CASE REPORT
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A rare cause of multiple liver metastases in a 65-year-old man

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Abstract

This article presents the case of a 65-year-old man who was admitted to hospital due to persistent diarrhoea and unintentional weight loss. During the initial diagnosis, ultrasound examination revealed numerous liver metastases, the most common causes of which are colon, lung, and breast cancers. However, in the presented case, further diagnostics revealed a highly malignant duodenal neuroendocrine tumour. Two years earlier, primary hyperparathyroidism was diagnosed, but this problem was neglected by the patient. The mentioned diseases can be a clinical manifestation of multiple endocrine neoplasia type 1 syndrome. Unfortunately, the patient died before the final diagnosis. The daughter of the patient was also encouraged to check for the disease. Extraordinarily, she was totally uninterested. Denial about terminal cancer and disregard of its consequences is a palliative issue affecting not only patients but also their families.

Key words: neuroendocrine tumour, liver metastases, multiple endocrine neoplasia type 1 (MEN1), denial about terminal cancer.

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INTRODUCTION

Neuroendocrine neoplasms, due to their rarity, diagnostic difficulties, complicated treatment, and polymorphism of symptoms, require specific treatment, also in the area of palliative care. Their predisposition to metastasis is sometimes very high [1]. The liver is an organ featured by relatively frequent location of cancer metastasis. This phenomenon has been attributed to 2 mechanisms. First is the dual blood supply of the liver; the portal and systemic circulation increase the probability of influx cancer cells along with blood. The second is the hepatic sinusoidal structure of epithelium, in which fenestrations allow colonization in the liver parenchyma [2–4]. The most common causes of liver metastases are colorectal, lung, and breast cancers [2]. In the article we present a case of a rare tumour, small in size in the primarily location, being the cause of extensive liver metastases.

CASE REPORT

A 65-year-old Caucasian male was admitted to the hospital with symptoms of persistent diarrhoea lasting for one month (up to dozen bowel movements daily). At the same time, he was complaining of periodic pain in the right hypochondrium and poor appetite. Moreover, in the preceding 6 months he had lost 10 kg of body weight. His current weight and height were 47 kg and 160 cm, respectively. In past medical history, the patient declared a low-energy radius fracture 2 years earlier treated efficiently by an orthopaedist using a plaster cast. Due to the diagnosis of low-energy fracture, primary hyperparathyroidism had been diagnosed at the time [5]. An analysis of hospital medical records from that period revealed values of iPTH 117.5 pg/ml (reference range: 15–65), with normal vitamin D3 (41 ng/ml, reference range: 31–50) and total calcium concentration, i.e. 2.29 mmol/l (reference range: 2.2–2.65). Because of the efficient orthopaedic treatment and well-being, the patient neglected further medical care, arbitrarily considering it unnecessary. Thus, additional diagnostic procedures, including densitometry, were not performed. During the medical history taking, the patient strongly denied ever taking lithium, bisphosphonate, denosumab, or diuretics. The patient was the only child in the family. His mother died of myocardial infarction at the age of 55 years, and that was the only burden in the family health

