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CASE REPORT

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Long-term complete remission of pancreatic cancer after first-line chemotherapy with gemcitabine and nab-paclitaxel in a patient with depressive disorder

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ABSTRACT

The article presents the case of a 64-year-old pancreatic cancer patient with complete remission of hepatic metastases after first-line chemotherapy with gemcitabine and nab-paclitaxel. Partial regression of metastatic tumours in the liver was achieved after three months of therapy, and after three more months complete remission was achieved. Grade 4 neutropaenia was reported once during the treatment. The patient was temporarily reluctant to start treatment. Better cooperation was achieved after using psychotherapy. The following case confirms the impact of the patient's mental condition on the treatmentinitiation. The possibility of obtaining long-term complete remission in advanced pancreatic cancer — a disease with poor prognosis — following the use of gemcitabine and nab-paclitaxel-containing chemotherapy is documented.

Key words: complete response, pancreatic cancer, gemcitabine, nab-paclitaxel, depression

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Introduction

Pancreatic cancer is a solid tumour with a very poor prognosis, in which the mortality is almost equal to the incidence, and less than 5% of patients survive five or more years. The only method of radical treatment is surgical resection. Unfortunately, due to the high biological and clinical tumour aggressiveness and lack of early symptoms, the cancer is usually diagnosed at a very advanced stage. In about 80% of patients after radical treatment relapse occurs within the first three years after diagnosis and the choice of appropriate chemotherapy is important to achieve maximum survival in metastatic pancreatic cancer [1]. For many years 5-fluorouracil was the standard of treatment for stage IV of the disease. Progress was associated with the introduction of gemcitabine — the results of a study by Burris et al. [2] showed the possibility of extending overall survival (OS) by 1.3 months compared to 5-fluorouracil.

The introduction of the multi-drug FOLFIRINOX regimen was important in the first-line treatment of patients with advanced pancreatic cancer. The results of the ACCORD 11/PRODIGE 4 phase III study, which compared the effectiveness of FOLFIRINOX with gemcitabine, showed prolongation of median OS, progression-free survival (PFS), and one-year survival rate (11.1 *vs.* 6.4 months; 6.8 *vs.* 3.3 months; 48% *vs.* 21%, respectively) [3]. Unfortunately, the FOLFIRINOX

regimen is toxic and only properly selected patients are able to tolerate it in full doses [4].

Recently, a new doublet chemotherapy regimen consisting of gemcitabine and nab-paclitaxel has been introduced into clinical practice [5]. In a multicentre phase III clinical study this doublet was superior to gemcitabine monotherapy in terms of OS (median 8.5 *vs.* 6.7 months; $P < 0.0001$), PFS (5.5 *vs*. 3.7 months; $P < 0.0001$) and the objective response rate (ORR) (23% *vs*. 7%). The aforementioned doublet is an important first-line treatment option in patients with metastatic pancreatic cancer because it is less toxic than the FOLFIRINOX regimen and gives comparable results, an example of which is the presented clinical case.

Depression very often coexists with pancreatic adenocarcinoma. The incidence of so-called major depressive disorder (MDD) in pancreatic cancer reported in the literature is up to seven times higher than in the general population [6]. A meta-analysis of six prospective studies in pancreatic cancer estimates that 43% of patients experience depression after being diagnosed. Depression and loss of psychomotor drive represent a particularly adverse syndrome occurring in some patients with pancreatic cancer [7]. In such cases, patients give up taking treatment that could potentially prolong their life or significantly relieve the symptoms of cancer, because they feel too tired to make the effort and visit the oncology centre.

Depression accompanying pancreatic cancer is most commonly diagnosed in patients over 65 years of age, who are not working, and it usually occurs within the first three months after surgery or in patients without the possibility of surgical intervention [8].

Case report

On January 2, 2017, a 64-year-old female patient underwent pancreatoduodenectomy for carcinoma of the *head* of the *pancreas*. Histopathological examination revealed pancreatic ductal adenocarcinoma (presence of necrosis, G2 malignancy, complete resection, pT2N1 stage, metastases in 2 out of 10 examined lymph nodes, features of vascular invasion). Computed tomography of the chest, abdominal cavity, and pelvis performed before the surgery did not reveal distant metastases. One month after surgery, CA19.9 and CEA levels were 87.7 IU/mL and 1.6 ng/mL, respectively. The result of the examination together with planned adjuvant treatment and prognosis were discussed with the patient. The patient refused the proposed treatment despite detailed information. She did not have a psycho-oncologist consultation. Three years before the diagnosis she had an episode of depression related to the sudden death of her daughter (no detailed medical documentation).

