

Getting ahead of pancreatic cancer and the future of early detection: A case report and mini-literature review

Sawsan Saeid^{1,A,C-F}, Michael Posala^{1,A,C-F}, Katarzyna Neubauer^{2,A,B,E,F}

¹ Gastroenterology Student Organization, Wrocław Medical University, Wrocław, Poland

² Department of Gastroenterology and Hepatology, Wrocław Medical University, Wrocław, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

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Address for correspondence

Sawsan Saeid

E-mail: sawsansaeid801@gmail.com

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Abstract

Pancreatic cancer (PAC) is an aggressive gastrointestinal cancer and the 7th leading cause of cancer mortality worldwide. About 95% of PACs are exocrine in origin and adenocarcinoma is the most common type. Risk factors include smoking, obesity and diabetes. It generally presents later in life, with more than half of all cases occurring in those over the age of 70. Pancreatic cancer is highly insidious and commonly diagnosed when advanced. It consequently carries a poor prognosis, with a 5-year relative survival rate of 6%. We report a case of a 57-year-old man with no known risk factors who was diagnosed with advanced PAC. His symptoms were mild and began a few months prior to the diagnosis. We also review the literature on the current approach to PAC, as well as ongoing changes in management and attitudes (for instance the Pancreatic Cancer Action Network), primarily concerning early diagnosis and targeted therapy. Findings indicating that hyperglycemia might be the first sign of PAC in asymptomatic patients are highlighted.

Key words: targeted therapy, hyperglycemia, pancreatic cancer (PAC), new-onset diabetes

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Introduction

Pancreatic cancer (PAC) is an aggressive gastrointestinal cancer and the 7th leading cause of cancer mortality worldwide.¹ It is the 4th leading cause of death from cancer in Europe² and the 5th in Poland.³ Interestingly, it has been found that countries with a higher Human Development Index (HDI) and gross domestic product (GDP) per capita have reported higher PAC incidence and mortality rates.⁴

Pancreatic cancer is primarily exocrine in origin (about 95%) and adenocarcinoma is the most common type.⁵ Between 60% and 70% of pancreatic adenocarcinomas occur in the head of the pancreas, with the remainder either in the body or tail.⁶ Risk factors include smoking, obesity, diabetes, and chronic pancreatitis.⁶ Pancreatic cancer generally presents later in life, with more than half of all cases occurring in those over the age of 70.⁶ In Poland, most cases occur after the age of 50.⁷

Pancreatic cancer is characteristically diagnosed late due to its predominantly asymptomatic early stage. Early symptoms are non-specific and can include nausea, pain in the upper abdomen, feeling of fullness, and constipation.⁸ “Red flag” signs/symptoms tend to appear once the disease has spread and involved other anatomical structures, making the cancer unresectable and thus incurable.⁹ The treatment is dependent on the stage of disease.⁶ If the cancer is localized and there is no local invasion or distant metastasis, it is amenable to resection, with adjuvant chemotherapy recommended. If it is found to be unresectable, the patient undergoes palliative chemotherapy. Pancreatic cancer classically has a very poor prognosis.¹⁰

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (CPG) provide oncological professionals with recommendations on PAC diagnosis, treatment and follow-up.¹¹ In Poland, the choice of systemic therapy used to be limited to gemcitabine and the less frequently used FOLFIRINOX.¹² In 2013, the drug nab-paclitaxel was approved by the U.S. Food and Drug Administration (FDA) for use in treating advanced PAC. It is now available in Poland and has been reimbursable since January 2017.

Recent studies have suggested that new-onset diabetes mellitus or impaired glucose tolerance in PAC is directly caused by the cancer itself.^{13,14} This information could be useful in the future, as new-onset diabetes or impaired glucose tolerance may be implemented as parts of a screening program for PAC.

Pancreatic cancer can affect even the most health-oriented individuals. Two ways to improve long-term survival include diagnosing the cancer at an earlier stage and enhancing or discovering new treatments. A recent review of clinical trials performed in the USA showed that patient enrollment remains unsatisfactorily low, and that many trials are proceeding to phase III despite not meet-

ing primary phase II endpoints.¹⁵ In order for the trials to proceed more effectively and efficiently, methods such as molecular profiling can and are starting to be used.¹⁵

Below we report a case of a very healthy and athletic man with very few (if any) risk factors, who presented to the hospital and was discharged diagnosed with terminal PAC.

