Depression as an early manifestation of pancreatic cancer

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SUMMARY

Ever since the early 1930's, an association between pancreatic cancer and depression has been noticed. The prevalence of depression is higher in patients with pancreatic cancer than it is in patients with other abdominal neoplasms, and psychiatric symptoms often precede somatic symptoms. Despite further research on this co-occurrence, the true mechanism of interaction is still not clear. Knowing what it is that forms the biological link between depression and the pancreatic tumour, could be of great importance to the future diagnostic and therapeutic workup of these patients.

Different theories are proposed. Plausible are the depression being induced through cytokines more specifically IL-6, alterations in the tryptophan-kynurenine, glutamate and serotonin pathways, and antibodies disturbing brain functioning directly or through serotonin. Depression causing cancer is also possible, but to date of unknown importance in pancreatic cancer. All this information brought together makes depressive symptoms of diagnostic importance in pancreatic cancer. The insights pave the way for the development of targeted therapies, hopefully to be implemented in clinical practice in the future.

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INTRODUCTION

In the early 1930's, pancreatic cancer was found to coincide with psychological symptoms.[1] It appeared to be specifically associated with a triad of nervous symptoms: depression, anxiety and sense of impending doom. What was even more remarkable was that these feelings could precede the somatic symptoms often seen in pancreatic cancer such as pain, jaundice, anorexia and weight loss. If so, the nervous alterations also preceded the diagnosis of pancreatic cancer and were less likely to be attributed to the patient knowing his disease and its poor prognosis. Ever since these findings were published, researches tried to objectify this link between pancreatic cancer specifically and depression. Fras *et al.* conducted a study in 1967, comparing the prevalence of depression prior to surgery in patients with pancreatic cancer to the prevalence in those with other intra-abdominal neoplasms.[2] In this retrospective study, 76% of the patients with a tumour of the pancreas had depressive symptoms, compared to only 20% of the patients with colon cancer. A few years later, Jacobsson and Ottosson confirmed these findings in a retrospective study reviewing patients treated for gastric and pancreatic cancer.[3] Interestingly, the first large prospective study came up with similar results as the retrospective ones.[4] Patients with advanced stages of pancreatic cancer (n=7,107) had greater total psychological disturbance, characterised by depression, anxiety, fatigue and confusion-bewilderment, than those with equally advanced stages of gastric cancer (n=111).

PATHOPHYSIOLOGY: DOES CANCER CAUSE DEPRESSION, AND HOW?

As the high prevalence of depressive symptoms in these patients has already been proved, questions arise as to the aetiology of this co-occurrence. First of all, pancreatic cancer in

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particular is characterised by a very poor prognosis. Its reputation as a deadly and painful disease can cause existential issues when confronted with this diagnosis.[5] However, when study results were controlled for poor prognosis and uncontrolled pain, the effect of high depression rates in pancreatic cancer remained.[6] Some cases of therapy-resistant anxiety and depression are reported, where psychiatric symptoms improved after the pancreatic tumour was excised.[7,8]

In 1996, Passik and Breitbart suggested the possible biological link could be the secretion of hormones, neurotransmitters, digestive enzymes or bicarbonate by the pancreatic tumour, causing alterations in the brain and therefore depressive symptoms. Another theory stated that alcohol abuse would be the link, being more frequently seen in both depression and pancreatitis. However, this could not be confirmed, as there was insufficient epidemiologic evidence for a causal relationship.[9] Other overlapping factors between depression and cancer in general such as smoking, obesity and family history are to date not studied for causal relationships in pancreatic cancer.[10]

CYTOKINES AS A POSSIBLE EXPLANATION

When looking for molecules likely to play a role in the association between pancreatic cancer and depression, the immune system provides our first candidate, namely cytokines.[11] In case of an infection, pathogens cause a cytokine release and adaptive *sickness behaviour.* The patient can develop sleepiness, lethargy and loss of appetite. On the other hand, in chronic illnesses a chronic release of cytokines might cause the brain to overreact and the sickness behaviour might turn into depression, a non-adaptive response.[12]

