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LETTERS TO THE EDITORS

Manic syndrome as the presenting feature of pancreatic cancer

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Cancer patients frequently present with psychiatric comorbidities, with mood and anxiety symptoms being most prevalent among these patients.[1] Comorbidity between pancreatic carcinoma and depression is high, occurring in up to 75% of cases, with depressive symptoms frequently preceding the diagnosis of cancer.[1] Although other psychiatric symptoms such as anxiety are also common, manic symptoms are infrequent presenting features of pancreatic cancer: to our knowledge, only two other cases have been reported.[1,2] We report the case of a 75-year-old patient who presented with a manic syndrome as the presenting feature of pancreatic cancer.

The 75-year-old white woman was admitted to a psychiatric emergency department with subacute behavioral changes of about 2 to 3 weeks' duration, with no obvious triggering factor, worsening in the last 48 h, with sleep impairment. The most striking symptoms at mental state examination were expansive mood, disinhibition, tachypsychia, and verbosity. No psychotic features were noticed. The patient was alert, and there were no changes in attention, orientation, or memory. She had no psychiatric history, substance misuse of any kind, or family history of mental disorders. Vital signs were normal, and she had no fever. A computed tomography (CT) scan of the head was normal. Laboratory tests were notable for anemia, borderline leukocytosis, thrombocytosis, and elevated liver enzymes. An internal medicine consult was requested, and subsequent abdominal ultrasound showed a 3-cm heterogeneous lesion in the uncinate process of the pancreas, consistent with pancreatic adenocarcinoma; a whole-body CT scan revealed probable hepatic and lung micrometastases. The patient was given haloperidol 5 mg and alprazolam 1 mg and admitted to a surgical ward for further management. During hospitalization, there was no record of behavioral changes, confusion, or disorientation. Reassessment by liaison psychiatry on day 3 of admission considered she was improving, with normalization of mood and sleep; haloperidol was kept on a PRN basis. Primary or secondary infections were excluded, and metastatic invasion of the liver, lungs, and peritoneum was confirmed. She was discharged to supportive care, given her unfavorable prognosis, and no further psychiatric medication was needed. In subsequent months, she had two other admissions to the surgical ward due to obstructive jaundice, without behavioral or psychopathological relapse. She was referred to an oncology hospital and died within 4 months of presentation.

The relation between cancer and psychiatric symptoms is well established. Nearly half of cancer patients meet diagnostic criteria for psychiatric disorders, particularly adjustment disorder, depression, and delirium; however, it is uncommon for cancer patients to experience hypomanic or manic episodes.[3]

While most manic states are "primary" and therefore considered a phase of bipolar disorder, a substantial proportion of manic episodes occur secondary to medical or pharmacological antecedents, especially in older people.[4] Identifying the etiology of mania is vital because although acute symptomatic treatment of both primary and secondary mania may be similar, appropriate treatment of secondary mania includes addressing its cause. In this clinical case, the patient had no personal or family history of mood disorders. Attending to this and considering the patient's age, secondary mania was considered, and potential causes were addressed through an exhaustive investigation. Brain metastases were excluded at the initial workup. In addition, the patient had not received cancer treatment before admission. No fever, signs of infection, or delirium were observed. Thus, leading causes of psychiatry comorbidity in oncological patients were excluded.[1]

To our knowledge, this is only the third published case of manic syndrome as the presenting feature of pancreatic cancer, although, in other reported cases, psychiatric features predated the cancer diagnosis by several months.[1,2] Murru et al.[2] presented a case of late-onset manic episode in a 91-year-old without previous psychiatric history as a manifestation of a pancreatic neoplasm, stating that hormonal or immune influences caused by direct or indirect action of the malignant tissue could be associated with the affective symptoms. Basterreche et al.[1] reported a similar case of a 66-year-old male, without personal or family antecedents of mood disorders, no brain metastasis, and no chemotherapeutic treatment before hospitalization, who had been admitted to an acute psychiatry unit for a manic episode with psychotic symptoms in the context of a recent diagnosis of pancreatic adenocarcinoma. They noted that those observations were consistent with the hypothesis that pancreatic cancer and mood disorders could have shared pathophysiology.[1] According to these authors, the inflammatory response induced by pancreatic cancer in individuals with a rare genetic susceptibility variant to bipolar disorder could explain the unusual development of mania in those patients.