history. He had one daughter at the age of 43 years, who was thus far healthy. The physical examination revealed liver with a smooth edge protruding 4 cm below the right costal margin in the mid-clavicular line. Moreover, in physical examination the other organs including the skin, spleen, and lymph nodes were free from the suspected lesions as well as from any other anomalies. Laboratory tests revealed abnormalities: alkaline phosphatase 270 U/l (reference range: 40–130), gamma-glutamyl transferase: 122 U/l (reference range < 60), albumin: 2.36 g/dl (reference range: 3.5–5.2), and total protein: 5.15 g/dl (reference range: 6–8). Haemoglobin concentration was 13.5 g/dl (reference range: 14–18) with normocytic and normochromic erythrocytes and normal white blood count both generally and in the smear. Alanine aminotransferase (34 U/l; reference range < 41), aspartate aminotransferase (31 U/l; reference range < 40), total bilirubin (0.30 mg/dl; reference range < 1.2), and INR (1.12; reference range: 0.8–1.2) were normal. Ultrasound examination revealed multiple metastases to the liver (Fig. 1). Abnormalities were not found in the chest X-ray. Supplementary laboratory tests were performed: prostate-specific antigen (0.294 ng/ml; reference range < 4.1), carcino-embryonic antigen (3.5 ng/ml; reference range < 5), and α-fetoprotein (1.6 ng/ml; reference range < 7). Diagnostics were complemented with standard endoscopy of the gastrointestinal tract. The colonoscopy disclosed 3 polyps with the macroscopic features of a benign lesion. The largest polyp was 7 mm in diameter. All of them were removed and histopathologically evaluated. During the upper gastrointestinal endoscopy, a lesion of about 15 mm was found in the initial section of the descending part of the duodenum on the lateral wall (Fig. 2). The samples for histopathological examination were taken immediately after locating the lesion. Pending the biopsy outcome, chromogranin A in the blood was evaluated, and the result was above the measuring range (> 1000.00 ng/ml; reference range < 100.00). Simultaneously, due to the tumour location in the gastrinoma triangle, the gastrin concentration was determined, but it was normal (29 ng/l; reference range: 13–115). Furthermore, the abdominal and pelvic contrast-enhanced computed tomography (CT) was performed, revealing the enlarged liver (length 218 mm in right mid-clavicular line) with many hypervascularised metastases with a diameter of 10–45 mm (Fig. 3). There were no significant changes found in the other structures and organs of the abdominal and pelvic cavity. No duodenal lesion was visible in CT. Histopathological examination of colonic polyps revealed 3 tubular adenomas with low-grade dysplasia, whilst the duodenal lesion proved to be an neuroendocrine tumour (NET) G3, in immunohistochemistry studies: CD AE1/AE3(+), synaptophysin(+), chromogranin(+), Ki-67(+) 50% in the hot spots. A hormonal test other than gastrin was considered, but we decided against it after histopathological confirmation of the high malignancy of the tumour. At this stage, we referred the patient to the oncology centre, remaining in contact with him and his daughter. We obtained information from them that due to advanced liver metastases, chemotherapy was started immediately without additional diagnostic procedures. The treatment was ineffective and patient died at home due to liver failure without consideration of the immediate cause (NET or complication of the treatment). Death was confirmed by a general practitioner. The patient died a few weeks after the NET diagnosis, and until the end of his life the aetiology of the hyperparathyroidism was unexplained. Posthumous analysis of medical documentation allows us to presume multiple endocrine neoplasia syndrome type 1 (MEN1). On the example of the described patient, an attempt to link a duodenal NET and primary hyperparathyroidism with MEN1 syndrome was

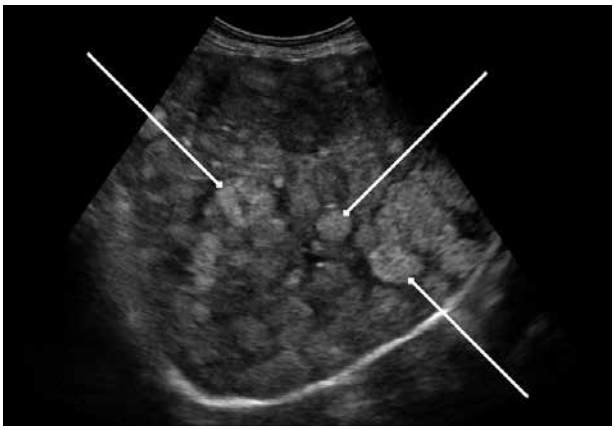

Fig. 1. Multiple hyperechogenic metastases to the liver visible in ultrasound examination (the convex probe). Three of them (the most visible) are marked with arrows