Regarding cytokines individually, interleukin 6 (IL-6) is interesting. Researchers measured serum levels of this cytokine in patients with pancreatic adenocarcinoma (n=41) and chronic pancreatitis (n=56) and compared it to serum IL-6 levels of 50 healthy subjects.[13] IL-6 was higher in, amongst others, pancreatic carcinoma and pancreatitis compared to healthy subjects; pancreatic tumours with a diameter ≥3,5 cm compared to the smaller tumours; and patients with liver metastasis compared to the ones without liver metastasis. Another interesting fact is that cytokine therapy given for cancer or viral infections is sometimes associated with the development of depression.[14] In a study on patients with renal cell carcinoma or melanoma treated with IFN-α, IL-2 or both, serum tryptophan and tyrosine levels were measured.[15] It was found that the magnitude of decrease in serum tryptophan was positively correlated with the development and severity of depressive symptoms. The authors suggested that, as the amino acid tryptophan is a precursor of the hormone serotonin, cytokines could facilitate the depression seen through reduced production of serotonin. The involvement of serotonin will be discussed more thoroughly further on in this review.

Breitbart *et al.* later used this information to set up a study on 75 subjects.[16] They recruited 43 patients with pancreatic carcinoma on a consistent chemotherapy regimen of which seventeen met the diagnostic criteria for Major Depressive Episode (MDE) and the other 26 did not; and 32 healthy subjects of which seven had MDE and the other 25 did not. A significant association was found between (amongst others): pancreatic cancer and higher IL-6 and IL-10 levels and lower TGF-β levels; depression and higher IL-6 levels and lower IL-2/IL-4 ratios; severity of depression and higher IL-6 levels. Also, no interaction between depression and cancer was found, making their effects on IL-6 (or the effect of IL-6 on each one of them) independent effects. Interestingly, IL-6 was not associated with other measures of psychological distress such as anxiety and hopelessness. The authors suggest that the relationship between IL-6 and depression might be unique to the symptoms of depression, and that other cytokines may have other specific impacts on physical or psychological functioning. In that light, *sickness behaviour* may result from the co-occurring effect of the illness on multiple cytokines.

THE INVOLVEMENT OF SEROTONIN

In order to better understand how the cytokines mentioned above could specifically cause depression, serotonin arrives on the scene. It is known that major depression comes with lower levels of serotonin than seen in healthy subjects. A tumour-induced decrease of those levels could therefore provide evidence for a causal relationship between cancer and depression.

Recently, Botwinick *et al.* proposed the kynurenine pathway as proof of this concept (*Figure 1*).[17] They based their hypothesis on the fact that kynurenine is both involved in depression and in tumour-induced immunosuppression. Seventeen patients with pancreatic adenocarcinoma were recruited prior to surgery. It was found that the ratio of plasma kynurenic acid/tryptophan was negatively correlated with both the score on the Beck Depression Inventory (BDI) and the score on the Beck Anxiety Inventory (BAI). This remained significant even after controlling for tumour burden. It appeared that the ratio of kynurenic acid relative to other metabolites was more important to mood than the absolute level of kynurenic acid. Regarding tumour burden, plasma kynurenine was found to be positively correlated with the percentage of metastatic lymph nodes and negatively correlated with the tumour's diameter.