After six months, at the instigation of the family, the patient went to an oncologist in another centre. The level of CA19.9 and CEA markers were 484.6 IU/mL and 4.4 ng/mL, respectively. A CT scan of the chest, abdomen, and pelvis was performed on June 6, 2017 (Fig. 1A). Based on the examination, numerous metastatic lesions were found in both liver lobes with diameters of up to 13 mm. A portocaval node (17 x 9 mm) was described in the hilum of the liver close to the celiac trunk. The result was compared to the examination from December 30, 2016, and progression of the disease in the liver was diagnosed (Fig. 2). The results of blood and biochemical morphology were within normal range.

On July 5, 2017, the patient decided to start palliative chemotherapy. She received nab-paclitaxel at a dose of 125 mg/m^2 with gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15 every 28 days. After administration of the first part of cycle 1, the values of white blood cells, neutrophils, and platelets were 2.98 G/L, 1.25 G/L, and 162 G/L, respectively. Filgrastim was given at a dose of 48 million units subcutaneously for three days. Before administration of the second part of cycle 2, the values of white blood cells, neutrophils, and platelets were 21.17 G/L, 17.0 G/L, and 123 G/L, respectively. After chemotherapy administration filgrastim was reused at a dose of 48 million units for two days as a secondary prevention of neutropaenia. Hair loss occurred after the first cycle. The patient did not report nausea and vomiting or symptoms of neurotoxicity, and the performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale was 0. The patient used a psycho-oncologist consultation and undertook regular psychotherapy.

After cycle 3 grade 4 neutropaenia was found (neutrophil count 0.26 G/L), and the ECOG PS was 2. Neutropaenic fever was not observed. Filgrastim was given at a dose of 48 million units subcutaneously for five days, and the number of leukocytes and neutrophils was 54.55 G/L and 45.91 G/L, respectively. Due to asthaenia and neutropaenia, at the patient's request, computed tomography was performed only on October 3, 2017 (after the second part of cycle 3; Fig. 1B). A single residual lesion with a diameter of 8 mm was found in segment 8 of the liver and almost complete regression was described. After administration of the second part cycle 4, grade 2 thrombocytopaenia (70 G/L) was found and chemotherapy was postponed for seven days. Complete blood count (CBC) prior to the third part of cycle 4 showed a platelet count of 510 G/L. A CT scan performed on January 4, 2018 showed several hypertensive areas visible only in the arterial phase (probably indicative of perfusion disorders). The total remission was determined according to the RECIST 1.1 criteria. Serum marker values were within normal range (CA19.9 — 7.31, CEA — 1.24).