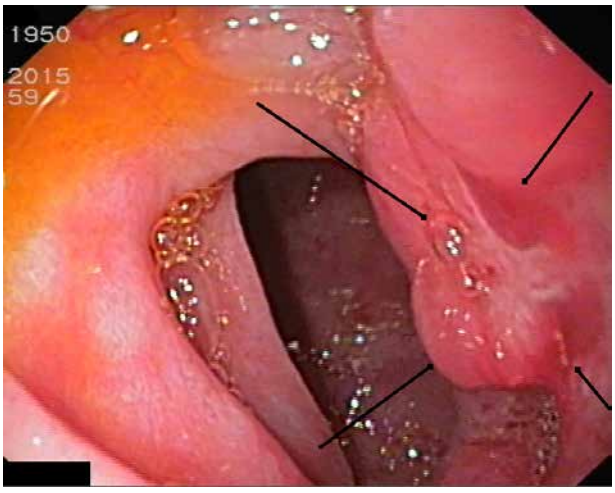

Fig. 2. Duodenal lesion found in upper gastrointestinal endoscopy (marked with arrows)

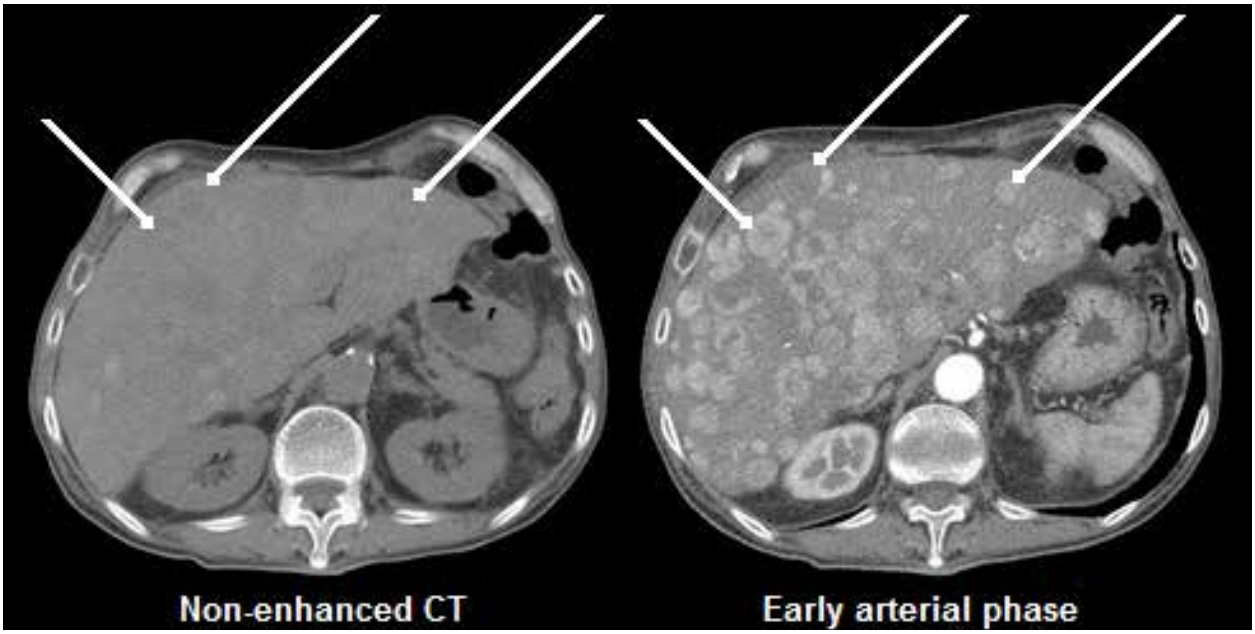

Fig. 3. Multiple metastases (with a diameter of 10–45 mm) to the liver visible in computed tomography. Three of them are marked with arrows. The scan on the left: the lesions before the contrast infusion. The scan on the right: the contrast enhancement of lesions in the early arterial phase

previously undertaken, especially in the context of negligence on the part of the patient causing procrastination in the diagnosis of the disease [5]. Subsequently, the daughter of the deceased patient was repeatedly encouraged to check if she was also burdened by the disease, but she was totally uninterested. The fear of confirming the diagnosis of MEN1 syndrome played a leading role in her reluctance to undergo diagnosis. Arguments concerning the risk of fatal cancer and the possibility of diagnosing it at a curable stage were not effective.