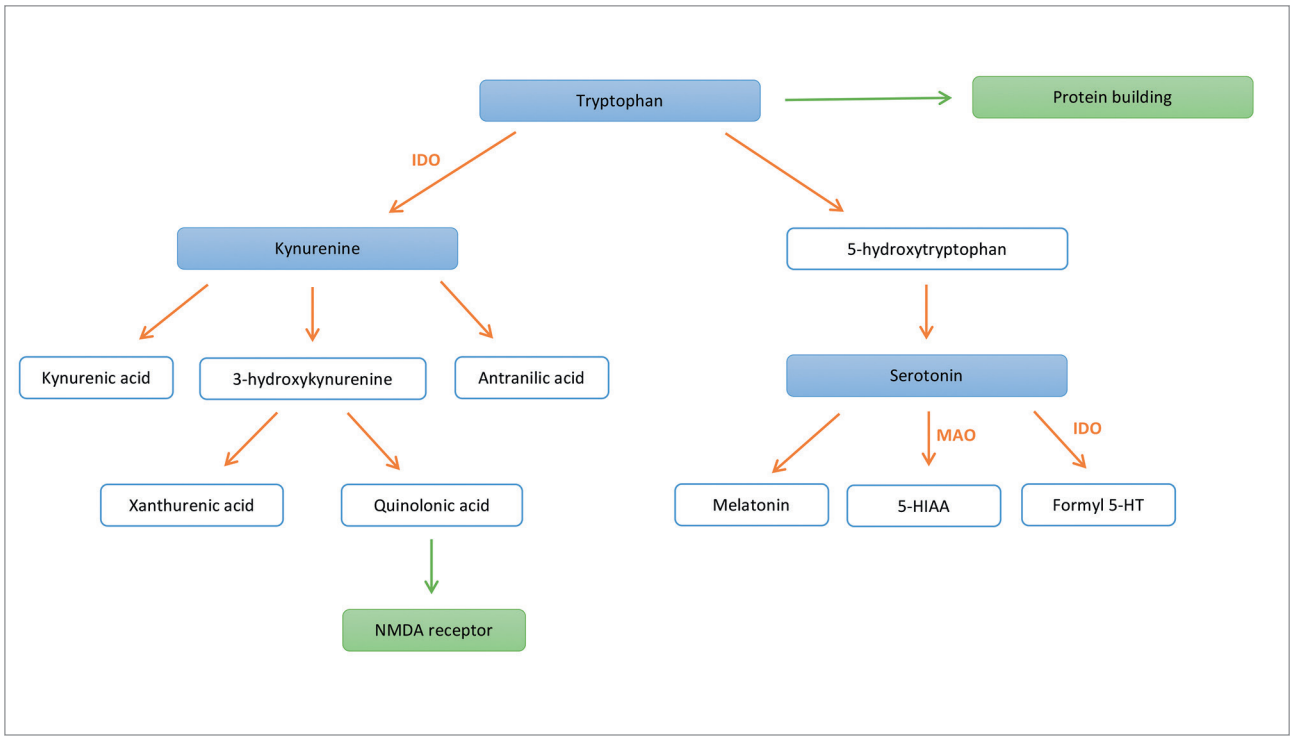

FIGURE 1. Tryptophan pathway.

Of course, these findings do not yet prove how malignant cells can have an influence on the kynurenic pathway. When reviewing the literature, Botwinick *et al.* suggested that the indoleamine 2,3-dioxygenase enzyme (IDO) could be the missing puzzle piece. It catalyses a first rate-limiting step in the degradation of tryptophan. In patients having both an inflammatory somatic disease and depression, levels of pro-inflammatory cytokines (IL-2, IFN-γ and TNF-α) but also of IDO were elevated.[18] High IDO causes more degradation of tryptophan and makes this precursor less available for serotonin production.[19] Upregulation of IDO can therefore cause neurological alterations through serotonergic deficiency and glutamatergic overproduction.

A study on the IDO enzyme in pancreatic adenocarcinoma revealed that the expression of this enzyme was higher in metastatic cells taken from affected lymph nodes than in cells of the primary pancreatic tumour.[20] Normal pancreatic tissue did not show IDO staining. Interestingly, the primary tumour cells of patients who did not have metastases (n=3) were just as well not staining for IDO, but they did when the cell lines were treated with IFN-γ for 48 hours. Normal pancreatic cells treated with the serum of a patient having pancreatic carcinoma with positive lymph nodes, also showed IDO-expression while not staining before the treatment. Combining these findings, one could suggest that this can be explained by the fact that the malignant cells migrating to the lymph nodes travel through a cytokine-rich environment and, by doing so, are stimulated to start expressing IDO. This is an advantage for the malignant cells, as they create a good immunological environment for themselves. IDO indeed starves the T cells of tryptophan and that turns them into regulatory T cells, which are immunosuppressive.[20] A possible explanation for Botwinick's negative correlation between tumour size and plasma kynurenine could be that tumours with high IDO expression metastasise earlier, when the primary lesion is still small, causing a bias in found correlations between tumour size and kynurenine levels.

The impact of IDO on psychological alterations is still hypothetical. However, this study provides interesting possible applications in clinical practice. For example, IDO mRNA in the serum of patients may one day be used to determine which patients have affected lymph nodes. Treatment with IDO pathway inhibitors could hypothetically become part of the treatment of pancreatic cancer.

