Pancreatic cancer: The importance of screening in atypical diabetes presentations

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Article points

1. Pancreatic cancer is hard to diagnose as most of its symptoms are common and non-specific.

2. It is associated with type 2 diabetes, often in people with a low or normal BMI.

3. Conducting a regular audit of people who have type 2 diabetes despite a low or normal BMI may help to identify people who would benefit from screening.

4. Earlier diagnosis could potentially increase 5-year survival significantly from the current rate of 4%.

Key words

– Atypical presentations
– Pancreatic cancer
– Screening
– Type 2 diabetes

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Survival times for pancreatic cancer in the UK are some of the worst in Europe; however, they could be increased dramatically by earlier diagnosis. Approximately 80% of people with pancreatic cancer have glucose intolerance or diabetes, and one atypical presentation of pancreatic cancer is new-onset type 2 diabetes in an individual with a low or normal BMI. This article reviews the links between pancreatic cancer and diabetes, and calls for a yearly or twice-yearly audit to identify people with an atypical presentation of type 2 diabetes, who may benefit from screening. This approach is endorsed by the charity Pancreatic Cancer Action.

Pancreatic cancer has one of the worst prognoses of all cancers, and indeed all diseases. If a person is diagnosed with pancreatic cancer, this currently equates to an almost inevitable death; only 4% of those diagnosed survive beyond 5 years. The average life expectancy is 5–6 months at diagnosis, and the proportion of people who survive for 5 years has barely changed in the last 40 years (Pancreatic Cancer Action, 2017).

Symptoms of pancreatic cancer

Classically, the symptoms of pancreatic cancer are epigastric pain (in approximately 70% of cases), jaundice (50% of cases) and unexplained weight loss (10–30% of cases; Pancreatic Cancer Action, 2017). Nausea, anorexia, malaise and vomiting are also common. Atypical symptoms include new-onset type 2 diabetes in a normal- or low-weight individual, resistant dyspepsia, altered bowl movements and deep vein thrombosis. However, the symptoms of pancreatic cancer often only present late in the illness. The more severe symptoms tend to represent a pancreatic cancer that is spreading and starting to block or interfere with other organs and systems.

Frustratingly, the aforementioned symptoms are vague, non-specific and ubiquitous in the GP consulting room. The symptoms are often evidence of other, potentially less devastating, illnesses. Pancreatic cancer is, therefore, commonly misdiagnosed as gallstones, gastritis, irritable bowel syndrome, indigestion and liver disease. People will often ignore their symptoms for months before going to the GP. Indeed, a survey by the charity Pancreatic Cancer Action (2015) found that over half of patients felt they had dismissed their own symptoms and 61% felt that their GP had initially dismissed those symptoms too.

The positive predictive values (PPVs) of individual symptoms give a clue as to why the diagnosis can be so difficult. Excluding jaundice, the PPVs of the most common symptoms of pancreatic cancer are all below 1% (Stapley et al, 2012). NICE (2015) sets the PPV for the 2-week-wait cancer referral system at 3%, and even this was reduced from 5% previously. Interestingly, surveys show that patients feel the figure should be 1% (Pancreatic Cancer UK, 2015). Even when weight loss is paired with another symptom, the PPVs go no higher than 2.7%, which is still below the referral threshold.

Pancreatic cancer survival times

Survival times in the UK are some of the worst in Europe. Quite why this is the case is difficult to unpick, but it is clear that the situation needs to improve. The survival time seems to be related

to how a person with pancreatic cancer presents to the medical profession. Those who present as an emergency have a 12-month survival rate of 9%, whereas those who are referred via the 2-week-wait system have a rate of 19%. The individuals who do best are those who are referred as routine or elective GP referrals: they have a 12-month survival rate of 26% (Siriwardena and Siriwardena, 2014).

These figures may be partly explained by the severity of illness, as those with more severe illness are more likely to present to Accident and Emergency, and it may be that the late features of pancreatic cancer (in particular jaundice from obstruction of the lower common bile duct) are what cause people to consult a healthcare professional.

Nevertheless, the survival times are unacceptably poor, and the percentages highlight that they could be improved if GPs consider the diagnosis as early as possible and then refer their patients onwards. It is estimated that 5-year survival rates would increase to 30–40% if earlier diagnosis of pancreatic cancer was achieved (Ghatnekar et al, 2013). A jump from 4% to 40% would clearly be fantastic.