DISCUSSION

Duodenal NETs are more commonly diagnosed in males, in the mean age of 6th decade of life, and if they are smaller than 20 mm, they can usually be efficiently removed during endoscopy due to lack of metastasis and low risk of invasion into the muscularis propria [6, 7]. The presented case is completely different than expected after endoscopy evaluation. Despite its relatively small size, the cancer was highly malignant, characterized by high value of Ki-67 index and expansive liver metastases, larger than the primary tumour. Thus, it was a leading factor causing the palliative condition at the moment of the NET diagnosis. When liver metastases with a high chromogranin A concentration are found, endoscopy of gastrointestinal tract is a required diagnostic procedure. Although endoscopy makes it possible to diagnose almost 100% of the primary NET in the stomach and about 86% in the large intestine, diagnosis of the small bowel tumour is much more difficult. However, the detection of a cancer in the initial descending part of the duodenum was possible because exploration of this section is a part of the standard procedures during endoscopy of the upper gastrointestinal tract. Over 50% of gastro-entero-pancreatic neuroendocrine neoplasms are found accidentally, during surgical procedures or in the diagnosis of distant metastases, mostly to the liver. This proves the relevant diagnostic difficulties encountered in non-advanced forms of the disease. Although the primary tumour was relatively small, low histological differentiation of the NET (Ki-67 50%) was a cause of multiple liver metastases, and thus the prognosis had become very poor [8–10]. Diagnosis of duodenal NET in combination with primary hyperparathyroidism implies clinical suspicion of MEN1. Confirmation of a parathyroid tumour as the cause of hyperparathyroidism would be needed to make a reliable diagnosis, but this was neglected [11]. Fragility fractures are significantly more frequent in hypercalcaemic parathyroidism than in normocalcaemic but are also involved in the clinical course of both disease types [12, 13]. When fractures occur in the course of cancer, bone metastases should also be considered as a cause [14]. In the presented case, after the success of exclusively conservative treatment only with the use of plaster casts in the past and then lack of bone symptoms, the current medical managing had been focused on the therapy of directly life-threatening liver metastases in an appropriate unit. The hyperparathyroidism is usually the first symptom of MEN1 in its natural history. Thus, a careful approach and diagnosis of MEN1, which is a genetic, inherited, autosomal

dominant condition, would allow the implementation of screening among family members [11, 15]. We tried to use the tools and competences for communicating a poor prognosis and to use the developed relationship with the patient and their relatives to communicate a poor prognosis openly and thus try to explain the medical problem to the patient's daughter [16]. The daughter of the deceased patient has been encouraged many times by the medical staff to screen for hyperparathyroidism and multiple endocrine neoplasia syndromes, but she did not agree to this. In palliative care, improving communication in relationships between medical staff on the one hand and the patient and their immediate family on the other could contribute to better quality healthcare. Palliative care should ensure effective communication with patients and their families [17]. We were not able to accomplish this. The daughter of the patient has remained adamant in her decision.

CONCLUSIONS

Although the most common causes of liver metastases are colorectal, lung, and breast cancers, the article presented a rare case of duodenal neuroendocrine tumour, coexisting with primary hyperparathyroidism. This describes a patient who died due to disseminated neuroendocrine tumour, suffering from hyperparathyroidism with unexplained aetiology to the end of his life. The daughter of the deceased patient was encouraged to check for the disease. Extraordinarily, she was totally uninterested. Denial about terminal cancer and disregard of its consequences are palliative issues not only affecting patients but also their families.

The authors declare no conflict of interest.

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