THE INVOLVEMENT OF GLUTAMATE

It has been proved that glutamine levels are high in cerebrospinal fluid of depressed patients and so are the glutamate levels in their serum.[21,22] Glutamate activity appears low in the prefrontal cortex and the anterior cingulate cortex of patients with major depressive disorder (MDD) when performing magnetic resonance spectroscopy. Moreover, it appeared that ketamine (which is an antagonist of one of the gluta-

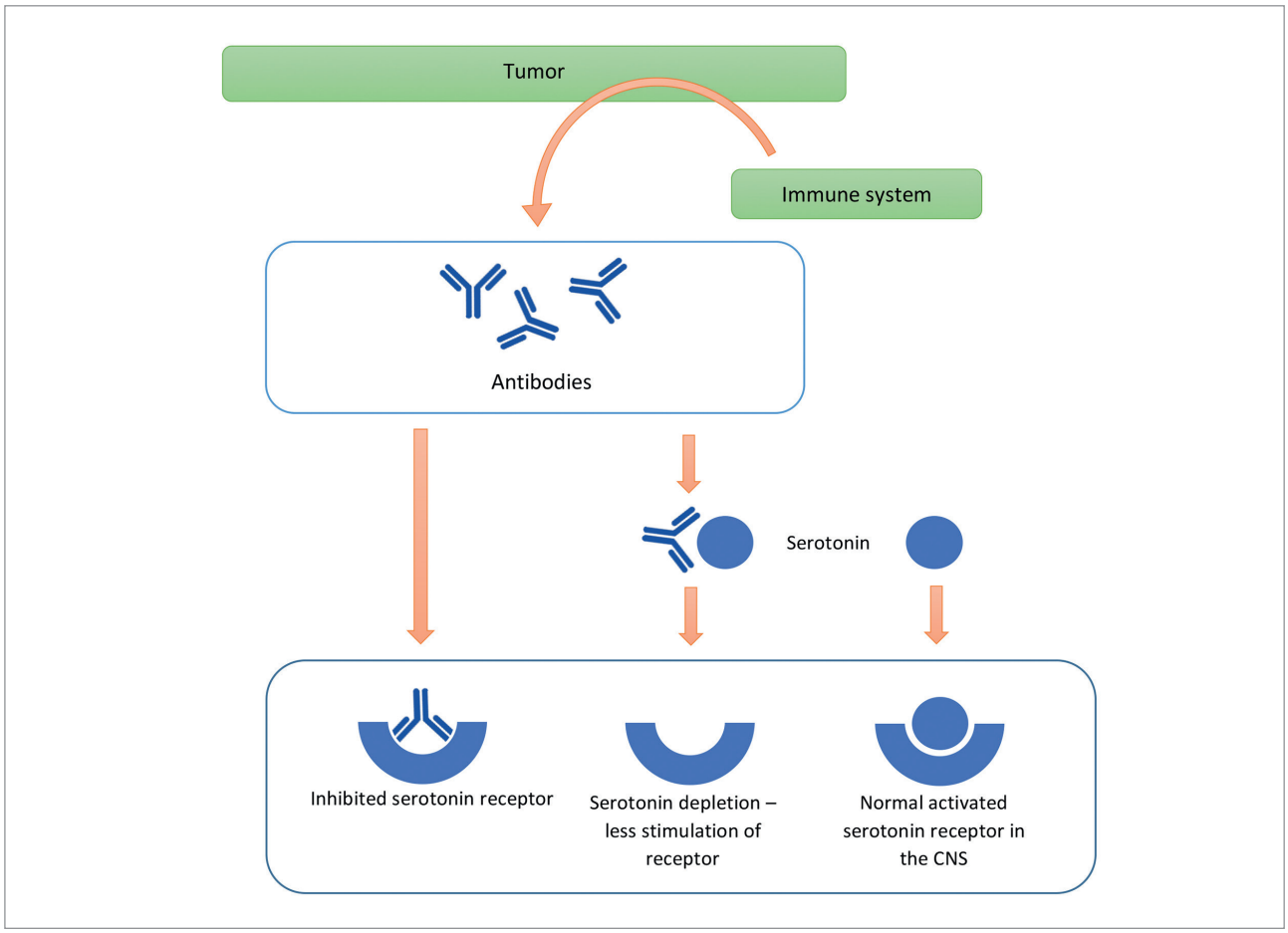

FIGURE 2. Possible ways of disturbance of serotonin by tumor-induced antibodies.

mate receptors) had clinical antidepressant effects.[23] Linking cancer to the glutamate alterations in depression brings up a few possible pathways. First, cancer cells can release large amounts of glutamate through a cysteine/glutamate antiporter. This is proved mostly for gliomas, but is also described in melanoma, breast and prostate cancer.[24] Secondly, peripheral cancers might weaken the blood-brain barrier that is normally impermeable for glutamate. This has been reported in breast cancer, and was mediated through substance P or IL-7 release by the tumour.[25,26] To date no direct evidence is available that these mechanisms are present in pancreatic tumours. However, the pathway that is suggested is interesting and can be valuable to further research.