Case report

A 57-year-old male was admitted to the Department and Clinic of Gastroenterology and Hepatology at the University Clinical Hospital in Wrocław, Poland. He had been referred to the hospital on suspicion of a pancreatic tumor, based on an outpatient ultrasound. He was a former athlete and in good general health. He had suffered only from a mild epigastric pain for a few months prior to his referral, with a recent exacerbation of the pain over the previous few weeks and a weight loss of 5 kg in the preceding month. He did not smoke or drink alcohol, had no significant family history of disease and led a very active lifestyle.

On admission, the general well-being of the patient was described as good. Lab results revealed elevated alanine aminotransferase (166 U/L), aspartate aminotransferase (94 U/L), alkaline phosphatase (386 U/L), gamma-glutamyltransferase (691 U/L), and an extremely high level (223,513 U/mL) of carbohydrate antigen 19-9 (CA 19-9). Glucose level (6.5 mmol/L) was also abnormal.

An abdominal ultrasound performed in the hospital showed metastatic-like changes within the liver (Fig. 1), and a focal change in the field of the pancreatic head measuring 34.6 × 31.2 × 35.4 mm (Fig. 2). Chest x-ray, colonoscopy and gastroscopy showed no significant changes.

We broadened the diagnostics to include computed tomography, in which a 23 × 37 × 27 mm focal lesion on the caudal end of the pancreatic head and within the uncinate process was identified, along with many focal changes within the liver, averaging from a few millimeters to one change in segment 7 (as per the Couinaud classification system) measuring 53 × 38 mm. There was fat and perivascular tissue infiltration medially and inferiorly to the tumor. In addition, direct adhesion of the infiltration to the superior mesenteric artery and vein was observed.

A fine-needle aspiration biopsy of a lesion from the left lobe of the liver was taken and metastatic changes originating from an adenocarcinoma of the pancreatic head were confirmed cytologically. The patient was discharged in a generally good condition with a referral to the Oncological Clinic for palliative treatment.

The patient had an ECOG (Eastern Cooperative Oncology Group) Performance Status of 0. In accordance with the ESMO guidelines,¹¹ he was put on a treatment regimen consisting of a combination of gemcitabine and nab-paclitaxel.

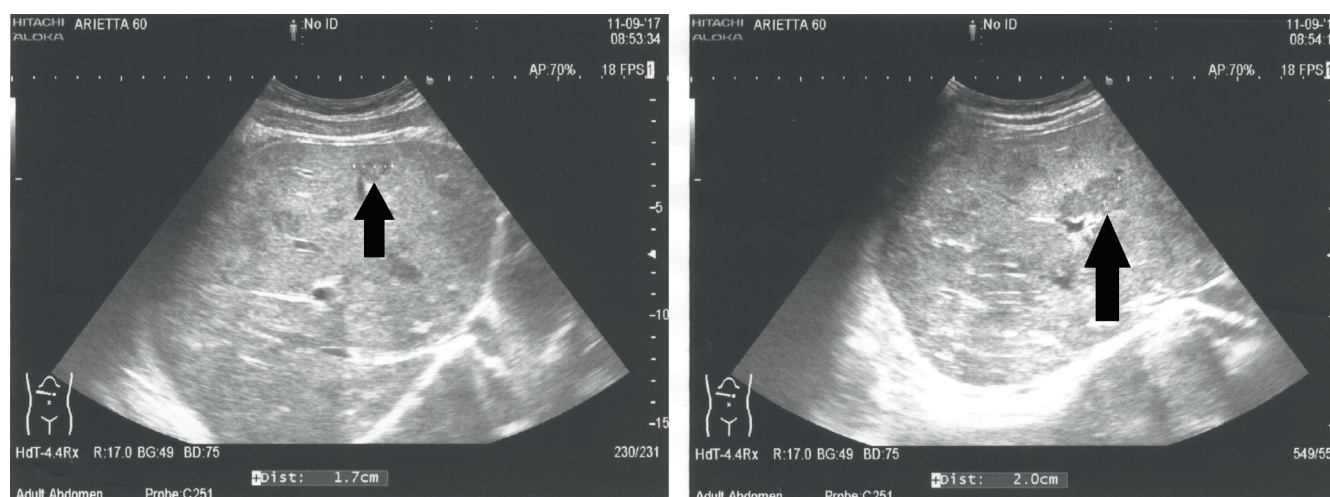


Fig. 1. Ultrasonography showing metastatic-like changes within the liver (arrowheads)

