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Neuroendocrine Tumour in Meckel's Diverticulum as a Cause of Acute Abdomen

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1. Abstract

Meckel's diverticulum is the most common congenital defect of the gastrointestinal tract, caused by an incomplete obliteration of ductus omphaloentericus (yolk sac) during intrauterine life. Given that the ductus omphaloentericus contains pluripotent cells during the intrauterine life, the diverticular mucosa may contain cell islets of different types of tissues, such as gastric and intestinal mucosa, pancreatic cells and others. However, the occurrence of neuroendocrine tumours in Meckel's diverticulum is very rare. Causes ileus, besides its tumorous tissue, are fibrous changes in mesentery induced by the neuroendocrine tumour as well.

The paper presents a case of a 48-year-old patient with an acute abdomen, caused by perforation of Meckel's diverticulum. Histological examination has revealed the presence of a neuroendocrine tumour spreading across muscularis propria and incipient spread into subserosa.

2. Background

Meckel's diverticulum occurs in approximately 1 – 2% of people. In most cases, it is asymptomatic. Clinically, Meckel's diverticulum manifests in 4% of patients by its complications. These most frequently include inflammation, haemorrhage, torsion, or strangulation, and ileocecal invagination [1]. Complications associated with cancer in Meckel's diverticulum are, according to literature, rare; their incidence ranges between 0.5 to 3.2% [2, 3]. Complication of Meckel's diverticulum caused by NET is the main focus of our take-home message. Small intestine is the most frequent location for a neuroendocrine tumour in the gastrointestinal tract (44.7%) [4].

3. Case Presentation

Patient born in 1968 had been sent by a GP for a further examination of cramping pains. The patient had not been previously treated for anything, had not taken any chronic medication, and had not undergone any surgery in the past. The patient presented with a one day history of abdominal pain in the navel area with increasing intensity, and intermittent cramps. There was no history of vomiting, however the patient did mention long-term problems with stool; occasional diarrhoea alternating with constipation, without blood or mucus admixture. An abdominal X-ray indicated an increased meteorism of the right and middle meso hypogastric regions with several air-fluid levels, see Figure 1. The abdominal ultrasound showed dilated loops of small intestine with liquid content in the left mesogastrium; free fluid was not found in the abdominal cavity. A hernia was apparent in the navel area with a fascial defect of 17 mm, the hernia sac contained intestinal loops; with no fluid in the vicinity. Other organs of the abdominal cavity were without pathology.

Due to a persistent colicky pain in the navel area and a suspected incarcerated umbilical hernia surgical revision was indicated. The dissection of umbilical hernia was performed and no signs of incarceration were found and so it was clear that this has not been the cause of the ileus state. Therefore a short median laparotomy was performed to inspect the abdominal cavity. Dilated loops of the

small intestine without any evidence of incarceration were found. The cause of acute abdomen was discovered on the terminal ileum, about 40 cm from the ileocecal valve – a perforated Meckel's diverticulum within adhesions to the mesenterium, caused by local peritonitis, see Figure 2. Subsequently, wedge-shaped resection of the diverticulum had been carried out with suture of the small intestine, and drainage of the abdominal cavity.

Histological examination of the resected Meckel's diverticulum revealed a neuroendocrine tumour, NET G2, with a spread to the muscularis propria and incipient focal spread into subserosa (pT3). The size of the tumour was 10 mm and its infiltration was 5 mm away from the edge of the perforation; it did not interfere with the resection line (R0 resection) The spherical neuroendocrine neoplasia had been formed by medium-sized cells with round nuclei with salt and pepper chromatin and solid islets and stripes in the desmoplastic stroma, see Figure 3. The number of mitoses 4-5/10 HPF; proliferation index Ki 67 was a maximum of 3%. Immunohistochemistry showed a strong diffuse expression of synaptophysin, chromogranin, and CD 57, see Figure 4.

The tumour had predominantly grown in the submucosa and mucosa, had ulcerated the epithelium in sections, and had penetrated into the muscularis propria; even tiny groups of cells had been focally discontinuously revealed in the subserosa.