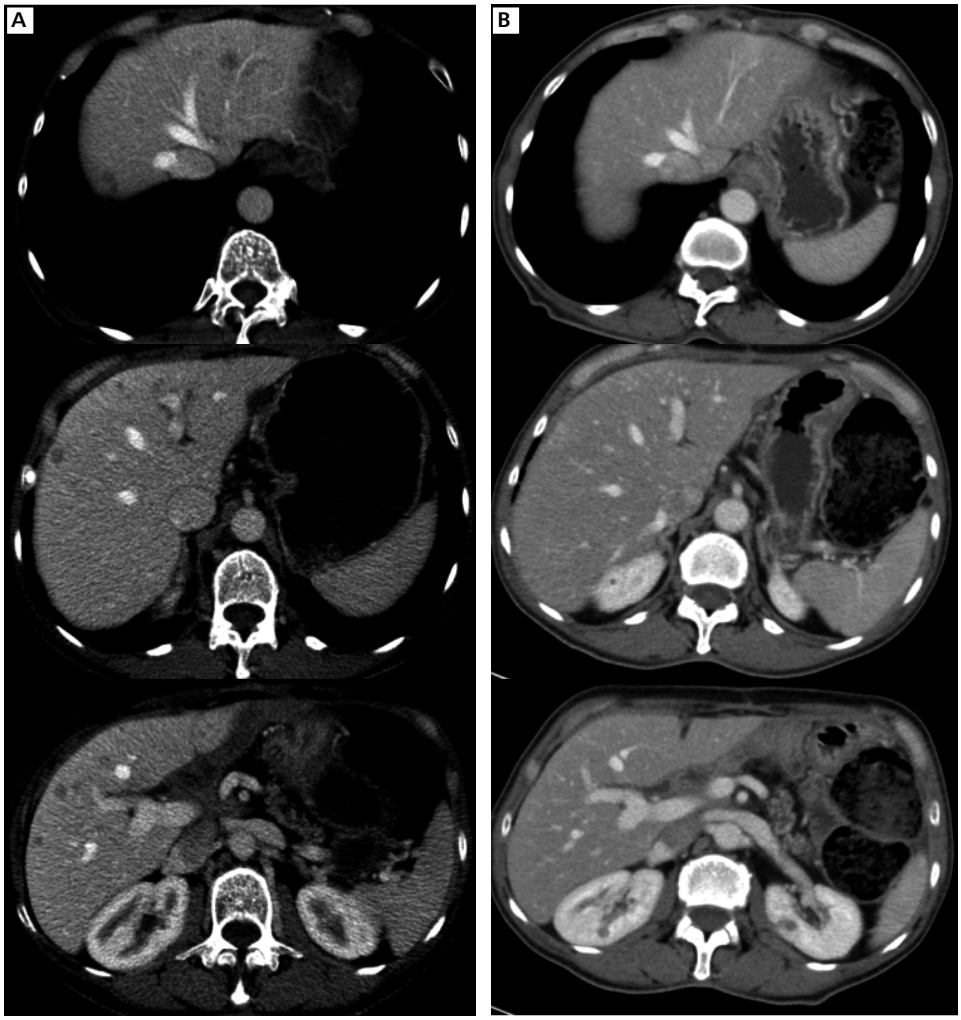

Figure 1. A. Computed tomography, 06.06.2017: numerous metastases in the liver; **B.** CT, 03.10.2017: complete regression

As per the patient's wishes and due to haematological toxicity, it was decided to discontinue chemotherapy and closely monitor the patient's state. Computed tomography performed on February 15, 2018 did not reveal metastatic changes or recurrence of the disease. Re-evaluation of serum markers on March 22, 2018 showed CA19.9 and CEA levels 7.08 IU/mL and 1.52 ng/mL, respectively. Computed tomography performed on April 13, 2018 and July 13, 2018 showed sustained complete remission. Marker levels were normal (CA19.9 — 6.8, CEA — 1.48), as was CBC. The patient gave up psychotherapy in June 2018 and took up her work.

A follow-up CT scan on November 15, 2018 showed complete remission, as did the last imaging test made on November 9, 2019. Marker levels were normal.

In 2019, the patient sporadically used the help of a psycho-oncologist. Complete remission of liver metastases lasts 24 months. Survival time from diagnosis is 36 months.

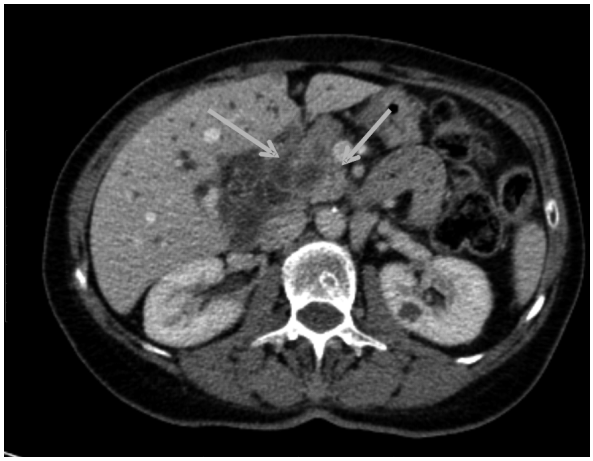

Figure 2. Computed tomography, 30.12.2016: tumour of the head of pancreas (↑↑), dilated bile ducts

Discussion

Improving the quality of life of cancer patients is an important issue for physicians, but it seems that mental disorders are much less frequently included in the history of the disease. The presented case of complete remission is undoubtedly a therapeutic success, but the perception of depressive symptoms and psychological therapy are of great importance in the entire recovery process.

There is evidence that in some patients the symptoms of mental disorders, especially depression, may precede the diagnosis of pancreatic adenocarcinoma by several or dozen months [9]. However, the authors of the cited publication agree that the diagnosis of depression and anxiety is not an indication for imaging tests for pancreatic cancer [10].

It is believed that high incidence of depression in patients with pancreatic cancer may be due to an increase in indolamine 2,3-dioxygenase, an enzyme in the kynurenine pathway that leads to a reduction in serotonin levels and the accumulation of cytotoxic metabolites in the brain [11]. Other reports, however, highlight the role of potentially common biomarkers for pancreatic cancer and depression, such as interleukin 6 (IL-6) or the *KRAS* gene [12].

The *KRAS* mutation is a well-validated factor stimulating the growth of pancreatic cancer cells. The significant importance of this biomarker in biological processes that lead to the appearance of depression has already been confirmed, especially in the population of patients over 65 years of age [12, 13]. In the described patient we did not assess the level of IL-6 and *KRAS* gene status due to the lack of patient consent.

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