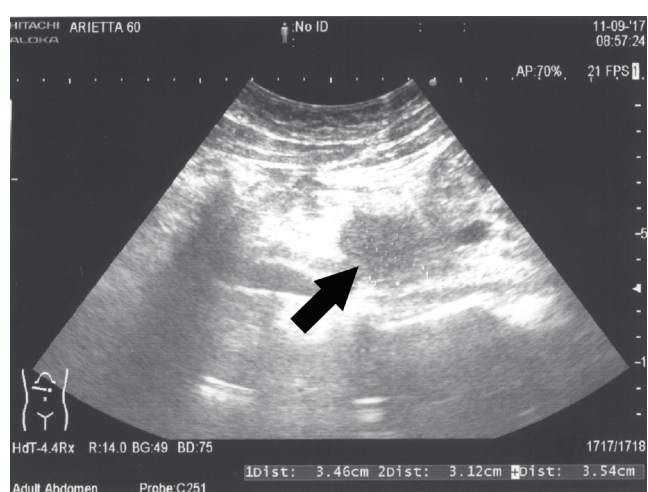


Fig. 2. Ultrasonography showing a focal change in the field of the pancreatic head measuring 34.6 × 31.2 × 35.4 mm (arrowhead)

Discussion

Pancreatic cancer is a major public health issue. Worldwide, it is the 12th most common cancer, with more than 330,000 deaths in 2012.¹ In Poland, the standardized incidence rate of PAC was 4.8/100,000 for both genders in 2010.⁷ In 2010, the total number of people newly diagnosed with PAC was 3,254, compared to 1,872 new diagnoses in 1980.⁷ Pancreatic cancer is highly aggressive and its 5-year relative survival rate of 6% is the lowest among all forms of cancer.¹⁰ This is primarily due to its remote location, the lack of screening tests or diagnostic markers, and its poor response to therapy.¹⁶ In the USA, PAC is projected to become the 2nd leading cause of cancer-related deaths by 2030, overtaking breast, prostate and colorectal cancers.¹⁷

In the case of non-metastatic exocrine PAC, surgical resection can potentially lead to a cure. Unfortunately, the disease presents late and only 15–20% of the patients are eligible for a pancreatectomy.¹⁸ However, underutilization of surgery is prominent. An examination of the National Cancer Database (NCDB) revealed that, among

those patients who were eligible for resection, 38% were not offered surgery. This could be connected to socioeconomic factors as well as physician pessimism regarding the prognosis for PAC.^{18,19}

According to the National Comprehensive Cancer Network guidelines, a clinical trial is the preferred course of treatment at all stages of PAC.²⁰ However, participation in these trials is low and they do not always match patients' needs, thus resulting in poor outcomes.¹⁵ Progress in advanced PAC can be measured by assessing the number of clinically significant therapeutic options available to patients as a "standard of care". In the USA, between 1997 and 2015, 35 different drugs or combinations were tested in 39 phase III clinical trials in advanced-stage PAC. The overall success rate of the phase III trials was 11%. However, in 85% of the cases where a prior phase II trial could be found, a phase III trial was done despite phase II not meeting its primary endpoint.¹⁵ If the future resembles the past, there is great concern that this pattern of negative trials will continue and diminish the chance for any major advancement in survival.

The European Union Clinical Trials Register is a useful resource for information on clinical trials conducted in the European Union (EU) and the European Economic Area (EEA).²¹ However, less than 2% of overall cancer research funding across Europe is directed toward PAC.²² In Poland, patients' access to clinical trials is limited. A low number of trials are conducted in Poland and as of the writing of this article, only 16 Polish studies involving PAC have been completed or have been active since 2010.²³ In comparison, there were 745 such studies in the USA.²⁴ More importantly, there is no Polish-language online resource to provide patients with information on clinical trials within Poland or elsewhere. Consequently, in the UK, 600,000 patients registered in clinical trials in 2016–2017, as opposed to only 30,000 in Poland.²⁵

Luckily, the tide is turning for PAC. A more optimistic attitude is now being embraced, exemplified by groups like Pancreatic Cancer Europe.²⁶ In addition, we

are observing greater innovation in the approach to this difficult disease, e.g., molecular profiling as a means of identifying subgroups of patients with cancer with a high probability of responding to a specific drug.¹⁵

One organization promoting this narrative is the Pancreatic Cancer Action Network (PanCAN), founded in 1999. They have adopted a multi-front approach (research, clinical initiatives, patient services, and advocacy); their aim is to double PAC survival by 2020. PanCAN has created an online global database to look for patterns in treatments, side effect management and diagnostics that could lead to improved treatment options and patient outcomes. PanCAN also maintains a database of PAC clinical trials in the USA. With the knowledge that every pancreatic tumor is different, PanCAN strongly endorses molecular profiling of a tumor to determine the best treatment options. This is the backbone of their Know Your Tumor initiative.²⁷