Due to peritonitis, in the early postoperative period a second revision of the abdomen was performed with findings of a persistent paralytic ileus; suture of the small intestine was intact and inflammation of the abdominal cavity was not evident. In the postoperative period the bowel peristalsis was gradually restored and the overall condition of the patient improved without significant complications.

Due to the histological findings the patient was referred to an oncologist. Oncological staging was performed, including a CT of the chest, abdomen, and pelvis, which were all without any evidence of dissemination of the NET. Laboratory values of NSE were 11.6 ug/l, chromogranin A 6.0 g/l, and 5-HIAA in the urine 11.1 umol/l. Given the tumour infiltration had not interfered with the resection line, or perforation edges and the size had been 10 mm, only monitoring of the patient without adjuvant oncological therapy was further indicated. Regular investigations at the oncological department twice a year for 5 years after operation have not detected any signs of dissemination or relapse of disease. Once per year in the first 2 years after operation a CT scan of abdomen and thorax was performed to exclude dissemination or relapse. In the following few years the screening was performed by abdominal ultrasound examinations. The laboratory results of testing Chromogranin A 6,0 ug/l and 5-HIOK at urine, made twice per year, were constantly physiological. 5 years after operation, the patient feels good and is observed by the oncologist once per year.

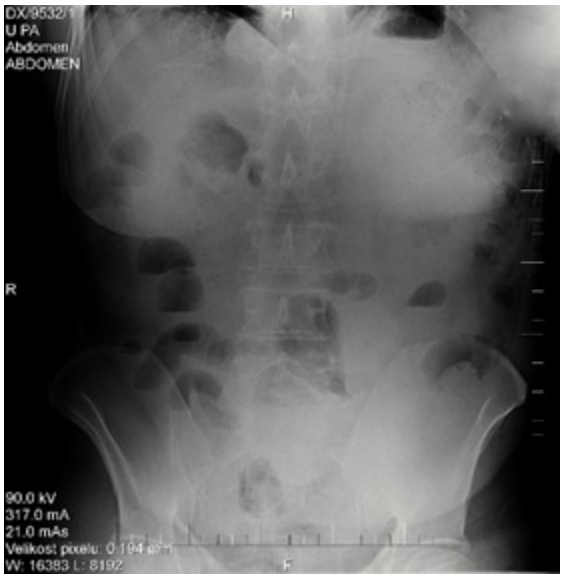


Figure 1: X-ray of Abdomen while Standing: apparent increased meteorism of the right and middle mesohypogastria with several air-fluid levels. (Photo: author's archive)

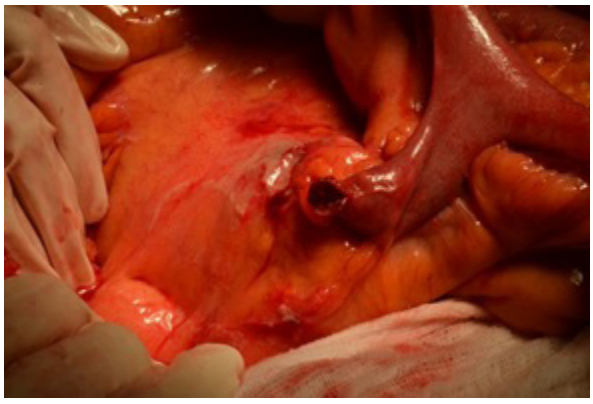


Figure 2: Perforated Meckel's Diverticulum (Photo: author's archive)

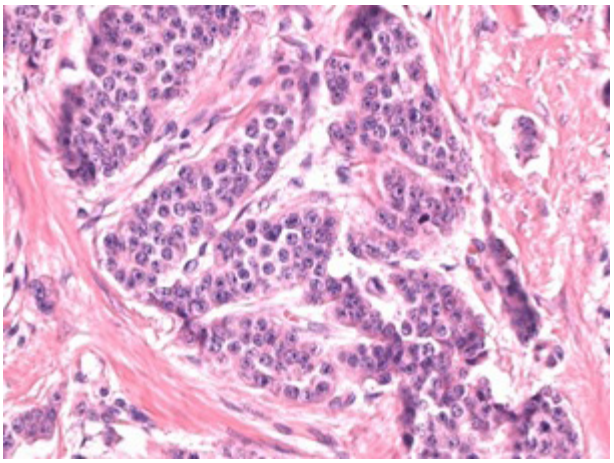


Figure 3: Detail of Tumour Cells: medium cell with minimal plesiomorfia, circular, or polygonal with rounded nuclei with a characteristic chromatin structure so-called "salt and pepper". Standard staining haematoxylin-eosin, magnification 400x. (Photo: author's archive)

