRP (C-reactive protein) 475 mg/l (normal values, inferior to 5 mg/l). An abdominal CT (Computed tomography) scan was performed immediately and revealed a pneumoperitoneum and free intraperitoneal fluid, particularly around the caecum and in the pelvis. A peritoneal carcinomatosis was present, as well as two lesions in segments VII and VIII of the liver. The lymph nodes in the area of the celiac trunk and the hepatic hilum were enlarged (Fig. 1 A and 1 B).

An emergency explorative laparotomy was performed, with a right hemicolectomy and omentectomy. Biopsies of the liver and of two suspicious lesions of the peritoneum were taken. Histopathological examination of the surgical specimen showed that the patient had a large mixed adeno-neuroendocrine carcinoma of the ileocecal region with infiltration of the small bowel, numerous large omentum and lymph node metastases as well as an angiolymphatic invasion (TNM stage: pT4a, pN2b(11/23), G3, pM1, RX) (Fig. 2 A, B and C).

The tumour architecture was predominantly (70%) solid, consisting of clusters of monomorphic tumour cells with abundant cytoplasms and large nuclei, marked by chromorgranin A, synaptophysin, pancytokeratin AE1/AE3, cytokeratin 20 and CDX2. Among these solid tumour proliferation, moderately differentiated glandular structures were also visible (Fig. 3A-E). The glandular component represented 30% of the
tumour, being marked by pancytokeratin AE1/AE3, cytokeratin 20, and CDX2, without positivity for chromogranin A and synaptophysin. Both components were negative for CD56 as well as for CD117 and DOG-1, excluding a diagnosis of gastro-intestinal stromal tumour (GIST).

These results were discussed during our multidisciplinary tumour board. The patient subsequently underwent chemotherapy according to the FOLFIRI (folinic acid, fluorouracil, irinotecan) protocol for four months. After this treatment, an abdominal CT scan showed an increase in size of the liver metastases. Second line chemotherapy with carboplatin and fluorouracil was then tried, but was highly neurotoxic, while not causing any improvement of the oncological status. This second line treatment was therefore stopped after a few cycles. Follow up over the following months showed a progression of the liver metastasis. As a last resort, an Avastin and Fluorouracil treatment was tried, without significate results. The patient died 10 months after initial surgery and less than one month after the last chemotherapy session.

Discussion

Although the first case of MANEC was described by Cardier in 1924, the term “Mixed adeno-neuroendocrine carcinoma” was only introduced by the World Health Organisation in 2010. The origin of these tumours is still not clear (5,6,7). MANECs are thought to arise from multi-potential stem cells which have differentiated bidirectionally (8) or from dedifferentiated adenocarcinomas with a neuroendocrine phenotype (7). However, the question of how two different neoplastic cell types - with different origins and behaviours – can coexist within a single tumour has still not been definitely solved. The prognosis of MANECs is poor due to late presentation, often at a metastatic stage. Spread most commonly occurs to the liver and regional lymph nodes. Peritoneal spread has been described in rare cases (9). Surgery is the only
curative option, but under the condition that the disease be discovered at an early stage.

Marando et al. published the case of a 65-year-old male with colonic MANEC with a staging identical to the case presented here, who died only one month after surgery (9).

Ito et al. report of a 39-year-old woman with colonic MANEC that died three and a half months after surgery, even with adjuvant chemotherapy (5).

The clinical behaviour of the disease depends on the grade of the neuroendocrine component. The characteristics of the adenocarcinomatous compound only influence the outcome in cases where there is a well-differentiated neuroendocrine counterpart. MANECs with well-differentiated neuroendocrine components should be treated as conventional colorectal adenocarcinomas, while MANECs with poorly differentiated neuroendocrine component should be treated as neuroendocrine carcinomas (3).

Due to the rarity of MANECs, the most effective chemotherapy treatment remains to be defined. The National Comprehensive Cancer Network recommends the use of cisplatin or carboplatin and etoposide (10,11). Currently, prognosis remains poor, with a median survival of 7 to 10 months (12).

Conclusions

MANECs are rare tumours that present late, usually after metastases have spread. If discovered early, surgery may be curative. However, in more advanced stages of the diseases, a multidisciplinary approach is required. Due to the rarity of the disease, chemotherapy guidelines remain poorly defined, and prognosis remains poor.

Authors’ contribution:


Conflict of interest

The authors declare that they have no conflict of interest.

References