Recognizing genetic factors that could predict patient response to various targeted or traditional therapies could have an immediate and major effect on patient care.¹⁵ For example, targeted therapies avoid the toxicity of multi-agent chemotherapy. Based on studies under the auspices of the Australian Pancreatic Cancer Genome Initiative, 4 subtypes of PAC have been defined: stable, locally rearranged, scattered, and unstable. Unstable genomes were found to contain more than 200 structural variation events, which often implies damage to the DNA repair pathways. This could mean that patients with PAC who have DNA damage repair alterations may be especially sensitive to platinum-containing chemotherapeutics and/or PARP inhibitors.²⁸ Another targeted approach involves measuring patients' levels of hyaluronan, which is a glycosaminoglycan present in the microenvironment surrounding PAC. Hyaluronan contributes to elevated interstitial pressure, and its inhibition with pegvorhyaluronidase alfa (PEGPH20) leads to the expansion of tumor-associated blood vessels, allowing the delivery of other drugs to the tumor.²⁹ Finally, PAC is a highly immunosuppressive disease, and in order to fight this immunosuppression and recruit T cells to the cancer microenvironment, immune checkpoint inhibitors such as anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies are being tested.^{15,30}

Early detection

Up to 80% of patients with PAC are hyperglycemic or diabetic, and this can be seen pre-symptomatically.^{13,31} In a study by Sharma et al., it was found that patients were hyperglycemic for a mean period of 30–36 months before diagnosis.³² Following resection of the tumor, condition of the patient regarding diabetes has been found to improve, suggesting that it is caused by the cancer.^{13,33} Interestingly, elderly patients with new-onset diabetes have an approx. 8-fold higher risk of having PAC than the general population.³¹ The pathogenesis of PAC-associated diabetes is

unknown. However, the excessive occurrence of diabetes in PAC indicates that β -cell dysfunction, possibly related to tumor-secreted products, is the primary cause.³¹ One proposed mechanism is the release of exosomes by PAC cells, which deliver adrenomedullin to β -cells, resulting in their dysfunction and death.^{34,35}

Since screening for asymptomatic PAC in the general population is not practical due to its low incidence, screening will have to be limited to people at high risk for PAC.^{31,36} The concept of using new-onset diabetes as a means of detection is prominent; it may lead to the diagnosis of asymptomatic, early-stage PAC, which, as noted above, is potentially amenable to surgical resection and cure. A risk prediction model could help recognize individuals at high risk for PAC among those with new-onset diabetes.³⁷

On the other hand, primary type 2 diabetes is quite common and clinically indistinguishable from PAC-associated diabetes. This dilemma can be solved by identifying a unique serologic marker capable of differentiating between the 2 types. Screening strategies applying this approach have already been proposed, e.g., new-onset diabetes as the 1st sieve, followed by a potential biomarker acting as the 2nd sieve.^{31,36} Currently, there is no reliable diagnostic biomarker. CA 19-9 is secreted by PAC tumor cells, but it is primarily used as a prognostic marker.¹² It performs poorly as a screening tool, with a low positive predictive value of 0.5–0.9%.³⁸ Looking into the future, the use of glycoprotein biomarkers could provide a solution.³⁹

Conclusions

Pancreatic cancer impacts all age groups, genders and ethnicities. It can affect anyone; our patient, for example, had none of the known major risk factors (e.g., smoking, obesity, etc.). Within a few months of the onset of symptoms, he was diagnosed with advanced PAC. Even with treatment, his prognosis was extremely poor.

Pancreatic cancer patients deserve treatments with better outcomes, e.g., through tumor typing, and better access to appropriate clinical trials. If this type of cancer is to be discovered early, testing will have to be done in asymptomatic individuals. Consequently, it is important to reiterate that hyperglycemia might be the first sign of PAC in asymptomatic patients.

It is our hope that the data presented here will mobilize a number of key groups within the healthcare system. In Europe, 64% of the general population admit to knowing almost nothing about PAC.⁴⁰ Increasing public awareness of the disease with the help of health officials may lead to increased activism and funding for research. Cooperation among officials, researchers and oncological specialists is paramount if clinical trials are to become more accessible and productive.

Last but not least, the role of general practitioners or primary care providers is crucial. Given the compelling

link between new-onset diabetes and asymptomatic PAC, their involvement is vital as the point of first contact and in checking patients' blood glucose. The establishment of early detection algorithms would better guide these doctors in the management of their patients, i.e., knowing who to test and who to refer to specialist care.

In the words of George MacDonald, "The best preparation for the future is the present well seen to".

ORCID iDs

Sawsan Saied  <https://orcid.org/0000-0002-9211-9249>
 Michael Posala  <https://orcid.org/0000-0002-0241-0279>
 Katarzyna Neubauer  <https://orcid.org/0000-0003-3650-9311>

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