CASE OF “PREMONITORY DEPRESSION” IN PATIENT WITH MAJOR DEPRESSIVE DISORDER FOLLOWED BY PANCREATIC CANCER

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Abstract

We present the case of a patient who was diagnosed with “premonitory depression.” It is well known that cancer patients have higher rates of depression than general population. This is particularly true for those who suffer from pancreatic cancer, and such patients have a high incidence of depression compared to those who suffer from other malignancies. According to some hypotheses depression disorder associated with pancreatic cancer may be related to immunological interference with the activity of serotonin.

Key words: *Depression; Pancreatic cancer; Immunological interference; Interleukin-1; Serotonin*

1. INTRODUCTION

To the best of our knowledge, the initial description of depressive symptoms comorbid with pancreatic cancer was reported by Scholz and Pfeiffer (1923). Later Fras et al. (1967) compared 46 patients with pancreatic cancer with 64 patients with colon cancer prior to surgery and reported that depression was diagnosed in 76% of the former group and only 20% in the latter group. Holland et al. (1986) compared 107 patients with advanced pancreatic cancer and 111 patients with advanced gastric cancer before the commencement of combination chemotherapy in a national cancer clinical trials group in 1986. They reported that pancreatic cancer patients had significantly higher self-rated depression after stratification for key medical and sociodemographic variables.

Conversely, Akechi et al. (2001) reported that there was no evidence of a high incidence of depression among patients with pancreatic cancer. Instead, they reported that the factors with most the significant psychological effects were disease stage and pain. However, Carney et al. (2003) found that depression was a risk factor for pancreatic cancer. Using longitudinal insurance claims data, they revealed that depression more commonly preceded pancreatic cancer than it did for other gastrointestinal malignancies.

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Premonitory depression is a psychiatric term that describes depression as the initial symptom of a severe physical illness, and especially as the initial manifestation of cancer. It was originally described by Lauter (1973), and the concept was introduced to Japan by Kido (1981). It is relatively well-known concept among clinicians in Japan, and hence, clinicians should be careful not to overlook the possibility of undiagnosed physical illnesses when they encounter an elderly patient with symptoms of depression. However, there is no corresponding mention of this condition in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) of the American Psychiatric Association or in the International Statistical Classification of Diseases and Related Health Problems 10th Revision by the World Health Organization. To the best of our knowledge, this is the first report on premonitory depression in the English literature.

2. CASE REPORT

Our patient was an 80-year-old Japanese man with no documented psychiatric history and history of substance abuse. He was a college graduate and worked as a company employee before he founded a company of his own in his fifties and retired in his seventies. Since his wife's death approximately 20 years ago, he was living on his own. He had not had any alcohol in the month before he presented at our hospital.

Six months before admission to the hospital, he gradually became inactive. Two months earlier, he was referred to the internal medicine department in a general hospital by his primary care physician. He was diagnosed with diabetes mellitus (DM) with an HbA1c level of 8.1% (normal range, <6%) and was administered glimepiride (3 mg/day).

The patient claimed he had money difficulties, according to his son who often visited him. His son mentioned that the patient made claims of not being able to pay 2000 dollars once a year for golf-club membership and that a bank tricked him out of several hundred thousand dollars and was still pressing him for payment." However, in reality, the patient was facing no financial difficulties. In addition, the patient was constantly anxious about water pipe explosions. He had gradually come to use meal delivery services instead of preparing food and often complained of nighttime insomnia.

Following this, the patient suffered physical delusions. He claimed he could not see and said his foot was rotting. These delusions became more serious. He did not drink water for a day because he believed that the room was filled with his urine. In addition, he was weakened as he did not eat because his intestine was clogged with stool. The patient lost 10 kg weight and lay down for most of the day. He said the air-conditioners and lights were costing him a great deal but that he could not stop using them. He also stated "I am feeling helpless. It is all over." He even mentioned suicide, stating "I would rather be dead."

The patient was found by his son lying on the floor on a day when he was scheduled for an outpatient visit. He was transported to the hospital by ambulance. However, he was awake and alert in the emergency room. After consultation with a physician, it was decided that he did not need to be admitted to the hospital's department of internal medicine.

He was then treated by a psychiatrist because of the psychiatric symptoms. He could walk independently, and there was no apparent tremor or paralysis of extremities. Abnormal neurological signs were absent. However, since the patient expressed a growing anxiousness and impatience, it took him a long time to answer the questions posed to him. He was courteous and tense when discussing his delusions. When he was asked about his physical condition, he said his foot was rotting and became gangrenous and that he was blind in both eyes. He also added "I am dead and gone." There were hypochondriac delusions and delusions of negation.

When the patient was told he would be psychiatrically hospitalized, he said he was worried about the cost of hospital stay. He said it would cost him 50,000 dollars to 100,000 dollars, which is the national government finance scale. Delusions of poverty and expansive

delusions were observed. He suddenly banged on the computer keyboard being used for the medical examination and said repeatedly "Radio waves make a crackling noise like this. Every crackle cost money." He denied having any auditory and visual hallucinations.