Pathophysiology

Pancreatic cancer is a cancer that conceals itself from detection and protects itself from treatment. Its mechanism has been described as akin to that of an invisibility cloak from the Harry Potter books. Work by researchers at the Washington University School of Medicine (2006) shows that T-lymphocytes can act as this invisibility cloak. Regulatory T-cells (previously known as suppressor T-cells) normally inhibit the immune system from killing unwanted cells, and this helps prevent autoimmune-type reactions. However, the pancreatic tumour cells hijack the regulatory T-cells' abilities and increase the number of T-cells around the tumour, effectively shielding it from attack by the body's immune system.

The invisibility cloak concept can be taken one step further when considering what is known as the desmoplastic reaction. This is sometimes seen as the hallmark of pancreatic tumours. The term describes the growth of the dense fibrillar collagen-rich matrix that surrounds the pancreatic tumour. This material acts both to create a microenvironment that promotes tumour growth and, at the same time, to shield or cloak the tumour from chemotherapy and radiotherapy (Merika et al, 2012).

Links with type 2 diabetes

Earlier in this article, new-onset type 2 diabetes in normal- or low-weight people was listed as an atypical presentation of pancreatic cancer. The debate about the relationship between diabetes and pancreatic cancer has raged for some time. It is a true chicken-and-egg scenario. Approximately 80% of people with pancreatic cancer have glucose intolerance or diabetes, and studies supporting either direction of causality abound (Wang et al, 2003).

The hypothesis that pancreatic cancer causes diabetes is supported by the observation that, when diabetes is found in cases of pancreatic cancer, it is usually identified within the 2 years preceding the cancer diagnosis. This short window suggests the pancreatic cancer causes the diabetes (otherwise, the longer one had type 2 diabetes, the more likely one would be to get pancreatic cancer). Furthermore, researchers have shown that, when pancreatic cancer was induced in hamsters, abnormalities appeared in the islet hormones that are essential for regulation of blood glucose, again suggesting that the cancer causes the diabetes (Permert et al, 2001).

Support for the alternative hypothesis, that type 2 diabetes causes pancreatic cancer, includes the observation that, in the petri dish, insulin promotes the growth of pancreatic cancer cell lines in rats, hamsters and humans (Wang et al, 2003). In addition, other studies have shown that higher blood glucose and free fatty acid levels, as found in diabetes, may promote pancreatic cancer growth (Fisher et al, 1995).

It is also possible that the two hypotheses are not mutually exclusive. It seems we are some way off from fully understanding the underlying biochemistry. However, the association between diabetes and pancreatic cancer is irrefutable, and

Page points

1. Pancreatic cancer survival times are related to how the individual presents to the medical profession. The 12-month survival rate of people who present as an emergency is 9%; however, this increases to 26% in routine or elective referrals.

2. Around 80% of people with pancreatic cancer have glucose intolerance or diabetes, and there is evidence for both directions of causality.

3. New-onset type 2 diabetes in people with a normal or low BMI is a potential marker of pancreatic cancer.

Scenario 1.

Charles was a 70-year-old man, very independent. Two years previously, he had had a non-ST-segment-elevation myocardial infarction. He was treated for this medically and he appeared to make an excellent recovery. He presented a few months after this to his GP with increasing tiredness and exhaustion. He was referred to cardiology, who saw him on multiple occasions, slowly increasing his cardiac medications. He was discharged to the cardiac nurse and GP, who both continued to aggressively treat him with cardiac medications.

The patient was a retired engineer and kept a close eye on his weight with regard to his fluid balance, as did his GP and cardiac nurse. He continued to lose weight, which was interpreted by all involved that his cardiac medications were working. A familiar discussion about the importance of managing his fluid weight was had on a regular basis.

Unfortunately, at no point did the patient improve clinically. He continued to complain of tiredness. Then he started to complain bitterly that he was losing weight and had no appetite. The GP and cardiac nurse were concerned that they were over-diuresing him and offered this as an explanation for his weight loss and general exhaustion. He developed type 2 diabetes and, as he had a low BMI, was picked up by a new diabetes audit. Unfortunately, an ultrasound scan showed an abnormality on his pancreas that transpired to be pancreatic cancer. It was too late for any intervention and he died shortly afterwards. It was the first time the audit had been run.

it offers an opportunity to hunt for a disease that does its utmost to hide from both the patient and the doctor.

Screening for pancreatic cancer

There are currently no validated screening tests or programmes for pancreatic cancer (Makohon-Moore and Iacobuzio-Donahue, 2016). However, the link between diabetes and pancreatic cancer, mixed with the power of data and the clinical acumen of GPs, can be harnessed in order to improve outcomes. A simple, low-cost audit run on a yearly or twice-yearly basis can identify a list of individuals who have both a new diagnosis of type 2 diabetes and a normal or low BMI. In a practice of 10 000 patients, this will probably generate a list of less than five people a year. With GPs generally having a list size of 2000–3000 each, it is likely that each GP will identify one or two people a year.