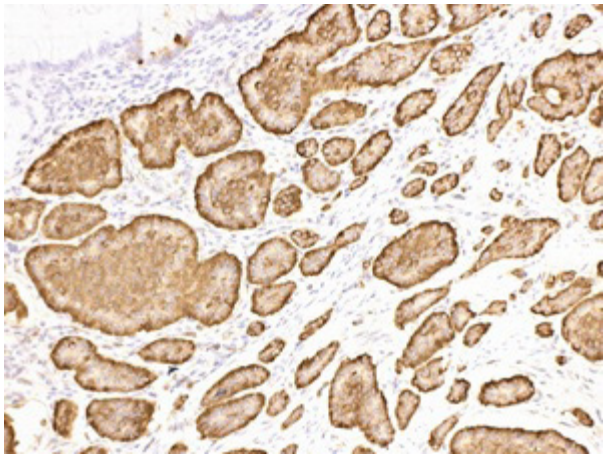


Figure 4: Immunohistochemical Evidence of Chromogranin in Tumour Cells; magnification 200x. (Photo: author's archive)

4. Discussion

Meckel's diverticulum is a true diverticulum that arises from the antimesenteric surface of the middle-to-distal ileum and is found in 0.3 to 2.5% of the population [5]. Its development relates to a ductus omphaloentericus that does not completely close around the 8th week of an intrauterine life [6]. Most often it is found about 20 to 60 cm proximally from an ileocecal valve. Its size varies from 1cm to 20 cm.

According to literature, there is no difference in the incidence of Meckel's diverticulum in men and women [7]. However, according to expert sources, prevalence of a symptomatic Meckel's diverticulum is five times higher in men than in women [6]. Soltero and Bill present in their study a risk of developing complications in Meckel's diverticulum in a lifetime for people under 20 years of age is 4%, 2% for people under the age of 40 years and 0% for elderly population [8].

According to literature, the most common cause of Meckel's diverticulum perforation is an inflammatory infiltration of diverticulum wall, often linked to a local peritonitis, or a foreign body causing pressure necrosis to the diverticulum wall. Cases of perforation of a diverticulum after a blunt abdominal trauma are rarely described [9].

The most frequent cancers of Meckel's diverticulum include neuroendocrine tumours, as well as pancreatic carcinomas, gastrointestinal stromal tumours, leiomyosarcomas, and lymphomas [10, 11]. Neuroendocrine Tumour (NET) in Meckel's diverticulum is usually small and asymptomatic. Diagnosis is made by a histological examination of a resected diverticulum or during an autopsy [12]. Neuroendocrine tumours, formerly also known as carcinoids, originate from enterochromaffin cells, initially located in a neural crest; represent the most common primary tumours in the small intestine. Theoretically, they can occur in any anatomical region, the most common occurrence has been described in the appendix. The second most frequent incidence of a neuroendocrine tumour is in the terminal ileum, usually within 60 cm from the ileocecal valve [13]. They may also be malignant in nature, but usually exhibit low aggressiveness. Up to 70-80% of patients do not have any symptoms [14]. According to a study carried out on 11,427 patients with carcinoid diagnosis, tumours have been found in the gastrointestinal tract in 54.5% of patients and 30.1% in lung tissue and bronchi.

Nies et al. present the average age of patients with neuroendocrine tumours in Meckel's diverticulum to be 57 years, 72% of those patients are men [15].