The patient's laboratory data showed an elevated blood glucose level of 360 mg/dL and HbA1c level of 8.7%. His urine sugar and ketone were + and 2+, respectively. The Mini-Mental State Examination score (MMSE; range, 0–30; 30 is the highest score) was 13 points. Head computed tomography (CT) revealed no remarkable abnormalities. However, since diminished interest and pleasure, weight loss, insomnia, psychomotor agitation, fatigue, and diminished ability to think and concentrate were all particularly prominent, his symptoms were causing clinically significant impairment in social areas of functioning and included mood-congruent psychotic features. He was diagnosed with a major single episode depressive disorder; this disorder was severe with psychotic features (DSM-IV; 296.24). Thus, he was admitted to the hospital's department of psychiatry.

Risperidone was administered at a dosage of 1 mg/day. As a result, insomnia and agitation resolved gradually. As he had no problems living in a ward with other people, there was no need to administer any psychotropic agents. Even though delusions of negation and poverty disappeared, he remained stubbornly attached to his stool. In fact, he was severely constipated and was given an enema to clear out any remaining stool.

Because psychiatric symptoms were relieved, the patient required re-examination using the MMSE and the Clinical Dementia Rating (CDR; range, 0–3, top score, 0) on day 10 of admission. His MMSE score was 21 points with a delayed recall score (range, 0–3; top score, 3) of 0 points and a CDR score of 0.5 points. His clinical cognitive function was assessed as mild cognitive impairment because his cognitive dysfunction was limited to impairment in recent memory. Although he was in a hyperglycemic condition, he did not need to be admitted to a hospital outpatient department. After consultation with a physician, insulin was administered, and this improved his glycemic control. He maintained a cooperative attitude toward physical treatment.

Since examination on admission revealed a slight elevation of D-dimer levels, ultrasound examinations of his lower legs and abdomen were conducted. Although no blood clots were present in the venous system of his lower legs, a pancreatic ductal dilatation was found. Abdominal CT and magnetic resonance cholangiopancreatography revealed the presence of a tumor in the head of the pancreas. Serum levels of tumor marker DUPAN-2 were markedly increased to 1,380 U/mL (normal, 0–400 U/mL). A specialist indicated that the patient's pancreatic tumor was inoperable and was to be monitored closely without therapy. The patient was then transferred to a hospital with sanatorium wards. Written informed consent was obtained from the patient for publication of this case report.

3. DISCUSSION

As described in this case report, the diagnosis of our patient at admission was a major depressive disorder, mentioned in the DSM-IV. After he was diagnosed with pancreatic cancer, we agreed in the weekly clinical conference that his most appropriate diagnosis was premonitory depression; this was because his clinical course was that as described by Lauter: the depressive phase preceded the detection of serious, often malignant disease, by several weeks or months.

Retrospectively, the patient's clinical course was pathogenomic in several aspects. Severe depressive symptoms were rapidly improved within about a week of administration, and a small amount of antipsychotic agent was administered. Therefore, there was no need for additional administration of antidepressive agents. Symptoms of his depression had some clinical characteristics; however, somatic delusion was absent, and there were no manifestations of melancholia, hopelessness, or sadness. In addition, instead of showing inhibition of thought, which is often accompanied by geriatric depression, our patient was

rather talkative when talking about his delusions. Given that he actually had a severe misdiagnosed DM, his delusions were understandable. They may have physical basis in diabetic pathology; his polyuria may have resulted in his delusion that his room was filled with his urine. He was so afraid of diabetic gangrene that he had a delusion that his feet were rotting. When he said "Actually, I am unable to see," he may have been anxious about diabetic retinopathy. Thus, some of his delusions can be explained in the context of his physical condition. Therefore, his delusions were, in retrospect, secondary.

The pathology of the link between depression and pancreatic cancer is yet to be fully elucidated. Some hypotheses involve cytokines and neurotransmitters. According to Brown and Paraskevas (1982), depressions associated with pancreatic cancer may be caused by immunological interference with the activity of serotonin; this activity is mediated in 2 ways: (1) antibodies against a protein released from cancer cells, which could bind to receptors for serotonin, thus blocking them; and (2) these primary antibodies could stimulate the production of anti-idiotypic antibodies, which would act as an alternative receptor for serotonin and reduce synaptic availability. According to the immuno-neuroendocrine hypothesis put forward by Uehara and Kubota (1995), interleukin-1 (IL-1) released from cancer cells promotes secretion of corticotrophin-releasing factor and eventually causes depression. Musselman et al. (2001) reported that higher-than-normal plasma IL-6 concentrations were associated with a diagnosis of major depression in cancer patients. According to Sumiyoshi et al. (1997), animal models indicated that the diabetic state may affect brain serotonergic activity via an increase in the density of 5-HT_{2A} receptors. They also proposed the possibility of increased vulnerability to major depression in patients with diabetes.