While exact mechanisms are not yet established, and more studies on the subject are needed, there is growing evidence that paraneoplastic manifestations, namely through cytokine-mediated immune response, could be involved in this uncommon psychiatric manifestation of pancreatic cancer.[1] Therefore, paraneoplastic syndromes could be a differential diagnosis to consider. It has also

been hypothesized that mood symptoms could be attributed to dysregulation of neuroendocrine signaling instead of an autoimmune basis.[5]

Overall, this case report supports, as a clinical rule of thumb, that organic pathology should be actively investigated when facing first manic episodes at advanced ages.

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Not only pharmacodynamic: the role of brain circuits in improving the treatment of suicidal thoughts and behaviors

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Recently, Watts et al.[1] published a letter in which they argue for the importance of understanding the underlying pharmacodynamic mechanisms of Ketamine in order to personalize its use and to help develop novel drugs designed for specific targets in both depression and suicidality, which they called "the dawn of precision psychiatry." Nevertheless, it is no less important to understand and specify different brain circuits underlying or associated with suicidality to determine the different clinical profiles for which each drug intervention might be more clinically effective.

Schmaal et al.[2] conducted a comprehensive review on the neurocircuitry of suicidal thoughts and behaviors, in which a wide body of evidence suggested that different brain circuits might be involved in each aspect (thoughts vs. behaviors) of suicidality. Suicidal thoughts are more linked with alterations in brain areas involved in regulating positive and negative emotions, such as the medial ventral prefrontal cortex, insula, amygdala, hippocampus, lateral temporal regions, posterior midline structures (posterior cingulate cortex and precuneus), dorsal anterior cingulate cortex, ventral striatum, thalamus, and cerebellum. Suicidal behaviors are more associated with dysfunction in regions involved in cognitive-behavioral control, such as the dorsal prefrontal cortex, inferior frontal gyrus, rostral prefrontal cortex, and dorsal anterior cingulate cortex. Even though there is a clear overlap among these areas, an understanding of these structures and their patterns of connectivity might orient specific circuit-based treatment interventions that can more precisely target different clinical profiles of suicidality.

In practice, there is still debate concerning whether the severity of depressive symptoms independently predicts more suicidal thoughts and behaviors.[3] Of note, improvement in suicidal thoughts after ketamine infusion might be independent of reductions in depressive symptoms,[4] which suggests independent underlying brain mechanisms. Recently, Ballard et al.[5] found that after a single ketamine infusion, reduced suicidal ideation was correlated with reduced activation of the infralimbic cortex (Broadmann area 25). Interestingly, this finding was not supported by overall mood scores, such as depressive symptoms in general.

All this debate might help clinicians more precisely comprehend each clinical profile associated with depression and/or suicidality, as well as encourage future research on therapeutics for each clinical profile, including new pharmacological (e.g., brexanolone, cannabidiol, glutamatergic agents) or neuromodulatory treatments, such as transcranial magnetic stimulation, among others. Previous studies have already stressed the importance of understanding neural circuit biotypes in order to better predict treatment-response for each neurophysiological subtype of psychiatric disorders.[6-8] Regarding suicidality, these clinical phenotypes might include: a) depression without suicidal thoughts, b) depression with suicidal thoughts, c) suicidal thoughts in absence of depression, d) depression without suicidal behaviors, e) depression with suicidal behaviors, f) suicidal behaviors in absence of depression. We hope that this knowledge could drive clinicians and researchers toward a more personalized psychiatric treatment.