According to Koh et al. neuroendocrine tumours occur in 33% of all malignant tumours in Meckel's diverticulum [10]. Modlin and Sandor indicate that about 0.48 to 0.74% of all neuroendocrine tumours are located right in Meckel's diverticulum [16]. According to studies at Mayo Clinic, the most common signs associated with symptomatic Meckel's diverticulum are; patient's age of less than 50 years, male gender, length of diverticulum of more than 2 cm, and presence of abnormal tissue in the mucosa diverticulum [17]. Inflammation and perforation of Meckel's diverticulum belongs to sudden inflammatory abdominal events, requiring urgent surgical treatment. Their symptoms most often mimic acute appendicitis [9]. The presented 48-year-old patient, however, had been admitted for colicky pain in the navel, mimicking rather a gastrointestinal obstruction as a cause of the acute abdomen. Laboratory examination revealed elevated inflammatory markers with leukocytes of 13.4 109/l and a CRP 63.3 mg/L, the diagnostic imaging methods were suggestive of ileus as well, with findings of thin dilated intestinal loops with air-fluid levels. Similar symptoms described by Caracappa et al., NET may manifest as a periodic abdominal pain, gastrointestinal bleeding, and obstruction [13]. In the patient, the inflammatory changes of the Meckel's diverticulum probably originated due to the tumour obstructing the diverticulum, as the site of the intestinal perforation was found outside of the tumourous infiltration. However as mentioned by Caracappa et al., clinical symptoms may be affected by the NET. Carcinoid syndrome occurs in 10-20%, with neuroendocrine tumours in Meckel's diverticulum with typical symptomatology such as flushing, diarrhoea, asthma attack, hepatomegaly, and development of a heart failure. None of these symptoms had been reported by the patient. Carcinoid syndrome, which is stimulated by secretion of serotonin, occurs in 45% of patients with the presence of liver metastases [13]. According to Niese et al. only 17% of patients have clinical symptoms and metastases occur in 24% of patients [15]. Due to the non-specificity of symptoms, particularly in the initial phase, an average time between the onset of symptoms and diagnosis varies from 2 to 20 years [18]. For this reason, at the time of diagnosis more than half of the patients have an advanced illness [19]. Even from historical sources, it is known that the incidence of distant metastasis is closely related to the size of tumorous infiltration. Moertel et al. states that carcinoids smaller than 1 cm metastasize in up to 2% of cases [20]. Distant metastases are found mainly in the liver, lungs

and consequently in bone [21]. Tumour size in the resected Meckel's diverticulum was 10 mm as determined by the histopathology, and according to the staging examination tumour dissemination was present. According to literature, for tumours smaller than 1 cm without local invasion, or metastatic lesions, local excision is sufficient [22]. Brief histological classification, grading, and degree of NET's differentiation is summarised in Table 1 [23, 24].