Although premonitory depression is relatively well known among psychiatrists in Japan, few researchers have studied this condition. Premonitory depression may have been forgotten in the contemporary diagnostic system, although in some cases, premonitory depression may be the most appropriate diagnosis.

The history of premonitory depression is worth considering. In 1930s, Yaskin (1931) first reported that depression might be the initial symptom of pancreatic cancer. In 1973, Lauter described elderly patients with symptoms of endogenous depression prior to diagnosis of severe physical illness, and he named such depression "premonitory depression." Kido introduced premonitory depression in Japan in 1981. He published an article that discussed the clinical characteristics of 5 patients who were admitted to a psychiatric ward due to depression and who were later diagnosed with severe physical illness. To our knowledge, no studies on premonitory depression have been published in Japanese psychiatric journals since then.

In his original study, Lauter (1973) pointed out the lack of sufficient physical assessment of elderly patients with depression. In addition, he specified that 35% of the patients that committed suicide were affected by this condition. He also argued that physical illness might be a major risk factor for suicide among elderly patients, which is now a very important issue in our society. Lauter wrote that we must assess the risk of suicide when we encounter patients with premonitory depression. He concluded his article saying, "The medicine, especially today's geriatrics will have to deal much greater extent than previously with the problem of the mental health of aged people." His article remains important in that it discussed geriatric depression comorbid with physical illness and the risk of suicide among such patients, approximately 40 years ago.

Unfortunately, in the current case, the urgent need for intensive treatment of physical illness was overlooked in the emergency room. However, after admitting the patient to a psychiatric ward, it was revealed that he had phenylketonuria and elevated blood glucose (360 mg/dL). Eventually, the clinicians correctly diagnosed his condition as severe DM and found that he was in need of insulin therapy. Furthermore, he was found to have pancreatic cancer, which was in close association with his worsening DM. From a retrospective viewpoint, our patient's admittance to a psychiatric ward resulted in the improvement of

physical illness, but led his family to discuss his will about his company and property, since there was no indication of active treatment of his pancreatic cancer. In conclusion, the presence of depression in this patient served as both a warning and an indicator. The depression in this case should be viewed within the framework of premonitory depression.

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REFERENCES

- Akechi, T., Nakano, T., Okamura, H., Ueda, S., Akizuki, N., Nakanishi, T., Yoshikawa, E., Matsuki, H., Hirabayashi, E., & Uchitomi, Y. (2001). Psychiatric Disorders in Cancer Patients: Descriptive Analysis of 1721 Psychiatric Referrals at Two Japanese Cancer Center Hospitals. *Japanese Journal of Clinical Oncology*, 31, 188 – 194.
- Brown, J.H., & Paraskevas, F. (1982). Cancer and depression: cancer presenting with depressive illness: an autoimmune disease? *British Journal of Psychiatry*, 141, 227-232
- Carney, C.P, Jones, L., Woolson, R.F., Noyes, R., & Doebbeling, B.N. (2003). Relationship between depression and pancreatic cancer in the general population. *Psychosomatic Medicine*, 65, 884-888
- Fras, I., Litin, E.M., Pearson, J.S. (1967). Comparison of Psychiatric Symptoms in Carcinoma of the Pancreas with Those in Some Other Intra-abdominal Neoplasms. *American Journal of Psychiatry*, 123, 1553-1562.
- Holland, J.S., Korzun, A.H., Tross, S., Silberfarb, P., Perry, M., Comis, R., & Oster, M. (1986). Comparative psychological disturbance in patients with pancreatic and gastric cancer. *American Journal of Psychiatry*, 143, 982-986
- Kido, M., & Takemura, K. (1981). So-called premonitory depression in physical illness especially in malignant disease. *Seishinigaku*, 23, 885-892,
- Lauter, H. (1973). Alters depressionen – Ursachen, Epidemiologie, Nosologie. *Akta Gerontologie*, 3, 247-252
- Musselman, M.R., Miller, A.H., Porter, M.R., Manatunga, A., Gao, F., Penna, S., Pearce, B.D., Landry, J., Glover, S., McDaniel, J.S., & Nemeroff, C.B. (2001). Higher Than Normal Plasma Interleukin-6 Concentrations in Cancer Patients With Depression: Preliminary Findings. *American Journal of Psychiatry*, 158, 1252-1257
- Scholz, T., & Pfeiffer, F. (1923). Roentgenologic diagnosis of carcinoma of the tail of the pancreas. *Journal of American Medical Association*, 81, 275-277.
- Sumiyoshi, T., Ichikawa, J., Meltzer, H.Y. (1997). The effect of streptozotocin-induced diabetes on dopamine2, serotonin1A and serotonin 2A receptors in the rat brain. *Neuropsychopharmacology*. 16, 183-90.
- Uehara, S., & Kubota, T. (1995). Psychosomatic treatment for hepatic, biliary and pancreatic diseases. Pancreatic cancer and depression. (In Japanese) *Shinshiniryō*, 7, 1066-1080
- Yaskin, J.C. (1931). Nervous symptoms as earliest manifestation of carcinoma of pancreas. *JAMA*, 96, 1664-1668