ROLE OF THE HUMORAL COMPONENT

When considering the relationship between depression and cancer, the humoral immune system is likely to contribute. It can respond to proteins released by cancer cells. Antibodies can then decrease the activity of serotonin by blocking its receptor, or by acting as a serotonin receptor and as so decreasing serotonin availability (*Figure 2*). Cell-mediated immunology can also be of importance, as T lymphocytes could cause non-metastatic tissue damage in the brain. Keeping that in mind, there is an interesting phenomenon called paraneoplastic limbic encephalitis (PLE). First described by Corsellis *et al.* in 1968, it is defined as a disorder characterised by personality changes, depression, irritability, seizures, memory loss and sometimes dementia caused by cancer. Out of 1,047 patients with tumours and neurological symptoms, 50 fulfilled the criteria of PLE.[27] In 30 of them, antineuronal antibodies were found (anti-Hu, anti-Ta, anti-Ma). This study provides the plausible hypothesis that tumours can cause depression through tumour-induced autoimmunity, acting against the limbic system.

CAN DEPRESSION CAUSE CANCER?

Depression is not necessarily a presenting symptom of the disease. It could just as well be the other way around: depression causing a higher risk on developing cancer. The incidence of cancer is slightly higher in a depressed population than it is in a reference population.[28] Psychological stress seems to cause alterations in the immune system and, when chronically present, also in autonomic and endocrinologic functioning. As we think of possible theories for depression

KEY MESSAGES FOR CLINICAL PRACTICE

1. Depression and pancreatic cancer are highly associated.
2. Depression can be the first symptom of and therefore caused by the pancreatic neoplasm.
3. Biological links between both are getting clearer, and are found in serotonin, tryptophan-kynurenine and cytokine pathways.
4. Treatment of the depression improves quality of life, but not yet survival.

causing an immune competence impairment, a few ideas come to mind: depression leading to impaired immunity, depression leading to an alteration in the hypothalamic-pituitary axis, a carcinogenic effect of antidepressants, common or adjacent genes involved in both depression and cancer, an indirect effect e.g. depressed woman getting pregnant less often and therefore being more at risk for breast cancer. Further investigation will be necessary to look at the specific impact of depression on the development of pancreatic cancer and how this can be of therapeutic importance in the future.

HOW TO DEAL WITH DEPRESSION

The incidence of depression in patients with cancer is associated with a higher mortality rate, even after controlling for confounding variables such as severity of illness.[29] However, at the current time there is no evidence on whether treatment of depression could improve survival. There is also no evidence that coping strategies can influence survival or reoccurrence rates, so no one should be pressured into adopting particular coping styles in order to improve prognosis. What we do see, is that proper treatment of depression can improve the patient's quality of life. With regards to the poor prognosis of pancreatic cancer, this makes it worth paying attention to.[30]

Treatment of depression in these patients consists of pain control, psychological support and antidepressants.[11] As to antidepressants, the efficiency of all classes was comparable in cancer.[5,11] The choice of antidepressant should therefore depend on the possible adverse effects of each one and on the main depressive symptoms of the patient. Keeping the possible causal relationships between depression and pancreatic cancer mentioned above in mind, SSRI's could be considered a targeted therapy.[10]

CONCLUSION

Data on the prevalence of depression in pancreatic cancer are unequivocal: a high association between the two is described in all studies. Depression often precedes the somatic symptoms (therefore it is less likely to be contributed to the patient knowing his diagnosis and poor prognosis) but is not yet regarded as a presenting symptom. Different theories are proposed to link the malignant process and the neurologic alterations biochemically. Depression causing cancer is possible, but of unknown importance in pancreatic cancer. Plausible are the involvement of cytokines, more specifically IL-6, alterations in the tryptophan-kynurenine, glutamate and serotonin pathways, and antibodies disturbing brain functioning directly or through serotonin. What is missing up till now is information on the diagnostic importance of depressive symptoms, which could make it a valuable presenting symptom leading to an earlier diagnosis of pancreatic malignancies.

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