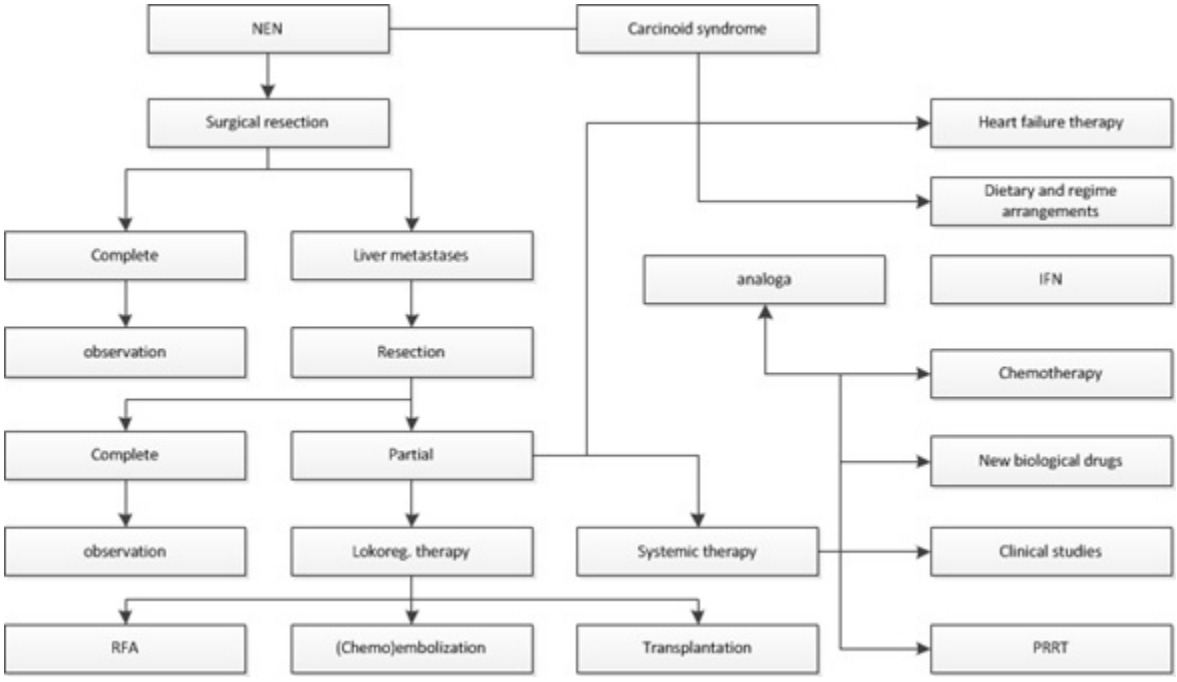
Primary treatment of NET is a surgical excision. Range of surgery is determined by the size of the primary tumour and presence of metastases. For tumours smaller than 1 cm without a local invasiveness, or metastases local excision can be sufficient. In case of tumour invasiveness resection of affected portion of bowel is recommended with resection edge of 10 cm orally and distally from tumour's infiltration. In case of NET in an area of the terminal ileum, the method of choice is a right-sided hemicolectomy. In case of distant metastases presence, palliative resection of the tumour, alongside oncological therapy is the treatment option of choice, also relieving the symptoms of the carcinoid syndrome [22]. Comprehensive approaches in treatment of neuroendocrine tumours have been summarised in Table 2.

The tumorous infiltration in the resected diverticulum, in our patient, has not interfered with the resection margins, or with the perforation edges; the proliferation index Ki 67 was at a maximum of 3%, therefore the performed wedge resection was an adequate choice of resection extent. Proliferation marker Ki 67 is an important prognostic factor in patients with neuroendocrine tumour, its value correlates with biological behaviour of the NET. Another prognostic factor is chromogranin A, whose serum levels correspond to the amount of tumour mass [25]. Postoperatively, the result of chromogranin A in the patient was 6.0 ug/l, which corresponded to a negative value. According to available studies, prognosis also depends on the degree of invasion of the tumorous infiltration. Favourable prognostic factors of the NET include: curative resection of primary tumour and an absence of liver metastases [26]. In a localised and well-differentiated NET in Meckel's diverticulum, treated by a full surgical resection, 5-year survival rate is up to 90% [27]. In contrast, almost all patients with metastatic disease have a relapse during 7-year monitoring, even after a successful treatment [28].

Table 1: Histopathology of Neuroendocrine Tumors (Taken from: Klimstra et al. 2010; Strosberg et al. 2008 [23,24])

Histological Classification	Well Differentiated (Low Grade, G1)	Moderately Differentiated (Intermediate Grade, G2)	Poorly Differentiated (High Grade, G3)
Appearance	Monomorphic population of small, round cells	Not well defined in medical literature	Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic Rate	< 2	2 – 20	> 20
Ki-67 Index	< 3 %	3 – 20 %	> 20 %
Necrosis	Absent	Not well defined in medical literature	Present

Table 2: NET Treatment Algorithm (Taken from: Barkmanová and Ulrych 2014 [25])



5. Conclusions

Preoperative diagnosis of complications of Meckel's diverticulum can be challenging. Symptomatology and results of imaging findings can mimic other diseases or acute abdomen of any aetiology. In our opinion diverticulum perforation had been caused by an inflammatory infiltration in the apex of diverticulum as a result of a partial obstruction of the diverticulum by the tumour. Clinical symptoms of the patient may have been affected by the presence of the NET. Precisely the presence of non-specific difficulties, such as enterorrhagia, or chronic, recurring colicky abdominal pains without a clear aetiology should be kept in mind in the differential diagnosis of complications of the Meckel's diverticulum and neuroendocrine tumours.

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