The important, and often difficult, next step – but one that the GP is by far best placed to do – is to decide how to action these data in a holistic manner. The first thing is simply

to review the patient's notes. With the mind focused on pancreatic cancer, ask whether something written in the notes warrants urgent investigation. If not, ask whether it is appropriate to contact the patient to discuss the findings? This will of course require the use of the sensitive communication that the vast majority of GPs excel in. When I have made this contact myself (usually by telephone), every single patient has been thankful that their surgery has been proactive, and I have been able to reassure them that any tests I organise are precautionary only, and that the chance of pancreatic cancer is low.

Since running this annual audit, the need for scanning in my practice has gone down. I get the same number of patients but the diabetes team is much more aware of the link and often initiates the scan (via the GP) as soon as it sees a new person with diabetes and a normal or low BMI. In effect, the audit becomes a backup, to catch the people who slip through the initial net. It picks up those who are diagnosed elsewhere, those who did not attend appointments, those who transfer from another practice and those who are simply missed due to human error.

When the list is generated, the next step may depend on access to scans and local guidelines. Most localities have good access to ultrasound scans. Some may have access to computed tomography (CT). Although CT scans are better, with high-resolution CT scans having a reported sensitivity and specificity of up to 100%, ultrasound performs fairly well (Siriwardena and Siriwardena, 2014). The latter has been shown to have a sensitivity of up to 90% and a specificity of 97%. However, a sensitivity of 90% means one in ten pancreatic cancers will be missed. So, even if your patient has a normal ultrasound and they have no worrying symptoms apart from the new-onset diabetes, they may still have pancreatic cancer. This is often the hardest situation for the GP and patient to manage. At this point, communication and shared decision-making become all-important.

It may be that you refer to the local secondary care team, explaining that you are concerned

your patient has been identified as having new-onset atypical diabetes and that you are aware there is an association between atypical diabetes and pancreatic cancer. You could ask for a review of the patient (which in all probability will culminate in a CT scan) or you could simply ask the consultant or radiology department whether they would consider requesting a CT scan of the patient's pancreas.

Concluding remarks

Unfortunately, as this article highlights, the diagnosis of pancreatic cancer is incredibly difficult. This is coupled with a lack of evidence for a clear screening programme. One option is to hide behind the well-worn phrase, "there is no randomised controlled evidence for that". I would argue that, when a disease is so devastating, when the path to diagnosis is unclear and when the only thing that currently improves survival is early diagnosis, then (with the caveat that the individual makes an informed choice) a proactive approach – one that may involve being persistent with referrals to secondary care – is justified.

One of the key messages about pancreatic cancer is that, if you don't think of it, you probably won't find it. It may, however, be argued that the inverse is true: if you think of it and then look for it, you will probably find it. Unfortunately, pancreatic cancer has long been the poor man of cancer awareness. This is no doubt partly to do with the diagnostic difficulties, but the peculiarities of Government and commercial funding priorities has not helped the situation. Currently, pancreatic cancer only receives 1% of cancer research funding despite the fact that it is the fifth most common cause of cancer-related death. The charity Pancreatic Cancer Action is trying to remedy this situation. It is heavily involved in promoting awareness of pancreatic cancer and has worked with the Royal College of GPs to produce a free pancreatic cancer e-learning module, which has received resoundingly good feedback (available at: **https://is.gd/RVePKK**). It is also supporting the drive towards the use of the simple, low-cost audit outlined in this article. ■

Scenario 2.

Mary was a 75-year-old woman with new-onset type 2 diabetes and a normal BMI. She was picked up by the diabetes audit. Options were discussed and she opted for an ultrasound scan of her pancreas. She had no symptoms of pancreatic cancer and only took one antihypertensive agent. She did not require metformin for her diabetes.

The ultrasound scan came back as normal. The problems with ultrasound scanning for pancreatic cancer, and options about how to proceed, were discussed. The patient came to a decision to undergo 6-monthly reviews. The specific remit of each review was to consider if there were any signs, typical or atypical, of pancreatic cancer.

Two years later, another ultrasound was carried out as the patient had a borderline amylase level. The scan was again normal. Five years after the diagnosis of type 2 diabetes, Mary remains well and there are no signs of pancreatic cancer. However, both she and her doctor feel confident of what signs and symptoms to look for. She knows to organise an urgent review by her GP if she develops any worrying signs. She and the GP both feel that the most important thing about pancreatic cancer is to "think of it".

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Pancreatic Cancer: Early Diagnosis in General Practice

The free e-learning module from the Royal College of GPs is available at:

https://is.gd/RVePKK